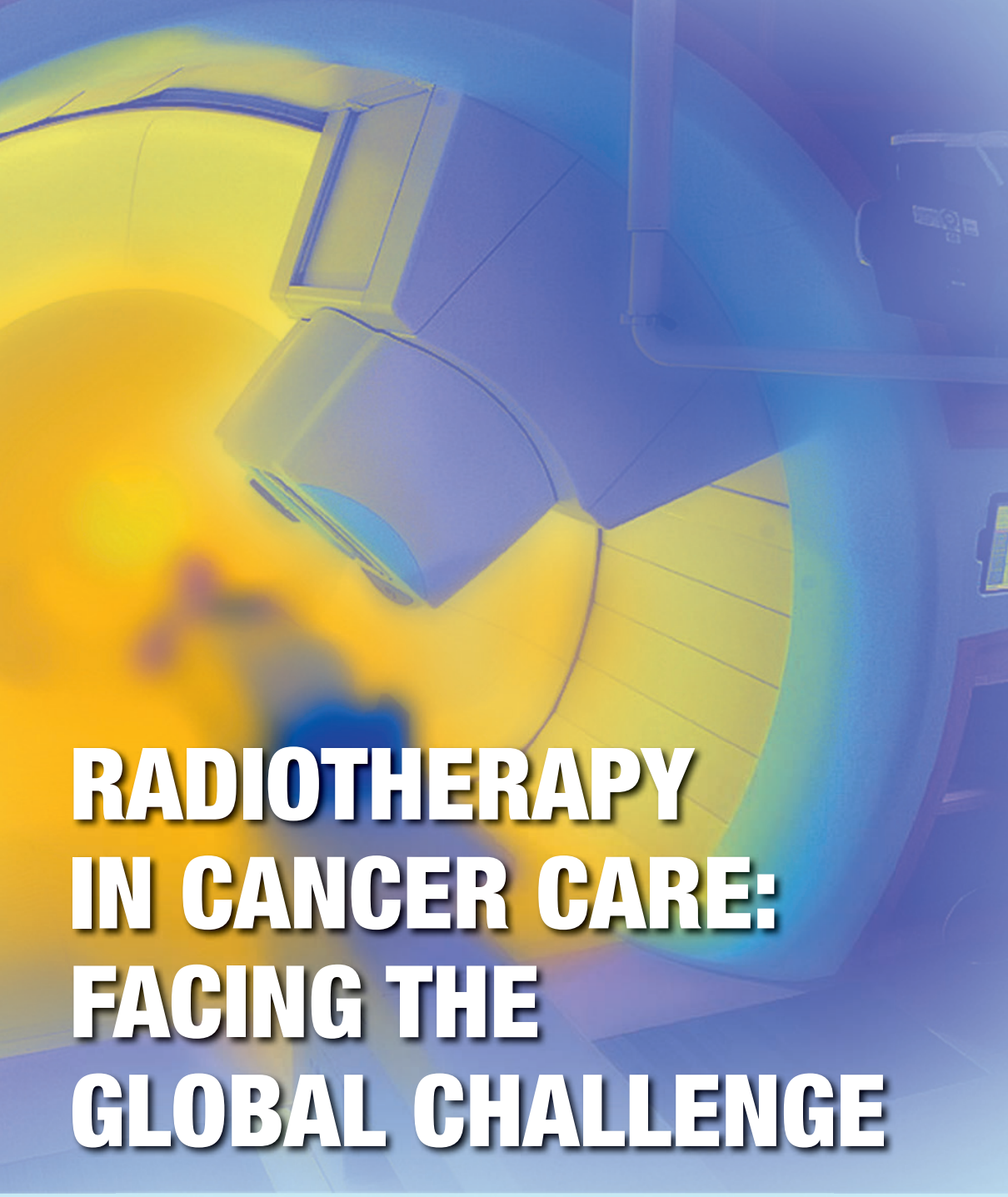

# RADIOTHERAPY IN CANCER CARE: FACING THE GLOBAL CHALLENGE

**Edited by:**
**Eduardo Rosenblatt**
**Eduardo Zubizarreta**

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# RADIOTHERAPY IN CANCER CARE: FACING THE GLOBAL CHALLENGE

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# FOREWORD

**Yukiya Amano**
**Director General**

Cancer affects people in all countries regardless of age, gender or social class. In developed countries, access to radiotherapy and other advanced forms of treatment is taken for granted. However, the picture is very different in developing countries. It is estimated that there is a shortage of around 5000 radiotherapy machines in the developing world. In Africa and some countries in Southeast Asia, millions of people have no access to diagnostic services or treatment. Too many die of conditions that are treatable. This is an immense human tragedy. Consequently, the IAEA's work in cancer control and radiation medicine will always be a high priority for me as Director General.

Thanks to early detection and modern treatment methods, millions of men and women in developed countries now live normal lives for decades after a cancer diagnosis. The IAEA works to help developing countries in their fight against cancer. Through our technical cooperation programme, we support over 130 projects in cancer diagnosis, management and treatment. We provide Member States with technical support in radiation medicine in general, and radiotherapy in particular. We help countries to establish oncology and radiotherapy centres. We provide extensive training for medical and technical staff.

The IAEA has delivered cancer related assistance totalling over US $260 million to developing countries over the past three decades. But the need is great and we cannot transform cancer care on our own. Only through partnerships with international organizations, universities, cancer centres, financial institutions and non-governmental organizations can the strengthening of radiotherapy services be addressed effectively throughout the world. The World Health Organization is a particularly important partner in this area.

This publication, Radiotherapy in Cancer Care: Facing the Global Challenge, presents an overview of the major issues to be taken into account by countries planning and implementing radiotherapy services. It has been written with the health care manager in mind. The book contains data on the current status of radiotherapy services around the world, established and novel technologies, social and economic factors, current issues and the role of international organizations. Frequently asked questions, such as whether developing countries should consider introducing proton therapy, are addressed. Readers will obtain an overview of the current state of the art in radiotherapy from recognized experts in each area. I hope this publication will make a valuable contribution to improving the lives of cancer patients in developing countries.

*EDITORIAL NOTE*

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# PREFACE

The IAEA has issued a series of publications providing guidance on the establishment and development of radiotherapy centres, as well planning radiotherapy services at the national level. A recent publication addresses the layout and construction of radiotherapy facilities, and a series of booklets describe the organization and curriculum for the training and education of radiotherapy professionals, including: radiation oncologists, medical physicists, technologists, radiation biologists and radiation oncology nurses.

Contrary to what was anticipated in the 1950s and 1960s, radiotherapy is playing an increasingly important role in the curative and palliative care of cancer patients. International organizations, professional societies, non-governmental organizations and the industry are all focusing attention on the problems of availability and access to adequate radiotherapy services in the context of health care systems.

The need for the present book arises from the interaction of the IAEA with many Member States at the time of planning and implementing radiotherapy and other radiation medicine services, in particular in developing countries. The book has a broad scope so as to discuss the different areas which require attention when developing or upgrading services.

The editors wish to thank Rethy K. Chhem (IAEA) for his conceptual input and encouragement in the production of this book. Our thanks also go to Ci (Ashley) Zhu for her work in editing and formatting the material, as well as her contribution to the note on radiotherapy in China.

E. Rosenblatt
E. Zubizarreta

# MILESTONES IN CANCER RADIOTHERAPY AND IMAGING: 120 YEARS OF DISCOVERY AND INNOVATION

| | | |
|---|---|---|
| **1895** | W.C. Röntgen | Discovery of X rays. |
| **1896** | H. Becquerel | Discovery of natural radioactivity from uranium. |
| **1896** | L. Freund | Treatment of nevus with X rays. |
| **1898** | M. Skłodowska-Curie, P. Curie | Discovery of polonium and radium. |
| **1901** | H.-A. Danlos | Treatment of cutaneous lupus with radium. |
| **1903** | S.W. Goldberg, E.S. London | Histologically proven cure of skin cancer with radiation. |
| **1903** | W.H. Bragg | Discovered the Bragg peak. |
| **1905** | R. Abbe | Cure of cervical cancer with radium sources. |
| **1906** | J. Bergonie, L. Tribondeau | Cell radiosensitivity law. |
| **1913** | W.D. Coolidge | First X ray tube. |
| **1913** | G. Forssell, J. Heyman, E. Berven, M. Strandqvist, R. Sievert, R. Thoraeus | Stockholm system of brachytherapy dosimetry. |
| **1919** | C. Regaud, A. Lacassagne | Brachytherapy for cervical cancer. |
| **1922** | H. Coutard, C. Regaud, A. Hautant | Cure of laryngeal cancer with fractionated radiotherapy. |
| **1928** | R. Wideröe | Radiofrequency linear accelerator for ions. |
| **1929** | E.O. Lawrence | Developed a basic theory of the cyclotron. |
| **1930** | R.F. Mottram | Oxygen effect on radiosensitivity. |
| **1930** | E. Quimby, G. Failla | Quimby system of dosimetry. |

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|---|---|---|
| **1933** | H. Crabtree, W. Cramer | Oxygen effect in radiotherapy. |
| **1934** | R. Patterson, H.M. Parker | Manchester system of dosimetry for interstitial brachytherapy. |
| **1934** | I. Joliot-Curie, F. Joliot-Curie | Discovery of artificial radioactivity. |
| **1937** | R.M. Sievert | Remote controlled afterloading. |
| **1938** | R. Stone | First treatment with neutrons. |
| **1941** | S. Hertz | Use of radioiodine ($^{131}$I) for thyroid cancer. |
| **1946** | R. Wilson | Proposed the application of ion beams for radiotherapy. |
| **1948** | G. Fletcher, M. Lederman, L.F. Lamerton | Fletcher's system of gynaecological brachytherapy. |
| **1951** | I. Smith, H.E. Johns | Cobalt-60 teletherapy. |
| **1951** | W.H. Sweet, G. Brownell | First treatments with boron neutron capture therapy. |
| **1951** | L. Leksell | 'Gamma knife' radiosurgery. |
| **1953** | U. Henschke | Afterloading brachytherapy.<br>Introduction of $^{192}$Ir sources for brachytherapy. |
| **1953** | Metropolitan-Vickers | First medical linear accelerator (Hammersmith). |
| **1954** | E.O. Lawrence, R. Wilson | First patient treated with protons at Berkeley Radiation Laboratory. |
| **1955** | F. Comas, M. Brucer | Caesium-137 teletherapy. |
| **1956** | H.S. Kaplan, E. Ginzton | Medical linear accelerator (Stanford). |
| **1957** | R. Nelson, M.L. Meurk | Computational methods applied to implant dosimetry. |
| **1960s** | J.F. Fowler, B.G. Douglas | Linear quadratic parameters from fractionation experiments. |

| | | |
|---|---|---|
| **1965** | U. Henschke, B. Hilaris | Oscillating source system for brachytherapy. |
| **1965** | S. Takahashi | Multileaf collimator. |
| **1965** | D. O'Connell, M. Wakabayashi | Cobalt-60 sources for high dose rate brachytherapy. |
| **1966** | B. Pierquin, A. Dutreix, D. Chassagne, G. Marinello | Paris system of brachytherapy dosimetry. |
| **1973** | G. Hounsfield | X ray computed tomography (CT) and first CT scanner. |
| **1976** | N. duV. Tapley | Standardization of the clinical use of the electron beam. |
| **1979** | M. Catterall, D.K. Bewley | Fast neutron therapy. |
| **1980** | P. Bottomley | First commercial magnetic resonance imaging (MRI) device. |
| **1982** | A. Brahme, A. Cormack, N.H. Barth | Inverse planning. |
| **1990** | Loma Linda University | Completed hospital-based proton facility. |
| **1993** | T.R. Mackie, P. Reckwerdt | Helical tomotherapy. |
| **1994** | NIRS Chiba, Japan | Radiotherapy with carbon ion beam. |
| **1994** | NOMOS Peacock | Intensity modulated radiation therapy (IMRT). |
| **1996** | L. Brewster, R. Mohan | Multileaf collimator adapted for IMRT. |
| **1999** | J.R. Adler | Robotic radiotherapy. |
| **2001** | A.L. Boyer | Volumetric modulated arc therapy (V-MAT). |
| **2002** | Eckert & Ziegler BEBIG (Germany) | Marketing of $^{60}$Co microsource system for high dose rate brachytherapy. |
| **2004** | J.F. Dempsey, B.W. Raaymakers, J.J. Lagendijk | MRI-linac. |

| | | |
|---|---|---|
| **2005** | C. Haie-Meder, R. Pötter, E. van Limbergen | GEC–ESTRO recommendations for image based planning for brachytherapy in cervical cancer. |
| **2006** | J.A. Bonner et al. | Targeted therapy and radiotherapy. |

# CONTENTS

# Part I

# INTRODUCTION

# INTRODUCTION

**E. Rosenblatt, E. Zubizarreta**

## I.1. BACKGROUND

The treatment of cancer continues to rest largely on three major modalities: surgery, radiotherapy and systemic therapies, including chemotherapy. To these we can add a number of other approaches: immunotherapy, targeted therapy and gene therapy.

The use of ionizing radiation to treat cancer started soon after the discovery of radium by M.S. Curie and P. Curie in 1898 (see Milestones in Cancer Therapy and Imaging). The first histologically documented cancer cures using radiation were in St. Petersburg in 1903 by S.W. Goldberg and Efim Semenovich London. These cases were reported in Dermatologische Zeitschrift [I.1] and described patients with basal cell carcinoma of the face. However, unlike the first documented histological cures by X rays (also for basal cell carcinoma of the face in 1899 in Stockholm) [I.2], no photographs are available of the patients treated in St. Petersburg before and after treatment.

More than a century after the discovery of radium, radiation medicine interventions continue to play a major role in the various stages of the continuum of cancer care: prevention, early detection and screening, diagnosis, treatment and palliative care. In this context, radiotherapy is an important contribution to the cure of many patients and to effective palliation in many others.

Radiotherapy is currently an essential component in the management of cancer patients, either alone or in combination with surgery or chemotherapy, both for cure and for palliation. Of those cancer patients who are cured, it is estimated that 49% are cured by surgery, about 40% by radiotherapy alone or combined with other modalities, and 11% by chemotherapy alone or combined [I.3].

The mechanism by which radiotherapy is effective in the treatment of cancer is described in more detail in Chapter 6. Clearly, ionizing radiation in sufficient doses has a cell killing effect, but it is not specific enough to differentiate between cancerous and normal cells. Strategies had to be found to improve the therapeutic index, either by physically improving target conformity or by increasing the radiation sensitivity of the cancer cells relative to the normal cells.

The main objective guiding the historical development of radiotherapy has always been the delivery of a curative radiation dose to the malignant tumour, while minimizing the dose received by healthy tissues and organs, thus optimizing the therapeutic index. This has been the ultimate goal of radiotherapy strategies

such as the use of hyperthermia, hyperbaric oxygen, high linear energy transfer (LET) radiation, radiosensitizers, concomitant chemoradiotherapy, manipulation of fractionation schemes and modulation of the radiation fluence.

In recent years, research into the molecular basis of radiation response in tumours and in normal tissues under various physiological and pathophysiological situations has continued to improve our understanding of radiosensitivity. In combination with the technological progress in radiation oncology, this new knowledge offers the potential to develop more specific targeted therapeutic strategies to optimize the curative principle of radiotherapy in the near future [I.4]. In addition, cancer genome analysis is expected to have a far-reaching impact on our understanding of cancer biology and will likely prompt new approaches to the detection, diagnosis, treatment and possibly prevention of the disease [I.5]. Through analysis of samples from early preinvasive lesions, from metastases, from recurrences after therapy, and from patients with known exposures or epidemiological risk factors, these studies should also provide insights into disease pathogenesis and progression, and mechanisms of radiation resistance.

## I.2. RADIOTHERAPY IN THE CONTEXT OF CANCER TREATMENT

Radiotherapy and surgery are local, or locoregional, approaches to cancer treatment. As long as the cancer is localized to its site of origin or has spread to the regional lymph nodes only, there is a chance of curing the disease using a locoregional approach. However, the natural history of many forms of cancer has taught us that in many situations the cancer cells are not confined locally or regionally, although they appear to be so using currently available diagnostic tools. In these situations, diagnostic and staging tools show only local or locoregional disease, but in reality malignant cells have already escaped the locoregional boundaries and will eventually induce disease recurrence and possibly distant metastasis. In this scenario, local or locoregional therapies are clearly not enough, and the treatment of cancer requires a systemic approach involving chemotherapy, hormonal therapy or targeted therapy.

Today, cancer patients who have access to the health care system are treated by a surgeon, a radiation oncologist, a medical oncologist or, preferably, a multidisciplinary team. The radiation oncologist, working in close collaboration with the other members of the radiotherapy team, is the physician responsible for prescribing, planning, monitoring and following the patient throughout and after a course of treatment with radiotherapy.

Radiation oncologists make multiple decisions affecting the fate of their patients on a daily basis. Their responsibility as physicians is to provide clear and unbiased options, based on scientific evidence, for optimal patient care.

However, in the real world, their recommendations are also influenced by health economics, the managed care environment, local practice limitations, the desires of patients and families, and even politics.

## I.3. THE WORLDWIDE SHORTAGE OF RADIOTHERAPY

The IAEA's Directory of Radiotherapy Centres (DIRAC) [I.6] is the world's authoritative source of information on radiotherapy centres. The DIRAC database counts more than 7600 radiotherapy centres, with about 13 000 teletherapy and 2600 brachytherapy machines serving the world's population. These radiotherapy machines play an important role in the fight against cancer.

Currently, the DIRAC database encompasses approximately 90% of the existing radiotherapy facilities, with comprehensive, up to date information for most countries. By offering a global assessment of the geographical distribution of radiotherapy facilities in relation to populations, cancer incidence and economic status, DIRAC offers a powerful tool for understanding the current trends in the accessibility of radiotherapy, as well as for planning future radiation oncology services.

DIRAC's global survey shows a dramatic discrepancy in the ability of cancer patients to access lifesaving radiotherapy across countries and regions of the world (see Chapter 5). In high income countries, one radiotherapy machine is available for every 120 000 people. In middle income countries, one machine serves over 1 million people. In low income countries, about 5 million people rely upon a single radiotherapy machine. In 51 countries, independent territories and islands, cancer patients have no access to radiotherapy; of these countries without radiotherapy services, 29 have populations of over 1 million people. To approach the level of access enjoyed in higher income countries, some developing nations would need to increase radiotherapy availability tenfold or more.

There is a clear need for additional radiotherapy facilities around the world [I.7]. Strategies for developing new radiotherapy facilities need careful planning at the local [I.8] and national levels [I.9], and have to be accompanied by substantial investments in infrastructure, equipment and staff training.

The radiotherapy utilization (RTU) rate is the proportion of cancer patients requiring at least one treatment course of radiotherapy during the evolution of their disease (Chapter 3). A country's teletherapy needs can be roughly approximated as follows. In developed countries, the RTU rate is approximately 50%. This means that 50% of patients diagnosed with cancer will require radiotherapy treatments at least once at some stage of the evolution of their disease. In developing countries, it is assumed that the optimal RTU rate should be higher (i.e. >55%) and that it may reach 70–80% of patients diagnosed with

cancer, with the higher rates in low income countries. In many low income countries, lack of prevention and screening programmes, and limited oncological surgical services mean that the majority of patients diagnosed with cancer have advanced disease and most will need radiotherapy for palliation. However, IAEA experience in conducting reviews of cancer services in low income countries has shown that the actual RTU rate is between 25% and 40%. In other words, only 25–40% of patients diagnosed with cancer actually receive radiotherapy in this particular group of countries. The IAEA has found a 52% optimal RTU rate and a mean 28% (9–46%) actual utilization rate in a group of 9 middle income countries [I.10]. The reasons for the discrepancy between *optimal* and *actual* RTU rate lie in underdiagnoses, under-reporting and under-referral of cancer patients to treatment facilities.

Chapter 30 includes a tentative calculation of the need for teletherapy machines worldwide in the foreseeable future.

## I.4. RESPONSE OF THE INTERNATIONAL COMMUNITY TO THE CHALLENGE

In 2000, the United Nations established the Millennium Development Goals (MDGs) to improve social and economic conditions in the world's poorest countries. The MDGs consisted of eight international development goals that all 193 United Nations Member States and at least 23 international organizations agreed to achieve by 2015. The need for treatment of cancer or non-communicable diseases (NCDs) was not explicitly mentioned in the MDGs, but Goal 6 states: "Combat HIV/AIDS, malaria and other diseases". Until recently, financing and sponsoring efforts have been globally oriented towards programmes against communicable diseases, malnutrition and, more recently, AIDS. This was justified by the prevalence and major negative impact of these diseases on the social and economic development of human society, particularly in less developed countries.

The international community is beginning to pay attention to NCDs, including cancer, as a problem not exclusive to affluent countries. The process started in 2005 with the World Health Assembly meeting in Geneva. In September 2011, the United Nations held a high level meeting of the General Assembly to address the prevention and control of NCDs worldwide, with a particular focus on socioeconomic impacts, particularly in developing countries. The General Assembly adopted a Political Declaration [I.11] that recognized the importance of strengthening prevention, early detection, diagnosis, treatment and palliation of NCDs, including cancer, particularly in developing countries. This important event and document represent a potential platform for the rechannelling

of resources to the areas mentioned, including cancer radiotherapy. It is hoped that this process will result in more resources being directed to cancer research and care as well as to coordinated efforts among the international stakeholders committed to the fight against cancer.

## I.5. THE IAEA'S DOSIMETRY SERVICES

The IAEA's subprogramme on Dosimetry and Medical Physics for Imaging and Therapy is responsible for the quality assurance (QA) aspects of the use of radiation in medicine to ensure safety and effectiveness, and deals with the science and technology involved in this area [I.12]. The accurate measurement of radiation dose (dosimetry) is important in various applications such as radiation oncology, diagnostic radiology, nuclear medicine and radiation protection.

By providing dosimetry calibration services to Member States through the network of secondary standards dosimetry laboratories (SSDLs), the IAEA establishes a link to the international measurement system. Dosimetry verification services are also provided both for SSDLs and for end-user institutions engaged in radiotherapy, diagnostic radiology and radiation protection. The primary beneficiaries of these activities are hospital patients undergoing medical procedures involving radiation, and radiation workers and the general public, who benefit from improved dosimetry practices.

The experimental work of the subprogramme is carried out in the IAEA's Dosimetry Laboratory, which is part of the IAEA's Laboratories in Seibersdorf, about 40 km from Vienna [I.13]. Specifically, standards for radiation measurements are disseminated in the fields of radiation protection, radiation medicine (radiotherapy and diagnostic X rays) and industrial applications. Traceable quality audits and comparisons are implemented to ensure controlled radiation dosages in radiotherapy, radiation protection and radiation processing in Member States.

## I.6. NUCLEAR MEDICINE AND DIAGNOSTIC IMAGING

The mission of the IAEA's subprogramme on Nuclear Medicine and Diagnostic Imaging is based on Article II of the IAEA Statute: "The Agency shall seek to accelerate and enlarge the contribution of atomic energy to peace, health and prosperity throughout the world" [I.14]. The subprogramme has the specific goal of fostering the application of nuclear medicine techniques as part of the clinical management of certain types of diseases.

The long term objective of the subprogramme in nuclear medicine and diagnostic imaging focuses on enhancing the capability of Member States to address health needs through the use of nuclear medicine techniques in both imaging and therapeutic applications as a complement to conventional techniques.

Different activities are conducted under this subprogramme: coordinated research projects; expert meetings to advise the IAEA on specific topics; publications and manuals, including educational material; an educational web site; and databases. Many projects run under the subprogramme are oriented towards the clinical applications of standard and emerging technologies in nuclear medicine such as single photon emission computed tomography–computed tomography and positron emission tomography–computed tomography for two of the major causes of death: cancer and cardiovascular diseases. There is also a focus on therapeutic applications, wherein the primary objective is to make available fundamental radiopharmaceuticals for routine clinical use in developing countries and to develop, evaluate and standardize new radiopharmaceuticals for effective use in diagnostic and therapeutic nuclear medicine procedures. Finally, the subprogramme manages projects related to quality improvement in the clinical practice of nuclear medicine.

## I.7. SUMMARY

Radiotherapy is one of the main pillars of cancer care. There are gross inequalities in the provision of and access to this service between developed and developing countries. The policy of the IAEA is that radiotherapy should not be addressed in isolation. Ideally, the establishment and strengthening of radiotherapy services should be coupled with efforts to improve prevention, early detection, diagnostics and palliative care. This holistic approach requires a coordinated effort that includes international organizations, governments, and non-governmental organizations, in particular scientific and academic centres, the donor community and the private sector.

The philosophy of the IAEA is that, in principle, all cancer patients deserve optimal available care, including radiation medicine techniques. However, recognizing the disparity of resources available around the world, it is more practical to approach planning in terms of a strategy that is adapted to the availability of resources.

The purpose of the present publication is to make the case for an adequate level of radiotherapy to meet current and future needs worldwide. It presents an overview of the ideas shared by the IAEA in more technical publications.

This publication presents an overview of the major topics and issues to be taken into account when planning and implementing radiotherapy services.

It has been planned with the health manager in mind, with the understanding that while the planning of cancer radiotherapy services is normally undertaken by managers, it should also involve collaboration with technical experts who have experience in the field.

The chapters in this book present topics of current importance to the general discussion of radiotherapy services. Each chapter has been written by an author, or authors, with direct experience and expertise in that particular area. The topics are addressed from a global perspective.

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# Part II

# RADIOTHERAPY IN CANCER CARE

# Chapter 1

# RADIOTHERAPY IN CANCER CARE

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## 1.1. INTRODUCTION

Cancer control, cancer care and cancer treatment are three different concepts, although the terms are often used interchangeably. *Cancer control* is the reduction in the incidence, morbidity and mortality of cancer, as well as the improvement in the quality of life of cancer patients and their families. As such, cancer control includes actions relating to prevention, early detection and screening, diagnosis, treatment and palliative care. *Cancer care* includes all actions and interventions aimed at supporting, assisting and treating cancer patients. Cancer care includes cancer treatment, but also other forms of support such as nutrition, symptom relief, speech therapy, physiotherapy, stoma care, nursing care, lymphoedema care and psychosocial care. *Cancer treatment* includes medical interventions aimed at the cure or palliation of a patient who has been diagnosed with cancer. As such, cancer treatment modalities include surgery, radiotherapy, systemic therapies such as chemotherapy, hormone therapy, immunotherapy, gene therapy and other investigational strategies.

Cancer is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues. Cancer cells can spread to other parts of the body through the blood and lymphatic system. Cancer is not just one disease, but many diseases. There are more than a hundred different types of cancer. Most cancers are named for the organ or type of cell from which they start — for example, cancer that begins in the basal cells of the skin epidermis is called basal cell carcinoma.

Cancer types can be grouped into broader categories according to the type of cells or tissue of origin. The main types are carcinomas, sarcomas, melanomas, lymphomas and leukaemias. With ongoing developments in genetic profiling, it is possible that in the future the response of cancers to therapy will be assessed by looking at their genetic expression rather than their histological type.

All cancers begin in cells, the body's basic unit of life. To understand cancer, it is helpful to know what happens when normal cells become cancer cells. The body is made up of many types of cells. Cells evolve and differentiate during embryonic development from relatively undifferentiated embryonic stem

cells through a complex process of signalling. These cells grow and divide in a controlled manner to produce more cells as they are needed to maintain the body structure and functions. When cells become old or damaged, they die and are replaced by new cells.

Sometimes, this orderly process goes wrong. The genetic material (particularly the nuclear deoxyribonucleic acid, or DNA) of a cell can become damaged or changed, producing mutations that affect normal cell growth and division. When this happens, cells do not die when they should and new cells form when the body does not need them. The extra cells will then form a non-functional mass of tissue called a tumour. These cells, the cancer cells, not only have lost the capacity to respond to normal control mechanisms, but for this very reason they are locally invasive, invade, push, infiltrate and destroy other tissues and have the potential to spread following the lymphatic channels and blood vessels to create distant deposits of cancer known as distant metastases.

The cellular origin of cancer was described by Virchow in 1863 [1.1]. The molecular structure of DNA was elucidated by J.D. Watson and F. Crick in 1953 [1.2]. At that time, the relative survival rate of cancer patients as a whole in the United States of America was 35% [1.3]. Hybridomas for the production of monoclonal antibodies were developed in 1995, and by this time the relative survival rate was 50%. The year 2005 saw the first absolute decrease in the total number of deaths from cancer in the United States of America. That year the relative survival rate was 68%. These figures highlight a steady improvement in the relative survival rates for cancer in an industrialized country, an improvement associated with ongoing medical research.

The aetiology of cancer is multifactorial, with genetic, environmental and lifestyle factors interacting to induce and maintain the process of malignant transformation. Knowledge of cancer genetics is rapidly improving our understanding of cancer biology, helping to identify at-risk individuals, furthering the ability to characterize malignancies, establishing treatment tailored to the molecular fingerprint of the disease, and leading to the development of new therapeutic modalities. This expanding knowledge base has implications for all aspects of cancer management, including prevention, screening and treatment.

The ultimate cancer cure will be possible when a therapeutic intervention will induce ‘cell kill’ limited to the malignant cells only, while sparing the non-malignant cells; a ‘magic bullet’, like many antibiotics against bacterial infections. Current research into targeted therapies, genetic research and gene manipulation may be steps in that direction.

## 1.2. RADIOTHERAPY IN THE CONTEXT OF CANCER CONTROL

Radiotherapy is the medical use of ionizing radiation in the treatment of disease, mostly cancer but also non-malignant disease. The historical development of the use of radiation as a medical tool to fight cancer can be seen through a series of historical milestones. The main principle guiding the historical development of radiotherapy as a medical discipline has been the search for strategies to deliver a higher radiation dose to a defined volume at the site of the tumour, while minimizing the dose to healthy tissues and organs. The effort to reach this goal has included strategies such as the use of hyperbaric oxygen, the exploration of radiosensitizers and radioprotectors, brachytherapy, particle therapy and others.

Modern radiotherapy makes use of highly precise collimating devices, and also offers the possibility of modulating the radiation fluence of an individual beam. Radiotherapy using charged particles such as protons or carbon ions is also a promising strategy (see Chapters 11 and 12).

Radiotherapy is one of the three pillars of cancer treatment, which also include surgery and systemic therapies. Radiotherapy is highly cost effective (see Chapter 18); while the acquisition of radiotherapy equipment usually represents a significant initial capital investment, the equipment has a long useful life during which a large number of patients can be treated. Radiotherapy has had a role in cancer cure, alone or in combined schedules with both forms of treatment mentioned previously. In addition, radiotherapy is highly effective in the palliation of cancer symptoms such as pain, bleeding and organ obstruction (see Chapter 23).

The optimal therapy for patients with certain types of cancer detected early — for example, cancer of the uterine cervix and corpus, breast and testicle, and early cutaneous melanoma — will result in five year survival rates of up to 75%. By contrast, five year survival rates for patients with cancer of the pancreas, liver, stomach and lung are normally less than 15%. Some of the cancers common in developing countries are highly responsive and potentially curable with radiotherapy. These include cervical cancer, as well as breast, head and neck, oesophageal and rectal cancers. Hence the important role of adequate radiotherapy services in these countries. Since the initial cost of establishing and maintaining such facilities is relatively high, they are normally initially located in the capital city or other urban or highly populated centres. Facilities are then expanded and new facilities are established in the periphery when additional resources become available.

Radiotherapy should be an important part of any national cancer control plan or programme. In fact, the overall clinical outcomes of radiotherapy are optimized when radiotherapy services coexist with effective prevention and early detection programmes, and good quality surgery. The reasons for this are easy to understand. In countries that have been able to implement and sustain effective early detection and screening programmes, more cancer patients are diagnosed when their disease is in the early, curable stages; smaller tumours or precancerous lesions are amenable to being cured by surgery alone or radiotherapy. Therefore, in this scenario, radiotherapy can yield optimal clinical outcomes. Conversely, in countries where there is no availability of prevention or early detection programmes, and referral systems and specialized surgical services are weak, most patients present with advanced stages of the disease and are beyond cure. In these situations, the role of radiotherapy is limited to offering the best palliation possible, but the chances for cure will be much more limited.

Access to radiotherapy services has a number of dimensions, which include availability of the service, geographical accessibility, affordability, accommodation, and awareness of physicians and patients. Physicians and patients need to be aware that radiotherapy services are available in their country and that cancer is a potentially curable disease when diagnosed early. Cultural traditions and popular and religious beliefs have an impact on access to radiotherapy services and should be taken into account. This factor has not been sufficiently explored and addressed in oncology research.

## 1.3. A PACKAGE CONCEPT FOR RADIOTHERAPY SERVICES

The optimal use of a teletherapy machine in terms of effectiveness and safety occurs when it is complemented by two additional sets of elements: supporting accessories and trained staff.

Supporting accessories include: modern imaging equipment (e.g. a conventional or fluoroscopic simulator, a computed tomography simulator); a treatment planning system with appropriate software and commissioned beam data; a mould room for shielding and immobilization devices; and dosimetry and quality assurance (QA) equipment. Teletherapy machines have to be conceived of as one element of a package that includes all of the above. In addition, initial commissioning, a programme of preventive maintenance and servicing, scheduled QA procedures and eventual repairs have to be planned for and budgeted.

Appropriately trained staff is essential too, and the lack of this component is a major obstacle for the modernization of radiotherapy services in some countries and regions of the world. Lack of training programmes, low wages, lack of

professional recognition and internal migration from the public to the private sector or migration to higher income countries are some of the issues involved.

The IAEA has published a guide on how to establish and develop a modern radiotherapy facility, including specifications for linear accelerators and high dose rate brachytherapy units [1.4]. This is complemented by another publication aimed at assisting Member States at the time of planning radiotherapy services at the national level [1.5].

## 1.4. MAKING RADIOTHERAPY MORE ACCESSIBLE

Radiation medicine is one of the most important groups of disciplines for detecting, diagnosing and treating cancer, with more than half of cancer patients requiring some form of radiotherapy during the course of their treatment [1.6]. As low and middle income countries (LMICs) face an expected rise in annual cancer incidence rates of nearly 25% by 2020 (Table 1.1), the question of providing affordable means of treating the growing number of patients has acquired greater prominence [1.8]. The basis of this increasing concern lies in the fact that, despite being home to 85% of the world's population, LMICs only maintain approximately 40% of the world's radiotherapy facilities, leaving only around 25% of cancer patients in LMICs with access to radiotherapy treatment [1.8].

TABLE 1.1. CRUDE CANCER INCIDENCE DATA, IN DEVELOPED AND DEVELOPING REGIONS OF THE WORLD, 2012, AND PREDICTIONS FOR 2020 AND 2030 (GLOBOCAN 2012) [1.7]

| | 2012 | 2020 | 2030 |
|---|---|---|---|
| World | 14 067 900 | 17 113 588 | 21 645 658 |
| More developed regions | 6 053 600 | 6 794 807 | 7 617 751 |
| Less developed regions | 8 014 300 | 10 009 819 | 13 091 083 |

This situation is even more inequitable when comparing the availability of radiotherapy services across regions. Europe maintains 17 times as many radiotherapy units as are available in Africa. Latin America and the Caribbean

combined have just one third the number of machines available in North America [1.9] (Fig. 1.1). The lack of availability of radiotherapy treatment does not stem from a lesser need in LMICs. In fact, due to the absence of effective prevention and screening services, a higher proportion of cancers in LMICs are detected at an advanced stage, leaving palliative radiotherapy as one of the few options for treatment, even for cancers that, when found at earlier stages, have other treatment options [1.5].

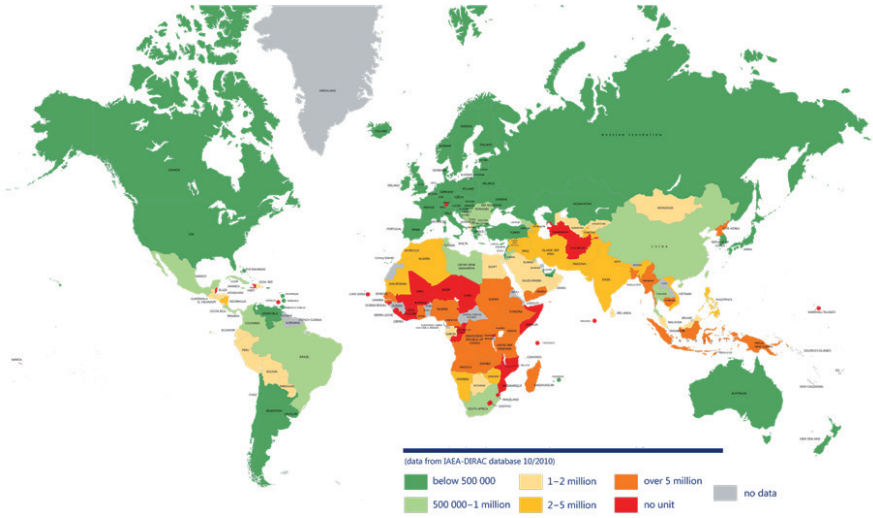


*FIG. 1.1. Number of people served by one radiotherapy unit.*

But inequity of access to radiotherapy goes beyond availability; in order for radiotherapy to be accessible, it must be provided in a manner that takes into account the geographical distribution of the population and the direct and indirect costs of receiving treatment, as well as affordability and the distribution of treatment, among other factors. Accessibility can even be an issue in upper middle income countries, which maintain large numbers of cancer centres but have variable accessibility to treatment across the country, with most radiotherapy clinics and modern equipment confined to the private sector.

Beyond the issues of availability and distribution of radiotherapy facilities, another factor influencing patient outcomes is affordability of treatment. The costs associated with treatment contribute to the overall inaccessibility of cancer services in most countries. When looking at the price of radiotherapy treatment compared with incomes in LMICs, the cost is staggering and most patients, having no health insurance, would find it impossible to pay for treatment on their own.

The inability to pay for treatment could create a different form of inaccessibility that prevents even those in close proximity to a cancer centre from receiving treatment. Even in LMICs that maintain government owned radiotherapy facilities with the potential to provide therapy for free or at a negligible cost to the patient, services at these facilities are commonly paid for through social security fees, which could make treatment unattainable for the poorest members of society [1.10]. For those who can afford social security, the economic cost of treatment is then shared with the government.

When governments bear a portion of the cancer treatment cost, it is generally for procuring and maintaining radiotherapy equipment, maintaining facilities and paying staff. With some radiotherapy packages selling for up to US $4 million, and with building costs for a radiotherapy treatment room ranging from US $40 000 to US $1 million, many countries are deterred by the capital costs associated with initiating a national radiotherapy service [1.11]. In addition to these costs there are auxiliary costs for source replacement (for $^{60}$Co units or brachytherapy afterloaders) and QA procedures. Yet, despite these expenses, the administration of radiotherapy, when evaluated per fraction throughout the lifetime of a machine, is actually a relatively cost effective procedure. Even after factoring in all levels of costs related to the procurement, maintenance and operation of a machine, estimates place the cost per fraction for a $^{60}$Co machine at a median of US $4.87 and for linear accelerators (linacs) at a median of US $11.02, which, compared with chemotherapy costs which can reach over US $600 per treatment, are comparatively inexpensive [1.11].

With radiotherapy's low fraction cost, it has been estimated that, when curative treatment has been received by an individual and upon his or her return to the workforce, the costs incurred by the government for providing this radiotherapy treatment will be regained in the form of that individual's economic contribution (increasing the gross national income per capita as defined by the World Bank) over the course of a few years, with the exact number of years required depending on a country's gross national income. The mean break-even point on a radiotherapy investment for low income, low middle and upper middle income countries is 12.1, 4.5 and 1.9 years, respectively [1.12]. When analysing results from treatment in high income countries, it is found that 60% of adult cancer patients are still alive five years after treatment, making the prospect of reaching these break-even points quite attainable [1.12]. In this respect, the cost of investing in a radiotherapy service will, in some cases, show future returns that provide a country with the potential to at least break even on its investment, making radiotherapy a cost effective solution to the growing cancer problem. However, it must also be noted that curative treatment is seldom administered in LMICs, as in the absence of public awareness and adequate cancer services, the majority of cases currently present with advanced stages, making palliative

radiotherapy and end of life care the only realistically possible form of treatment for most patients [1.9].

Outside the realm of costs, other challenges can arise in the establishment of a radiotherapy service, particularly in the selection and procurement of radiotherapy equipment. For LMICs, the radiotherapy manufacturer from which the government is purchasing a unit is generally located far from the purchasing country, most commonly in Europe or North America. Besides the additional transportation costs associated with shipping from distant locations, there are also issues that arise in terms of unit maintenance, particularly the length and extent of a unit's warranty. If the warranty is inadequate, countries that are already operating with limited resources could be confronted with the need to replace a radioactive source or bring in maintenance workers from Europe or North America, at high cost. Often, if the warranty has expired or does not cover the costs, a cancer centre may be forced to leave a machine non-operational, if insufficient funds are available to support maintenance or source replacement. In recent years, the transport of radioactive sources, such as those in $^{60}$Co units, has also become more complicated and costly. In many cases, special authorization and licensing is required from other transit countries, unless the supplier is able to use international routes and direct means of transport.

Other issues can arise in relation to the technical support needed to run a radiotherapy unit. The number of professionals actually involved in the operation of a radiotherapy service can vary widely between centres, often depending on the number of available professionals. An example of best practice is to have a staff of approximately 20 for each basic radiotherapy clinic, consisting of a radiation oncologist in chief, one staff radiation oncologist per 200–250 patients, one radiation physicist for every 400 patients, one dosimetrist or physics assistant per 300 patients, several radiotherapists (one per mould room for every 600 patients, plus four per megavoltage unit treating up to 50 patients per day, plus an additional two for every 500 patients simulated annually and one for brachytherapy as needed), as well as a nurse, a social worker, a dietician, a physiotherapist and a maintenance engineer or electronics technician [1.4].

Meeting the staff requirements for a radiotherapy clinic can be difficult, as the world faces a shortfall of 4.3 million trained health workers and 57 countries are currently experiencing a health care workforce crisis, leaving health systems everywhere with insufficient staff to meet patient needs. Looking solely at cancer professionals, it is estimated by the World Health Organization (WHO) that in Africa alone there will be a deficit of 3000 cancer health professionals over the next ten years. Considering that some of the positions necessary to establish a radiotherapy service require a university degree, postgraduate studies and at least two years of clinical training, staffing radiotherapy centres will continue to be a challenge.

The problem is exacerbated in LMICs, where a lack of resources and the prospect of better pay drives trained professionals to work in high income countries. In many cases, the cancer care professionals who remain in LMICs have had limited access to radiotherapy and other radiation medicine equipment, due to a lack of equipment availability, and require additional training to operate newly acquired technologies. Additionally, workforce strength may require that a small group of professionals take on an overstretched role in the operation of equipment, requiring further specialized training to operate a radiotherapy unit efficiently and safely. As procuring a machine is pointless (and even hazardous) without a proper understanding of its utilization and an adequate workforce to operate it, it is important that manufacturers provide specialized training or tutorials on the use and maintenance of their products to ensure that those operating the machines do so with the highest level of expertise possible.

Understanding the radiotherapy needs of its developing Member States, the IAEA has, for over thirty years, worked in some 115 LMICs to deploy robust radiotherapy and nuclear medicine programmes, expending over US $250 million on cancer related assistance under its technical cooperation programme, with technical support provided by its human health programme. This has enabled many Member States to establish safe and effective diagnostic imaging and increase radiotherapy capacity to provide treatment and higher quality care to many of their cancer patients. The IAEA also helps establish new nuclear medicine facilities and encourages their integration with diagnostic imaging procedures by facilitating appropriate advice and support for human resources capacity building. This helps Member States achieve and maintain high standards of professional practice.

The global survey of the IAEA's Directory of Radiotherapy Centres (DIRAC) [1.13] shows a dramatic discrepancy in the ability of cancer patients to access lifesaving radiotherapy across countries and regions of the world (see Chapter 5) (Fig. 1.2). With the incidence of cancer on the rise in LMICs, there is an increased demand for IAEA assistance to introduce or expand radiotherapy capacity. The resources available to the IAEA are, however, inadequate to address the global need. Although the existing cancer infrastructure in these countries is far from being able to respond fully to all needs, it is the best available option and a useful starting point to extend the IAEA's assistance by encouraging investments and advancements in other cancer system components, especially prevention, screening, early detection, advocacy and palliative care.

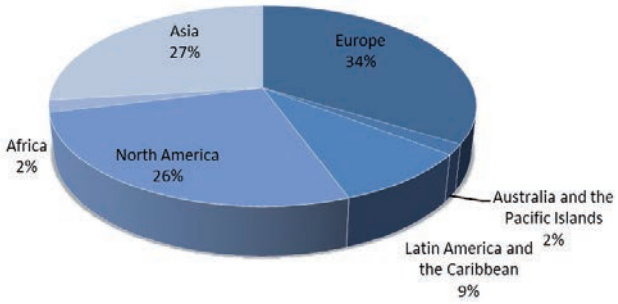


*FIG. 1.2. Distribution of megavoltage units per region of the world.*

## 1.5. CANCER CONTROL AND NATIONAL CANCER CONTROL PROGRAMMES

The concept of national cancer control programmes (NCCPs) was introduced and developed by WHO in the mid-1980s. The first version of an NCCP guide appeared following a WHO meeting in November 1991:

> "A national cancer control programme is a public health programme designed to reduce the number of cancer cases and deaths and improve quality of life of cancer patients, through the systematic and equitable implementation of evidence-based strategies for prevention, early detection, diagnosis, treatment, and palliation, making the best use of available resources." [1.12]

NCCPs represent an attempt to apply current evidence based knowledge and medical achievements to populations in order to decrease morbidity and mortality from cancer. The rationale is that cancer should be prevented. Since not all cancers can be prevented, mechanisms should be put in place to detect, very early on, those cancers that do develop in order to treat them successfully. There must be adequate and effective diagnostic procedures available, and for those patients diagnosed with cancer there should be effective and cost effective therapy options. Finally, for patients with recurrent, metastatic and terminal disease, appropriate palliative strategies and treatments should also be available.

In countries without an operational NCCP, the usual approach is to 'treat the cancers when they appear'. Naturally, the first steps usually involve the establishment of one or more cancer treatment centres that will provide diagnostic services, imaging, surgery, radiotherapy and systemic therapy. With this approach, patients who have been diagnosed with cancer have a place to

go where diagnostic, staging and treatment interventions will be carried out. Unfortunately, in this scenario, most patients will present with advanced disease and the majority of treatments offered will be palliative in nature. Undue reliance on this approach, which may involve the use of sophisticated and often expensive technologies, can result in inequitable selection of patients, rapid depletion of scarce resources, and a shift in emphasis away from more affordable prevention activities [1.12].

Usually it is only when cancer treatment centres are already established and operational that a hospital based cancer registration system is initiated and the importance of community based cancer control interventions such as prevention and screening programmes becomes clear.

## 1.6. THE WORLD HEALTH ORGANIZATION AND CANCER CONTROL

The World Health Organization is the international agency within the United Nations system responsible for health. Established in 1948, its objective is the attainment by all peoples of the highest possible level of health, based on the "Health for All" concept.

The mission of WHO, through the Noncommunicable Diseases and Mental Health Cluster, is to provide leadership and the evidence base for international action on surveillance, prevention and control of NCDs, including cancer. The strategic directions are based on the mandates given by the resolutions of its governing bodies, the general directions and priorities of the Medium-Term Strategic Plan for 2008–2013, and the lessons learned from international experience and WHO's work with its Member States.

Given cancer's human and economic cost, WHO has intensified its efforts to respond more effectively to the cancer pandemic [1.14]. The World Health Assembly has passed five key resolutions in an effort to put knowledge into action concerning cancer control. The most significant of these was in 2005, when the resolution on cancer prevention and control strategy was adopted by the 58th World Health Assembly [1.15]. The resolution listed a number of objectives, in particular the development of the WHO cancer control strategy at the global, regional and national levels, which aims at improving knowledge to implement effective and efficient programmes for cancer control, leading to a reduction of the cancer burden and improving quality of life for cancer patients and their families [1.16].

## 1.7. ROLE OF THE IAEA IN CANCER CONTROL

The IAEA's statutory objectives are to: "seek to accelerate and enlarge the contribution of atomic energy to peace, health and prosperity throughout the world" and "ensure, so far as it is able, that assistance provided by it or at its request or under its supervision or control is not used in such a way as to further any military purpose." In fulfilling this objective, the IAEA has emerged as a unique multidisciplinary organization in the United Nations system to address global challenges related to nuclear technology, including global energy security, human health, food security and safety, and water resource management, and to nuclear safety and security and non-proliferation.

Established in 1957, the IAEA works with its Member States and multiple partners worldwide to promote the safe, secure and peaceful use of nuclear technologies. The IAEA has more than 40 years of field experience in supporting its Member States in developing capacity in the use of radiation medicine and related regulatory and safety infrastructure. Health is an important part of the IAEA's mandate and of its programmes, mainly because nuclear techniques play a major role in medicine. Often, radiation medicine techniques are the sole means of diagnosis and treatment, and they play a particularly prominent role in fighting cancer. More importantly, the IAEA also provides advice, support and assistance to ensure that radiation techniques and technologies in health care are used safely and securely. Focusing on capacity building through education and training, the IAEA's assistance, through its technical cooperation and human health programmes, has enabled over 100 low and middle income Member States to establish or upgrade radiotherapy and nuclear medicine services to provide quality care to at least a portion of their cancer patients. However, existing IAEA resources are insufficient to address the enormous needs in developing countries to provide cancer care services for the growing number of patients, particularly with regard to the shortfall of diagnostic imaging capabilities, radiotherapy equipment and trained personnel.

The IAEA has extensive experience in establishing a first cancer centre in various countries, including a radiotherapy unit (see Chapter 26). This is usually a complex project. The ultimate success of such projects depends not only on the availability of resources to purchase and install equipment and train staff. Local expertise, the personal involvement of local stakeholders and, in particular, the commitment of local governments are also essential factors.

With the rising number of cancer cases in LMICs, the existing radiation medicine infrastructure and available resources can cover only a small portion of their needs. Currently, up to 70% of cancer patients worldwide have no access to radiotherapy. Furthermore, due to a lack of early detection or screening services, and other socioeconomic factors such as fear, stigma, and job and family demands, up to 80% have advanced cancer by the time they present for treatment. Therefore, expanding radiotherapy capacity alone is simply not enough to fight cancer, and other interventions that focus on cancer information, public education, cancer prevention and early detection are needed to reduce cancer morbidity and mortality, improve survival rates and, ultimately, make a significant difference in the big picture of cancer control.

## 1.8. THE IAEA PROGRAMME OF ACTION FOR CANCER THERAPY

In response to the developing world's growing cancer crisis, the IAEA established the Programme of Action for Cancer Therapy (PACT) [1.10, 1.17, 1.18] in 2004 to fully realize the public health impact obtained through technology transfer in radiotherapy and nuclear medicine. PACT was launched as an IAEA initiative, but its vision is for a global public–private partnership and fund to confront the cancer crisis, including the formation of a Joint Programme on Cancer Control with WHO. This Joint Programme, established in 2009, allows close collaboration with WHO and other key international health organizations, through a coordinated global response, in developing strategies and specific plans for working with low and middle income Member States in the design and implementation of comprehensive cancer control programmes.

PACT presents ambitious long term goals. The principal goals are:

(a) To build a global public–private partnership of interested organizations committed to addressing the challenge of cancer in LMICs in all its aspects;
(b) To mobilize resources from charitable trusts, foundations, and others in the public and private sectors to assist low and middle income Member States to develop and implement their radiation medicine capacities within an NCCP;
(c) To ensure the effective and sustainable transfer of radiation medicine technologies and/or knowledge to all low and middle income Member States where unmet needs exist.

In the short term, the IAEA is working through PACT with WHO and other partners to raise cancer awareness on a global scale, assess needs in individual countries or regions and develop successful demonstration projects that attract donors to support these life saving initiatives to help sustain and replicate positive outcomes.

## 1.9. THE WHO–IAEA JOINT PROGRAMME ON CANCER CONTROL

The main purpose of the WHO–IAEA Joint Programme is to coordinate activities and resources to provide evidence based and sustainable support to comprehensive cancer control programmes in LMICs [1.17]. The Joint Programme further seeks to raise cancer awareness, assess cancer control needs, develop cancer control demonstration projects, and attract bilateral or multilateral donors in order to establish effective new funding mechanisms beyond those currently available from the IAEA and WHO individually. The Joint Programme's strategy includes support for cancer control reviews and assessments at the country level. Strategic planning and capacity building for cancer therapy cannot occur without extensive collaboration with other international key players: international organizations, governments, non-governmental organizations, academia and the private sector, including radiotherapy equipment manufacturers.

Under the Joint Programme, a number of missions have taken place to review the current status of cancer control in many countries and provide technical advice and recommendations on the establishment of operational cancer control programmes.

## 1.10. KEY POINTS

— Radiotherapy is one of the three pillars of cancer treatment, which also include surgery and systemic therapies.
— Radiotherapy should be an important part of any national cancer control plan.
— Access to radiotherapy services has a number of dimensions, which include availability of the service, geographical accessibility, affordability, accommodation and awareness on the part of physicians and patients.
— The optimal use of a teletherapy machine in terms of effectiveness and safety occurs when it is complemented by two additional sets of elements: supporting accessories and trained staff.
— A national cancer control programme is a public health programme designed to reduce the number of cancer cases and deaths and improve the quality of

life of cancer patients, through the systematic and equitable implementation of evidence based strategies for prevention, early detection, diagnosis, treatment, and palliation, making the best use of available resources.

— In response to the developing world's growing cancer crisis, the IAEA established the Programme of Action for Cancer Therapy in 2004 to fully realize the public health impact obtained through technology transfer in radiotherapy and nuclear medicine.

— In March 2009, WHO and the IAEA established the WHO–IAEA Joint Programme on Cancer Control. The main purpose of the Joint Programme is to coordinate activities and resources to provide evidence based and sustainable support to comprehensive cancer control programmes in low and middle income countries.

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# Chapter 2

# CONTRIBUTION OF RADIATION ONCOLOGY TO CANCER CURE AND PALLIATION

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## 2.1. BACKGROUND

Over the past 30 years, computed tomography and magnetic resonance imaging have made possible the three dimensional (3-D) visualization of gross tumour volume as well as organs at risk, enabling 3-D treatment planning and conformal therapy techniques. These techniques form the backbone of a large number of prospective, randomized clinical trials exploring radiation dose escalation, altered fractionation (in particular hypofractionation) and/or the addition of a variety of systemic agents. These trials constitute the basis of much of the contemporary practice of evidence based radiation oncology even today. Some illustrative examples are summarized below. More recently, for many kinds of cancers the use of FDG-PET (fluorine-18 fluorodeoxyglucose positron emission tomography) for staging has improved patient selection by identifying patients with distant metastases for whom 'curative' radiotherapy would be futile.

During the past decade, intensity modulated radiation therapy (IMRT), stereotactic radiotherapy, proton radiotherapy and carbon ion radiotherapy have attracted a great deal of publicity and resources, but their evidence base remains weak at present. They have not been proven to prolong the survival of cancer patients over standard 3-D conformal techniques. Furthermore, implementing adequate quality assurance measures for these techniques has proven difficult not only in less developed countries, but even in some more developed countries such as the United States of America.

This chapter describes selected radiation oncology studies that have had a significant impact in the routine treatment of common adult cancers with radiotherapy. The authors have selected studies which in their opinion have changed or have the potential to change the practice of radiation oncology and improve the outcomes for cancer patients, both for cure and for effective palliation.

## 2.2. BREAST CANCER

The British Columbia randomized radiotherapy trial [2.1] was designed to determine the survival impact of locoregional radiotherapy in premenopausal patients with lymph node positive breast cancer treated by modified radical mastectomy and adjuvant chemotherapy. Three hundred and eighteen patients were assigned to receive no further therapy or radiotherapy (37.5 Gy in 16 fractions).

At the 20 year follow-up (the median follow-up for live patients was 249 months), compared with chemotherapy alone, chemotherapy and radiotherapy were associated with a statistically significant improvement in all end points analysed, including survival free of isolated locoregional recurrences (74% versus 90%, respectively; relative risk (RR) = 0.36, 95% confidence interval (CI) = 0.18 to 0.71; p = 0.002), systemic relapse free survival (31% versus 48%; RR = 0.66, 95% CI = 0.49 to 0.88; p = 0.004), breast cancer free survival (48% versus 30%; RR = 0.63, 95% CI = 0.47 to 0.83; p = 0.001), event free survival (35% versus 25%; RR = 0.70, 95% CI = 0.54 to 0.92; p = 0.009), breast cancer specific survival (53% versus 38%; RR = 0.67, 95% CI = 0.49 to 0.90; p = 0.008) and overall survival (47% versus 37%; RR = 0.73, 95% CI = 0.55 to 0.98; p = 0.03). Long term toxicities, including cardiac deaths (1.8% versus 0.6%), were minimal for both arms.

For patients with high risk breast cancer treated with modified radical mastectomy, treatment with radiotherapy (schedule of 16 fractions) and adjuvant chemotherapy led to better survival outcomes than chemotherapy alone, and it was well tolerated, with acceptable long term toxicity.

## 2.3. LUNG CANCER

A randomized controlled trial in locally advanced non-small cell lung cancer (NSCLC) [2.2] compared CHART (continuous hyperfractionated accelerated radiotherapy), which employs 36 fractions of 1.5 Gy three times per day to give 54 Gy in 12 consecutive days, with conventional radiotherapy — 30 fractions of 2 Gy to give a total dose of 60 Gy in six weeks. A total of 563 patients were entered between April 1990 and April 1995. This report is based upon the data updated to 1 April 1998.

Overall, there was a 22% reduction in the relative risk of death with CHART, which is equivalent to an absolute improvement in two year survival of 9% from 20 to 29% (p = 0.008) and a 21% reduction in the relative risk of local progression (p = 0.033). In the large subgroup of patients with squamous cell cancer, which accounted for 81% of the cases, there was a 30% reduction

in the relative risk of death, which is equivalent to an absolute improvement in two year survival of 13% from 20 to 33% ($p = 0.000\ 7$) and a 27% reduction in the relative risk of local progression ($p = 0.012$). Furthermore, in squamous carcinoma, there was a 25% reduction in the relative risk of local and/or distant progression ($p = 0.025$) and a 24% reduction in the relative risk of metastasis ($p = 0.043$). There was no evidence that CHART yielded more or less benefit in any other subgroup.

This analysis of mature data confirms that CHART is superior to conventional radiotherapy in achieving local tumour control and survival in locally advanced NSCLC. This indirectly suggests the importance of cell repopulation as a cause of failure in the conventional radiotherapy of NSCLC. The reduction in the risk of metastasis confirms that improved local tumour control, even in lung cancer, can reduce the incidence of distant metastasis. This trial shows that local tumour control in NSCLC can lead to an improvement in long term survival.

While the CHART regimen demonstrated superior outcome compared to conventional radiation alone, treating three times a day is logistically challenging, which prevents its wide implementation. Furthermore, the Radiation Therapy Oncology Group RTOG 0617 [2.3] investigated dose escalation, where 76 Gy was compared with 60 Gy once a day with concurrent and adjuvant chemotherapy. The preliminary data were presented at the 2011 ASTRO meeting and demonstrated worse outcomes with the dose escalation arm: 12 month overall survival of 74% versus 81% ($p = 0.02$) and median survival of 20.7 months versus 21.7 months, respectively [2.4].

A total of 610 patients were randomly assigned to two concurrent regimens and one sequential chemotherapy and thoracic radiotherapy regimen in a three arm phase III trial [2.5]. The sequential arm included cisplatin at 100 mg/m$^2$ on days 1 and 29 and vinblastine at 5 mg/m$^2$ per week for five weeks with 63 Gy of thoracic radiotherapy delivered as a once daily fraction beginning on day 50. Arm 2 used the same chemotherapy regimen as arm 1, with 63 Gy of thoracic radiotherapy delivered as a once daily fraction beginning on day 1. Arm 3 used cisplatin at 50 mg/m$^2$ on days 1, 8, 29 and 36, with oral etoposide at 50 mg twice daily for ten weeks on days 1, 2, 5 and 6, with 69.6 Gy delivered as 1.2 Gy twice daily fractions beginning on day 1. The primary end point was overall survival.

Median survival times were 14.6, 17.0 and 15.6 months for arms 1–3, respectively. Five year survival was statistically significantly higher for patients treated with the concurrent regimen with once daily thoracic radiotherapy compared with the sequential treatment. With a median follow-up time of 11 years, the rates of acute grades 3–5 non-haematological toxic effects were higher with concurrent than with sequential therapy, but late toxic effects were similar.

Concurrent delivery of cisplatin based chemotherapy with thoracic radiotherapy confers a long term survival benefit compared with the sequential delivery of these therapies. Radiation doses of 60–66 Gy given daily are considered the standard radiation approach at this time. While there are no phase III data supporting dose escalation, it is hoped that ongoing clinical trials investigating novel agents with new radiation techniques and doses will improve outcomes.

## 2.4. STOMACH CANCER

Post-operative chemoradiotherapy following surgical resection of adenocarcinoma of the stomach is curative in less than 40% of cases [2.6]. This clinical trial investigated the effect of surgery plus post-operative (adjuvant) chemoradiotherapy on the survival of patients with resectable adenocarcinoma of the stomach or gastro-oesophageal junction.

A total of 556 patients with resected adenocarcinoma of the stomach or gastro-oesophageal junction were randomly assigned to surgery plus post-operative chemoradiotherapy or surgery alone. The adjuvant treatment consisted of 425 mg/m$^2$ of fluorouracil per day, plus 20 mg/m$^2$ of leucovorin per day for five days, followed by 45 Gy of radiation at 1.8 Gy per day, given five days per week for five weeks, with modified doses of 5-FU and leucovorin on the first four and the last three days of radiotherapy. One month after the completion of radiotherapy, two five day cycles of fluorouracil (425 mg/m$^2$ per day) plus leucovorin (20 mg/m$^2$ per day) were given one month apart.

The median overall survival in the surgery only group was 27 months, as compared with 36 months in the chemoradiotherapy group; the hazard ratio for death was 1.35 (95% CI 1.09 to 1.66; $p = 0.005$). The hazard ratio for relapse was 1.52 (95% CI 1.23 to 1.86; $p<0.001$). Three patients (1%) died from toxic effects of chemoradiotherapy; grade 3 toxic effects occurred in 41% of the patients in the chemoradiotherapy group, and grade 4 toxic effects occurred in 32%.

Post-operative chemoradiotherapy should be considered for all patients with adenocarcinoma of the stomach or gastro-oesophageal junction at high risk for recurrence following curative resection for T3 disease and/or positive regional lymph nodes.

## 2.5. PROSTATE CANCER

The United States Preventive Services Task Force issued a grade D recommendation against prostate-specific antigen (PSA) screening for

healthy men of all ages, regardless of race or family history [2.7–2.9]. This recommendation was based upon the conflicting results of the US Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial [2.10] and the European Randomized Study of Screening for Prostate Cancer (ERSPC) [2.11]. At 11 years of follow-up in the ERSPC study, 1055 men needed to be screened to prevent one death. Another study with longer follow-up demonstrated that only 293 men need to be screened to prevent one death at 14 years [2.12]. Thus, longer follow-up appears to demonstrate the benefits of screening for appropriate patients. Finally, 44% of the men in the PLCO trial underwent PSA screening before randomization and 85% of men in both arms had at least one PSA screening.

The Prostate Cancer Intervention Versus Observation Trial (PIVOT) [2.13] comparing surgery to observation did not demonstrate a difference in all-cause mortality at ten years as reported by Wilt et al. in 2012. These results were in contrast to the trial reported by the Scandinavian Prostate Cancer Group Study-4 [2.14], where there was a reduction in the rate of death from prostate cancer at 13 years with radical prostatectomy. The PIVOT trial may have been unable to detect a difference in survival as only 740 out of 2000 planned patients were randomized. Furthermore, the follow-up was shorter compared with the Scandinavian study, and this was an elderly group with significant co-morbidities, as only 14% of the deaths were from prostate cancer.

Long term toxicities and costs were assessed for external beam radiotherapy (EBRT), surgery and brachytherapy using data from the SEER (Surveillance, Epidemiology, and End Results) database [2.15] for 137 427 low risk prostate cancer patients and reported at the 2012 Genitourinary Cancers Symposium of the American Society of Clinical Oncology. EBRT was much more toxic and expensive compared with surgery and brachytherapy. Despite the very favourable profile of brachytherapy (relatively low cost, well established efficacy and convenience), only 12% of patients were treated with this modality compared with 44% treated with EBRT and 44% with surgery. Interestingly, another SEER study [2.16] reported at the same ASCO GU symposium demonstrated equivalent cancer control rates between IMRT and proton therapy; however, proton therapy was markedly more expensive, with more bowel toxicity compared with IMRT.

Active surveillance for low risk prostate cancer patients is another possible strategy. However, brachytherapy is less expensive than surgery or 3-D conformal radiotherapy (3-D CRT), IMRT, image guided radiation therapy and proton based radiation, and is less expensive than active surveillance once someone has been observed for five to seven years, as more than half of these men come off surveillance within ten years and are then treated. Hence one can make the case for upfront treatment of those patients, as it is less expensive than surveillance and delayed treatment.

Whether the addition of radiotherapy improves overall survival in men with locally advanced prostate cancer managed with androgen deprivation therapy (ADT) is unclear. The aim of the following study was to compare outcomes in such patients with locally advanced prostate cancer [2.17].

Patients with locally advanced (T3 or T4) prostate cancer (n = 1057) or organ confined disease (T2) with either a PSA concentration of more than 40 ng/mL (n = 119) or a PSA concentration more than 20 ng/mL and a Gleason score of 8 or higher (n = 25) were randomly assigned to receive lifelong ADT and radiotherapy (65–69 Gy to the prostate and seminal vesicles, 45 Gy to the pelvic nodes). The primary end point was overall survival. The results presented here are of an interim analysis planned for when two thirds of the events for the final analysis were recorded. All efficacy analyses were done by intention to treat and were based on data from all patients.

Between 1995 and 2005, 1205 patients were randomly assigned (602 in the ADT only group and 603 in the ADT and radiotherapy group); median follow-up was 6 years (interquartile range = 4.4–8.0). At the time of analysis, a total of 320 patients had died, 175 in the ADT only group and 145 in the ADT and radiotherapy group. The addition of radiotherapy to ADT improved overall survival at seven years (74%, 95% CI = 70–78 versus 66%, 60–70; hazard ratio = 0.77, 95% CI = 0.61–0.98, p = 0.033). Both toxicity and health related quality of life results showed a small effect of radiotherapy on late gastrointestinal toxicity (grade >3 rectal bleeding, 3 patients (0.5%) in the ADT only group, 2 (0.3%) in the ADT and radiotherapy group; grade >3 diarrhoea, 4 patients (0.7%) versus 8 (1.3%); grade >3 urinary toxicity, 14 patients (2.3%) in both groups).

The benefits of combined modality treatment — ADT and radiotherapy — should be discussed with all patients with locally advanced prostate cancer.

## 2.6. RECTAL CANCER

Pre-operative chemoradiotherapy has been established as standard treatment for locally advanced rectal cancer after the first results of the German Cancer Society trial, published in 2004 [2.18], showed an improved local control rate. However, after a median follow-up of 46 months, no survival benefit could be shown. Here, we report long term results of this study with a median follow-up of 134 months [2.19].

A total of 823 patients with stage II to III rectal cancer were randomly assigned to pre-operative chemoradiotherapy with 5-FU, total mesorectal excision surgery and adjuvant 5-FU chemotherapy, or the same schedule of chemoradiotherapy used post-operatively. The study was designed to have 80% power to detect a difference of 10% in five year overall survival as the primary

end point. Secondary end points included the cumulative incidence of local and distant relapses and disease free survival.

Of 799 eligible patients, 404 were randomly assigned to pre-operative chemoradiotherapy and 395 to post-operative chemoradiotherapy. According to intention-to-treat analysis, overall survival at ten years was 59.6% in the pre-operative arm and 59.9% in the post-operative arm ($p = 0.85$). The ten year cumulative incidence of local relapse was 7.1% and 10.1% in the pre- and post-operative arms, respectively ($p = 0.048$). No significant differences were detected for ten year cumulative incidence of distant metastases (29.8% and 29.6%; $p = 0.9$) and disease free survival.

There was a persistent significant improvement of pre- versus post-operative chemoradiotherapy on local control; however, there was no effect on overall survival. More effective systemic treatment has been integrated into the multimodal therapy in the CAO/ARO/AIO-04 trial to possibly reduce distant metastases and improve survival. Other advantages of pre-operative chemoradiotherapy include a reduction in acute toxicities as the treatment volumes become smaller, the potential to convert some patients from an abdominoperineal resection (APR) to a low anterior resection (LAR) and the potential to convert some patients from inoperable to operable status.

A coordinated research project (CRP) by the IAEA is currently testing standard chemoradiotherapy (50 Gy in 25 fractions with 5-FU/leucovorin or capecitabine) versus a short fractionation of 25 Gy in five fractions of 5 Gy in one week as pre-operative treatment in inoperable or borderline inoperable rectal cancer patients. End points are survival, operability conversion rate and toxicity.

## 2.7. OESOPHAGEAL CANCER

To compare the locoregional control, survival and toxicity of combined modality therapy using high dose (64.8 Gy) versus standard dose (50.4 Gy) radiotherapy for the treatment of patients with oesophageal cancer, a total of 236 patients with clinical stage T1 to T4, N0/1, M0 squamous cell carcinoma or adenocarcinoma were randomized [2.20]. Patients selected for a non-surgical approach were randomized to receive combined modality therapy consisting of four monthly cycles of 5-FU (1000 mg/m$^2$ per day for 4 days) and cisplatin (75 mg/m$^2$ bolus day 1) with concurrent 64.8 Gy versus the same chemotherapy schedule, but with concurrent 50.4 Gy. The trial was stopped after an interim analysis. The median follow-up was 16.4 months for all patients and 29.5 months for patients still alive.

For the 218 eligible patients, there was no significant difference in median survival (13.0 versus 18.1 months), two year survival (31% versus 40%), or

locoregional failure and locoregional persistence of disease (56% versus 52%) between the high dose and standard dose arms. Although 11 treatment related deaths occurred in the high dose arm compared with 2 in the standard dose arm, 7 of the 11 deaths occurred in patients who had received 50.4 Gy or less. The higher radiation dose did not increase survival or locoregional control. Although there was a higher treatment related mortality rate in the patients assigned to the high dose radiation arm, it did not seem to be related to the higher radiation dose. The standard radiation dose for patients treated with concurrent 5-FU and cisplatin chemotherapy is 50.4 Gy in 28 fractions of 1.8 Gy. Unfortunately, the local failure rates are still quite high at 50%, justifying the rationale for trimodality therapy (see below).

For the palliation of dysphagia caused by oesophageal cancer, 219 patients were randomized to adding EBRT or not, after receiving two fractions of high dose rate brachytherapy (HDRBT) within one week [2.21]. Each HDRBT consisted of 8 Gy prescribed at 1 cm from the source centre. Patients randomized to EBRT received 30 Gy in ten fractions. The primary outcome was dysphagia relief experience (DRE). Additional outcomes included various scores, performance status, weight and adverse events. A majority of charts, imaging and radiotherapy plans were externally audited.

Median follow-up was 197 days, with a median overall survival of 188 days and an 18% survival rate at one year. DRE was significantly improved with combined therapy for an absolute benefit of +18% at 200 days from randomization ($p = 0.019$). In longitudinal regression analyses, scores for dysphagia ($p = 0.000\ 05$), odynophagia ($p = 0.006$), regurgitation ($p = 0.000\ 05$), chest pain ($p = 0.003\ 8$) and performance status ($p = 0.001\ 5$) were all significantly improved. In contrast, weight, toxicities and overall survival were not different between study arms. In conclusion, symptom improvement occurred with the addition of EBRT to standard HDRBT. The combination was well tolerated and relatively safe.

In the CROSS (Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study) [2.22] by van Hagen et al., pre-operative neoadjuvant chemotherapy consisting of carboplatin and paclitaxel for five weeks concurrent with radiation of 41.4 Gy in 23 fractions was compared with surgery alone. Three hundred and sixty-six patients (75% adenocarcinomas, 23% squamous cell carcinomas and 2% large cell undifferentiated carcinomas) were enrolled. The trimodality group had a complete resection rate of 92% (R0) compared with 69% in the surgery alone group, with a median survival of 49 months and 24 months, respectively.

For medically fit patients who have stage II or III disease, there appears to be a role for pre-operative chemoradiotherapy to maximize regional control and overall survival, as found in the CROSS study.

## 2.8. CERVIX UTERI

A randomized trial [2.23] compared the effect of radiotherapy to a pelvic and para-aortic field with that of pelvic radiation and concurrent chemotherapy with 5-FU and cisplatin in women with advanced cervical cancer. Between 1990 and 1997, 403 women with advanced cervical cancer confined to the pelvis (stages IIB through IVA or stage IB or IIA with a tumour diameter of at least 5 cm or involvement of pelvic lymph nodes) were randomly assigned to receive either 45 Gy of radiation to the pelvis and para-aortic lymph nodes or 45 Gy of radiation to the pelvis alone plus two cycles of 5-FU and cisplatin on days 1–5 and days 22–26 of radiation. Patients were then to receive one or two applications of low dose rate intracavitary radiation, with a third cycle of chemotherapy planned for the second intracavitary procedure in the combined therapy group.

Of the 403 eligible patients, 193 in each group could be evaluated. The median duration of follow-up was 43 months. Estimated cumulative rates of survival at five years were 73% for patients treated with radiotherapy and chemotherapy and 58% for patients treated with radiotherapy alone ($p = 0.004$). Cumulative rates of disease free survival at five years were 67% among patients in the combined therapy group and 40% among patients in the radiotherapy group ($p < 0.001$). The rates of both distant metastases ($p < 0.001$) and locoregional recurrences ($p < 0.001$) were significantly higher among patients treated with radiotherapy alone. The seriousness of side effects was similar in the two groups, with a higher rate of reversible haematological effects in the combined therapy group.

The addition of chemotherapy with 5-FU and cisplatin to treatment with external beam and intracavitary radiation significantly improved survival among women with locally advanced cervical cancer.

Additional randomized trials comparing radiation alone to various chemotherapy regimens have demonstrated an approximate 10% improvement in survival with the addition of cisplatin weekly at 40 mg/m$^2$. The standard approach in the USA is 45 Gy to the whole pelvis, HDRBT at 5 to 5.5 Gy per fraction in five fractions, and weekly chemotherapy consisting of cisplatin. Unless there is obvious lymphadenopathy in the common iliac or para-aortic lymph nodes, external radiation fields target the whole pelvic region (see recent IAEA guidelines on the treatment of cervical cancer [2.24]). Lack of benefit for concomitant chemotherapy has been found in two studies conducted in India and Uganda [2.25, 2.26].

### 2.8.1. Endometrium — PORTEC 2

The investigators carried out a multicentre prospective randomized trial to determine whether post-operative pelvic radiotherapy improves locoregional control and survival for patients with stage I endometrial carcinoma [2.27]. Patients with stage I endometrial carcinoma (grade 1 with deep (≥50%) myometrial invasion, grade 2 with any invasion, or grade 3 with superficial (<50%) invasion) were enrolled. After total abdominal hysterectomy and bilateral salpingo-oophorectomy, without lymphadenectomy, 715 patients from 19 radiation oncology centres were randomized to pelvic radiotherapy (46 Gy) or no further treatment. The primary study end points were locoregional recurrence and death, with treatment related morbidity and survival after relapse as secondary end points.

Analysis was done according to the intention-to-treat principle. Of the 715 patients, 714 could be evaluated. The median duration of follow-up was 52 months. Five year actuarial locoregional recurrence rates were 4% in the radiotherapy group and 14% in the control group ($p < 0.001$). Actuarial five year overall survival rates were similar in the two groups: 81% (radiotherapy) and 85% (controls) ($p = 0.31$). Endometrial cancer related death rates were 9% in the radiotherapy group and 6% in the control group ($p = 0.37$). Treatment related complications occurred in 25% of radiotherapy patients, and in 6% of the controls ($p < 0.000\ 1$). Two thirds of the complications were grade 1. Grade 3–4 complications were seen in eight patients, of whom seven were in the radiotherapy group (2%). Two year survival after vaginal recurrence was 79%, in contrast to 21% after pelvic recurrence or distant metastases. Survival after relapse was significantly better ($p = 0.02$) for patients in the control group. Multivariate analysis showed that for locoregional recurrence, radiotherapy and age below 60 years were significant favourable prognostic factors.

Post-operative radiotherapy in stage I endometrial carcinoma reduces locoregional recurrence, but has no impact on overall survival. Radiotherapy increases treatment related morbidity. Post-operative radiotherapy is not indicated in patients with stage I endometrial carcinoma below 60 years of age and in patients with grade 2 tumours with superficial invasion.

The role of vaginal cuff brachytherapy was also investigated in the PORTEC-2 study [2.28, 2.29]. This trial randomized patients with ‘high intermediate risk’ endometrial cancer to receive either pelvic external beam or vaginal cuff brachytherapy irradiation following hysterectomy. Patients eligible for this study were: (1) patients whose age was greater than 60 years with grade 1 or 2 disease invading the outer half of the myometrium, or grade 3 invading the inner half of the myometrium; or (2) patients of any age with endocervical gland involvement (apart from grade 3 with greater than 50% myometrial invasion).

There was no significant difference in the vaginal recurrence rate between the two arms (1.8% versus 1.6%, p = 0.74). The five year pelvic relapse rate was 3.8% in the vaginal cuff brachytherapy arm and 0.5% in the pelvic radiotherapy arm (p = 0.02). Patients with deeply invasive grade 3 disease were not eligible for this study. Central pathology review, performed after enrolment, demonstrated that the vast majority of patients (79%) had grade 1 disease. These results support the use of vaginal cuff brachytherapy in patients with intermediate risk presentations such as deeply invasive grade 1 disease. However, PORTEC-2 included very few patients with deeply invasive grade 2 disease and none with deeply invasive grade 3 disease, so this study does not provide support for vaginal cuff brachytherapy in the place of pelvic irradiation in these specific subgroups of patients.

Vaginal cuff brachytherapy is as effective as pelvic radiotherapy for patients with intermediate risk factors, such as deeply invasive grade 1 tumours. Patients with multiple risk factors, including age, deep invasion, high grade, and lymphovascular space invasion, may be better treated with external beam pelvic radiation.

## 2.9. KEY POINTS

— Three dimensional conformal radiotherapy has become the standard technique for the appropriate curative irradiation of most cancers.
— For patients with high risk breast cancer treated with a modified radical mastectomy, radiotherapy and adjuvant chemotherapy lead to better survival outcomes than chemotherapy alone.
— In locally advanced non-small cell lung cancer (NSCLC), the CHART (continuous hyperfractionated accelerated radiotherapy) regimen is superior to conventional radiotherapy in achieving local tumour control and survival.
— In NSCLC, concurrent cisplatin and thoracic radiotherapy confer a long term survival benefit compared with the sequential delivery of these therapies.
— Post-operative chemoradiotherapy should be considered for all patients at high risk of recurrence of adenocarcinoma of the stomach or gastro-oesophageal junction.
— Radical prostatectomy, external beam radiotherapy, brachytherapy and proton beam therapy yield comparable tumour control outcomes in patients with early localized prostate cancer. Proton beam therapy is clearly more expensive.

— The question of whether radical prostatectomy is preferable to observation alone has not been resolved.
— The added benefit of combined modality treatment — androgen deprivation therapy and radiotherapy — should be discussed with all patients with locally advanced prostate cancer.
— Pre-operative chemoradiotherapy has become the standard approach for patients with intermediate stage (stages II–III resectable) and patients with inoperable non-metastatic or borderline inoperable rectal cancer.
— In patients with oesophageal cancer treated with combined chemoradiotherapy, radiation doses above standard do not improve survival or locoregional control.
— Adding external beam to intraluminal high dose rate brachytherapy improves palliation in obstructive squamous cell carcinoma of the oesophagus.
— The addition of concomitant chemotherapy (cisplatin alone or combined with fluorouracil) significantly improved survival among women with locally advanced cervical cancer.
— In some low income countries, however, these results have not been reproduced.
— In endometrial carcinoma stage I, post-operative radiotherapy reduces locoregional recurrence but has no impact on overall survival.
— Vaginal cuff brachytherapy is as effective as pelvic irradiation for patients with intermediate risk factors.
— Patients with high risk factors (age, deep myometrial invasion, high grade and lymphovascular space invasion) may be better treated with external beam pelvic irradiation.

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# Chapter 3

# ASSESSING NEEDS AND DEMAND FOR RADIOTHERAPY

**M. Barton, M. Williams**

## 3.1. INTRODUCTION

Cancer services, such as screening, surgery, chemotherapy or radiotherapy, should be delivered in the type and amount that meet local demand. Estimating demand requires knowledge of the types and numbers of cancers and the indications for services. For example, the demand for breast screening can be calculated by determining the number of women aged 50 to 70 years old. It is more complicated to determine the demand for services, such as radiotherapy or chemotherapy, that have a large number of indications relevant to small proportions of the cancer population.

Different populations will have different incidence rates of cancer, and the proportions of the common types of cancer may vary. Cancer registries provide information on the types and frequency of cancer in a population. They may also record data about stage at presentation, which has a critical influence on the outcomes. In addition, factors relating to specific groups of patients, such as performance status and co-morbidities, may alter treatment recommendations. Unfortunately all these details are often poorly recorded by cancer registries. Nevertheless, planning of sufficient services to meet the needs of the treatment population is vital in providing optimal care.

This chapter describes an evidence based approach to estimating the demand for radiotherapy, and its application to different treatment modalities and different populations. The work was done mainly for Australia [3.1], but has been used in Europe [3.2, 3.3] and North America [3.4]. Cancer services include all cancer control interventions, such as screening, early detection, diagnosis, treatment, palliation and rehabilitation. The estimation of the demand for radiotherapy will be described in detail, and examples given of how this approach has been adapted to other modalities and other populations.

## 3.2. INDICATIONS FOR RADIOTHERAPY

Radiotherapy has a role to play in the treatment of nearly all forms of cancer [3.5]. It is the treatment of choice when it offers:

— The best chance of cure;
— The best improvement in local cancer control;
— The best chance of preventing organ/function loss;
— The best palliation;
— The fewest side effects.

Radiotherapy may be used alone or in combination with surgery and/or chemotherapy. It may be used for cure or to relieve symptoms (palliation). The use of radiotherapy has been examined in the treatment of every cancer that makes up 1% or more of all cancers notified to central cancer registries [3.1, 3.6–3.14].

Data on indications can be combined with the epidemiological data on the frequency of each indication for radiotherapy to produce an overall estimate of the proportion of cancer patients for whom radiotherapy is indicated as the treatment of choice at least once during their illness (Table 3.1). The study was subject to sensitivity analysis and extensive peer review by surgeons, radiation oncologists, medical oncologists and epidemiologists. Overall, 52% of new cancer patients would benefit from radiotherapy at least once [3.1]. Radiotherapy is indicated to cure or improve survival in nearly 85% of the cases where radiotherapy is indicated [3.15], but may be less effective when the stage at presentation is more advanced.

Other authors have also developed epidemiologically based estimates [3.4, 3.16, 3.17]. A criterion based benchmarking method has been used to estimate need on the basis of utilization in regions where radiotherapy was assumed to be optimal [3.18]. This method uses the highest utilization rates as a benchmark, but does not relate this to the clinical evidence. In developed countries, radiotherapy demand is dominated by prostate, breast and lung cancer, and the three methods for estimating demand have been compared with uptake in British Columbia, Canada. The criterion based method fitted actual practice better. This is something of a self-fulfilling prophecy and is not directly translatable to other populations [3.19].

TABLE 3.1. OPTIMAL RADIOTHERAPY UTILIZATION RATE BY CANCER TYPE

| Tumour type | Proportion of all cancers in Australia in 2000 | Optimal proportion of patients receiving radiotherapy (%) | Patients receiving radiotherapy (% of all cancers) |
|---|---|---|---|
| Breast | 0.13 | 83 | 10.8 |
| Lung | 0.10 | 76 | 7.6 |
| Melanoma | 0.11 | 23 | 2.5 |
| Prostate | 0.12 | 60 | 7.2 |
| Gynaecological | 0.05 | 35 | 1.8 |
| Colon | 0.09 | 14 | 1.3 |
| Rectum | 0.05 | 61 | 3.1 |
| Head and neck | 0.04 | 78 | 3.1 |
| Gall bladder | 0.01 | 13 | 0.1 |
| Liver | 0.01 | 0 | 0.0 |
| Oesophageal | 0.01 | 80 | 0.8 |
| Stomach | 0.02 | 68 | 1.4 |
| Pancreas | 0.02 | 57 | 1.1 |
| Lymphoma | 0.04 | 65 | 2.6 |
| Leukaemia | 0.03 | 4 | 0.1 |
| Myeloma | 0.01 | 38 | 0.4 |
| Central nervous system | 0.02 | 92 | 1.8 |
| Renal | 0.03 | 27 | 0.8 |

TABLE 3.1. OPTIMAL RADIOTHERAPY UTILIZATION RATE BY CANCER TYPE (cont.)

| Tumour type | Proportion of all cancers in Australia in 2000 | Optimal proportion of patients receiving radiotherapy (%) | Patients receiving radiotherapy (% of all cancers) |
|---|---|---|---|
| Bladder | 0.03 | 58 | 1.7 |
| Testis | 0.01 | 49 | 0.5 |
| Thyroid | 0.01 | 10 | 0.1 |
| Unknown primary | 0.04 | 61 | 2.4 |
| Other | 0.02 | 50 | 1.0 |
| Total | 1.00 | — | 52.3 |

## 3.3. DISTRIBUTION OF TYPES OF CANCER AND THE NEED FOR RADIOTHERAPY

The proportion of cancer patients in low and middle income countries (LMICs) with an indication for radiotherapy is likely to be higher than that in high income countries because of the types of cancers [3.5]. In addition, these cancers are often diagnosed at a more advanced stage, which limits surgical options.

To demonstrate the effect of differences in types of cancers, the model by Delaney et al. [3.1] has been adapted to assess the needs for radiotherapy by substituting the distribution of cancer types estimated by the International Agency for Research on Cancer (IARC) in its Globocan project for the year 2008 [3.20] for IAEA regions, as reported in the Directory of Radiotherapy Centres (DIRAC) [3.21]. Because the types of cancer vary from region to region, the proportion with an indication for radiotherapy varies from 48% of new cases of cancer in Mexico and Central America, and the Middle East, to 55% in the Caribbean (Table 3.2).

The numbers of new cancers by site and region are shown in Fig. 3.1, and the numbers with an indication for radiotherapy are shown in Fig. 3.2. This shows the larger number of cases of lung cancer and stomach cancer in East Asia.

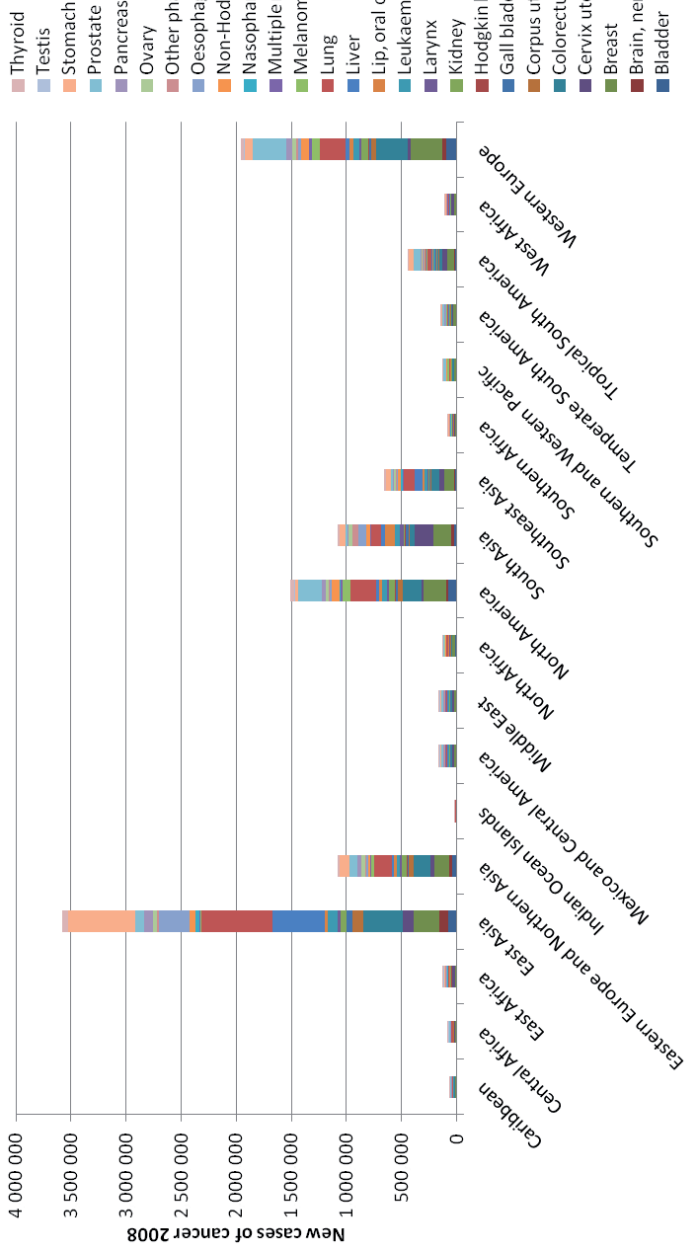


*FIG. 3.1. Number of new cases of cancer by tumour site for IAEA regions.*

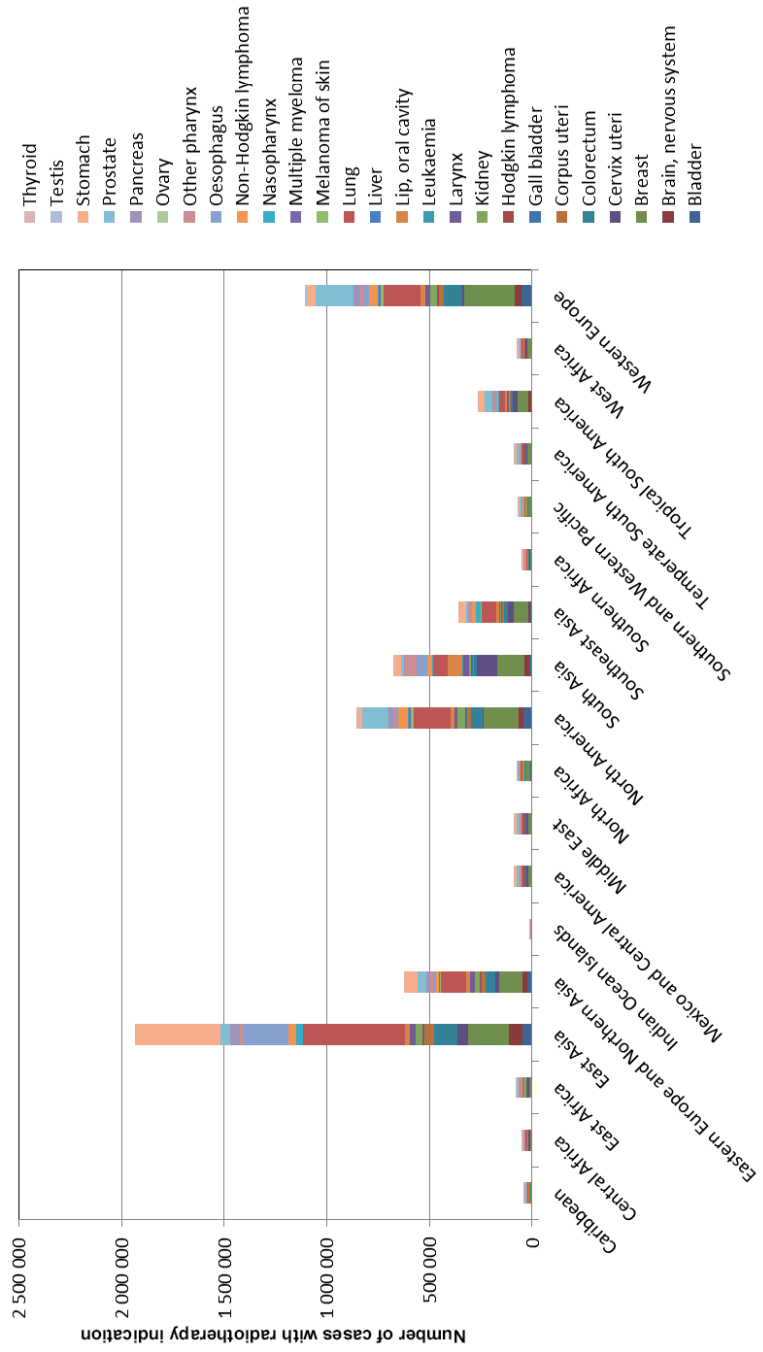


*FIG. 3.2. Number of cases by tumour type with an indication for radiotherapy by IAEA regions.*

It is likely that the estimates given in Table 3.2 significantly underestimate the demand for radiotherapy in LMICs because:

— The distribution of stages at presentation will be skewed to more advanced stages where radiotherapy has a higher utilization rate (see below).
— If surgery is not available, then radiotherapy will have a greater role to play in the treatment. This is often the case for cervical and lung cancers.

TABLE 3.2. OPTIMAL RADIOTHERAPY UTILIZATION RATES FOR IAEA REGIONS

| DIRAC region | Radiotherapy utilization rate (%) |
|---|---|
| Caribbean | 55% |
| Central Africa | 53% |
| East Africa | 52% |
| East Asia | 52% |
| Eastern Europe and Northern Asia | 54% |
| Indian Ocean Islands | 52% |
| Mexico and Central America | 48% |
| Middle East | 48% |
| North Africa | 51% |
| North America | 53% |
| South Asia | 53% |
| Southeast Asia | 49% |
| Southern Africa | 54% |
| Southern and Western Pacific | 49% |

TABLE 3.2. OPTIMAL RADIOTHERAPY UTILIZATION RATES FOR IAEA REGIONS (cont.)

| DIRAC region | Radiotherapy utilization rate (%) |
|---|---|
| Temperate South America | 53% |
| Tropical South America | 53% |
| West Africa | 53% |
| Western Europe | 53% |

The estimates of the numbers of cases with an indication for radiotherapy should thus be viewed as minima.

## 3.4. THE EFFECT OF STAGE AT PRESENTATION ON THE NEED FOR RADIOTHERAPY

In LMICs, patients present with more advanced stage cancers [3.5]. Between 50% and 80% of breast cancers are advanced at diagnosis [3.22], compared with 15% in high income countries [3.23]; 56% of cervical cancers in Bangalore, India, were stage III, compared with 15% in high income countries [3.24]. More advanced cancers are less likely to be amenable to surgery and therefore are more likely to be treated by radiotherapy. As an example of the effect of staging on the need for radiotherapy, the data for indigenous Australians, who have health outcomes very similar to those in many LMICs, were examined [3.25]. Limited staging data [3.26] have been used to calculate the optimal radiotherapy utilization rate for this population. It shows that there is a 59% need for radiotherapy for cancers in indigenous Australians compared with 52% for the general population. This is because indigenous Australians present with later stage cervical, breast and colorectal cancers. Advanced stage cervical cancer was seen in 39% of cases, compared with 12% of non-indigenous cases; advanced stage breast cancer was seen in 55% of cases, compared with 38% of non-indigenous cases; and advanced colorectal cancer was seen in 57% of cases, compared with 48% of non-indigenous cases.

Lung cancer was the only cancer where indigenous patients presented with earlier stage cancers, perhaps because of detection by chest X rays taken as part of tuberculosis screening. In LMICs, lung cancer is usually found at

more advanced stages. Reports of the distribution of stages of lung cancer are scant; a pattern of care study in Turkey showed that 72% of cases of lung cancer were stage III or IV [3.27]. Radiotherapy is often the only treatment option for advanced cancers.

## 3.5. CALCULATING THE DEMAND FOR RADIOTHERAPY MACHINES

The demand for radiotherapy services is made up of treatments for new cases and re-treatments for recurrence or cancer spread. About 50% of new cases of cancer would benefit from radiotherapy and about 25% of these may benefit from further treatments [3.28]. The re-treatment rate may be lower in LMICs with limited resources that prioritize palliative treatment.

The bulk of radiotherapy is delivered by $^{60}$Co or linear accelerator machines. These machines deliver high energy X rays in the megavoltage range and are known collectively as megavoltage (MV) machines. The capacity of an MV machine is between 400 and 600 courses of treatment per year. These courses will include new patients, re-treatments (second or subsequent treatment) and treatment of non-malignant disease cases such as pituitary tumours or those not notified to a cancer registry such as non-melanomatous skin cancer. The potential number of new cases with an indication for radiotherapy and the number receiving second or subsequent courses (re-treatment) in a geographical region can then be used to calculate the number of MV units required in that region. This can be compared against the actual supply of units in a country or region to determine the shortfall.

In practice, it is better to use two scenarios that reflect the different demands and conditions in high income countries and in LMICs. In LMICs, the demand for radiotherapy is likely to be greater (see above), radiotherapy techniques are often less complex and operating hours are longer because staff wages are relatively low [3.29]. Thus, the radiotherapy utilization rate will be higher, the number of courses per machine will be higher and the re-treatment rate will be lower (Table 3.3).

Table 3.4 and Fig. 3.3 show these calculations for IAEA regions. Only in North America and the Middle East does the number of MV machines approach or exceed calculated optimal demand using the high income planning parameters. Mexico, Central and South America, Southern and Western Pacific and Western Europe all have more MV machines than required for the low and middle income parameters.

TABLE 3.3. PARAMETERS FOR CALCULATING DEMAND FOR MV MACHINES

| | Low and middle income countries | High income countries |
|---|---|---|
| Optimal utilization rate | 55% | 50% |
| Re-treatment | 10% | 25% |
| New courses per MV machine per year | 600 | 400 |

TABLE 3.4. OPTIMAL CALCULATED NUMBER OF MV MACHINES VERSUS ACTUAL SUPPLY

| IAEA region | Demand for MV machines | | Actual number of MV machines |
|---|---|---|---|
| | LMICs | High income countries | |
| Caribbean | 68 | 117 | 46 |
| Central Africa | 87 | 149 | 14 |
| East Africa | 137 | 234 | 11 |
| East Asia | 3551 | 6054 | 2660 |
| Eastern Europe and Northern Asia | 1141 | 1945 | 891 |
| Indian Ocean Islands | 15 | 26 | 4 |
| Mexico and Central America | 156 | 266 | 167 |
| Middle East | 156 | 266 | 346 |
| North Africa | 134 | 228 | 121 |
| North America | 1566 | 2669 | 4258 |
| South Asia | 1238 | 2111 | 581 |

TABLE 3.4. OPTIMAL CALCULATED NUMBER OF MV MACHINES VERSUS ACTUAL SUPPLY (cont.)

| IAEA region | Demand for MV machines | | Actual number of MV machines |
|---|---|---|---|
| | LMICs | High income countries | |
| Southeast Asia | 651 | 1110 | 215 |
| Southern Africa | 88 | 151 | 71 |
| Southern and Western Pacific | 120 | 204 | 189 |
| Temperate South America | 151 | 258 | 181 |
| Tropical South America | 477 | 813 | 534 |
| West Africa | 127 | 216 | 17 |
| Western Europe | 2030 | 3461 | 2624 |

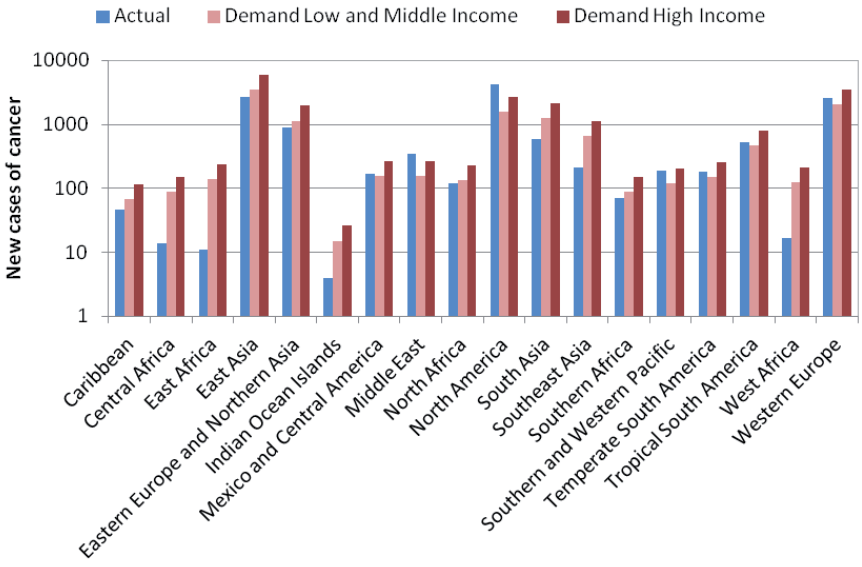


*FIG. 3.3. Actual versus optimal number of MV machines.*

## 3.6. OPTIMAL GEOGRAPHICAL LOCATION OF RADIOTHERAPY SERVICES

Where should cancer radiotherapy centres be located? The intuitive answer is that radiotherapy centres should follow the population concentration distribution in a country [3.30]. A single centre may suffice in small countries or even in large countries with a small population if transportation services between centres of population are adequate. In general, however, a network of oncology services will be required, with a radiotherapy centre within each region of a country. For those patients living at a distance from the radiotherapy centre, funding will have to be set aside to pay for the costs of transportation and accommodation.

Countries where a significant proportion of the population are living at a distance or geographically isolated from the main centres may also consider either the implementation of consultation clinics as focal points for further referral (primary care clinics can fulfil this role) or, alternatively, facilitate patient commuting through an organized transportation service.

A study from Ontario, Canada [3.31], showed that the province's highly centralized radiotherapy network did not provide adequate or equitable access to care to the province's dispersed population. In this study, the radiotherapy utilization rate was 29%, which is much lower than the generally accepted rate for a developed country. A similar study from the north of England showed socioeconomic gradients in access to services [3.32] related to education levels and car use.

## 3.7. SUMMARY

About 50% of all cancer patients need radiotherapy at least once in order to cure their cancer, increase the chance of cure or relieve symptoms caused by cancer. It is likely that the proportion that need radiotherapy is greater in LMICs because patients present with more advanced cancers and alternative treatments, such as complex surgery, are less likely to be available.

The demand for radiotherapy can be estimated from cancer registry data and used to determine the number of MV machines and staff required to meet the demand.

## 3.8. KEY POINTS

— Estimating demand requires knowledge of the types and numbers of cancers and the indications for services.
— Cancer registries provide information on the types and frequency of cancer in a population. They may also record data about stage at presentation, which has a critical influence on outcomes.
— Planning sufficient services to meet the needs of the treatment population is vital in providing optimal care.
— The proportion of cancer patients in low and middle income countries (LMICs) with an indication for radiotherapy is likely to be higher than that in high income countries because of the types of cancers.
— In addition, these cancers are often diagnosed at a more advanced stage, which limits surgical options.
— Because the types of cancer vary from region to region, the proportion with an indication for radiotherapy varies from 48% of new cases of cancer in Mexico and Central America, and the Middle East, to 55% in the Caribbean.
— About 25% of these may benefit from re-treatments (re-irradiation).
— The capacity of a megavoltage machine is between 400 and 600 courses of treatment per year, depending on the complexity of the techniques used.
— In LMICs, the radiotherapy utilization rate will be higher, the number of courses per machine will be higher and the re-treatment rate will be lower.

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# Chapter 4

# SCREENING FOR CANCERS RESPONSIVE TO RADIOTHERAPY

**R.C. Burton, E. Trapido**

## 4.1. INTRODUCTION

In 1968, the World Health Organization (WHO) produced a report [4.1] which adopted the definition of 'screening' proposed by the United States Commission on Chronic Illness [4.2, 4.3]. This definition stated that screening is:

> "the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment."

"Presumptive identification" is important, because it implies further diagnostic follow-up in order to definitively diagnose pathology and to treat it as necessary. However, in the case of visual inspection of the cervix with acetic acid followed by cryotherapy, 'see and treat' [4.4] screening is not followed up by further diagnostic tests. "[U]nrecognized disease" is also subject to interpretation because lesions in the mouth, anus or cervix are a sign of pathological changes, which can be viewed as disease. A screening test should be able to be "applied rapidly", although the results of the test may take some time. As for not being "intended to be diagnostic", the example of visual inspection with acetic acid (VIA) would not be considered as screening under this definition. Finally, patients with suspicious findings being "referred to their physicians for diagnosis and necessary treatment" is anachronistic with today's differentiation of health care providers. Certainly in developing countries, and even in developed countries, involvement of a physician is neither practical nor necessary.

The concept of screening for cancers in their preclinical stages is an appealing one, at least for those sites and geographical areas where screening is effective. The results can be interpreted accurately and quickly, and appropriate therapy can be instituted, allowing a more effective response than that which can be offered when the preclinical tumour is diagnosed later. This is precisely

the intention of disease screening; namely, to detect a disease and lead to rapid treatment and a meaningful reduction in mortality. The current WHO guidelines on early detection of cancer clearly distinguish two approaches to early detection: early diagnosis, which focuses on detecting cancer early in symptomatic patients; and screening, which focuses on detecting pre-cancers and early cancers in asymptomatic at-risk populations [4.5]. Detecting pre-cancers should reduce the number of new cases (the *incidence*) and thereby reduce mortality. Detecting cancers early should reduce mortality.

The number of cancer sites for which screening of asymptomatic individuals is efficacious — in terms of reduced morbidity or mortality/longer survival — is few. Even in optimal circumstances, controversy exists about the screening of asymptomatic patients for most cancer sites.

Prostate cancer screening is no longer recommended using prostate-specific antigen (PSA). Annual mammography and breast self-examination have been subject to unresolved discussion, and even the age at which Papanicolaou (Pap) smears are first performed, and the interval between tests, is controversial.

In this chapter, the discussion of screening is limited to those cancers for which: there is a screening test with high sensitivity and specificity; the predictive value of a positive or negative test is high; and the test has high acceptability. In addition to the aforementioned limitations, it is further restricted to those sites which respond well to radiotherapy. Therefore, the following sites are included: breast, uterine cervix, prostate, rectum and oral cavity.

## 4.2. SCREENING VERSUS EARLY DIAGNOSIS

Earlier detection of tumours may include those found among asymptomatic individuals (screening), but also among those with symptoms (early diagnosis). When initiating either a population based screening programme or an opportunistic programme (such as one offered at a health fair), both symptomatic and asymptomatic individuals will be present. Technically, the characteristics of screening tests and screening programmes are not measured on symptomatic individuals. However, the need for follow-up of individuals who screen positive is the same for both groups, although the type, extent and speed of follow-up are likely to differ. Furthermore, once someone has become symptomatic, it may be prudent to skip a screening procedure and go immediately to a more definitive diagnostic assessment. This often happens during a clinical examination, in which case screening may cause a delay and unnecessary expenditure. Once a screening programme is established and people return on a regular basis (e.g. every two years), the likelihood of finding asymptomatic cases increases, albeit not all persons will be without symptoms.

## 4.3. CANCER OF THE BREAST

Radiotherapy, as external beam teletherapy or locally as brachytherapy, can be used after surgery to reduce the risk of disease recurrence. It can be used alone, or in combination with chemotherapy. Sometimes, if surgery is impossible, or the patient opts not to have surgery, radiation may be used as the primary treatment for breast cancer. Radiotherapy is also used to treat cancer which has metastasized to the bone or brain. In addition, radiotherapy can be used for palliative treatment.

For many years, mammography was recommended for women aged 50 and older, on either a yearly or biennial follow-up basis. Controversies existed about the 40–50 year age group. More recently, however, the effectiveness of mammography has been questioned in a number of high income countries. Breast cancer mortality in women who are treated with adjuvant therapy has a similar survival rate, whether or not they participated in screening programmes [4.6–4.10]. The United States Preventive Services Task Force (USPSTF) recommends biennial screening mammography for women aged 50–74 years. It states that "[t]here is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial". It further states that "[t]he decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take patient context into account, including the patient's values regarding specific benefits and harms". Finally, it states that "[t]he USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small". The USPSTF concludes that the current evidence is insufficient to assess the additional benefits and harms of clinical breast examination (CBE) beyond screening mammography in women 40 years or older. An inquiry into benefits versus harms of mammographic screening has just been initiated in the United Kingdom, which is one country where analyses have shown little benefit from mammographic screening [4.11]. Women in whom abnormalities are detected by mammographic screening are exposed to the harms of false positive mammograms and overdiagnosis with unnecessary treatment.

WHO recommends using mammographic screening only where resources are available for wide coverage of the population. It states further that:

> "Screening programmes should be undertaken only when their effectiveness has been demonstrated, when resources (personnel, equipment, etc.) are sufficient to cover nearly all of the target group, when facilities exist for confirming diagnoses and for treatment and follow-up of those with

abnormal results, and when prevalence of the disease is high enough to justify the effort and costs of screening" [4.12].

In the absence of a population wide programme of mammographic screening, two other approaches, breast self-examination and CBE, have been attempted. Evidence does not support the effectiveness of breast self-examination as a means of detecting early cancers. However, CBE could be a valid tool for screening, particularly in low and middle income countries (LMICs). Its effectiveness at reducing the stage at presentation has been demonstrated, and its effectiveness at decreasing mortality has been suggested by statistical simulation studies. Studies show that although CBE screening is a little less sensitive than mammography, it is also less resource demanding and much more cost effective. However, a population based screening intervention remains a very resource intensive health programme regardless of which tool is used [4.13].

WHO recognizes that in LMICs, CBE may be performed annually by health workers in clinics. However, it states that among women aged 40–60, the cost is US $522–$722 per year of life saved [4.14].

## 4.4. CANCER OF THE UTERINE CERVIX

Radiotherapy is the treatment of choice for cervical cancer and is best delivered locally to the cancer by brachytherapy. Teletherapy has an important role, usually prior to brachytherapy. There is also a place for surgical treatment of early and in situ cervical cancer.

Besides breast cancer, WHO recommends population based screening only for cervical cancer. Regardless of the test used, the key to an effective programme is to reach the largest proportion of women at risk with quality screening and treatment [4.15].

Several methods for screening for cervical cancer are currently available:

(a) Pap test, a smear or brushing of the uterine cervix, for cytological examination;
(b) Direct visualization of the cervix after the use of dilute acetic acid (VIA) or iodine (VILI) to look for areas of abnormal cells visible as white (when using VIA) or yellow (when using VILI) patches, at the squamocolumnar junction at the cervical os;
(c) Testing of cervical cells for the DNA of oncogenic human papillomavirus (HPV) types (primarily HPV 16 and HPV 18).

These tests have problems with high false positive rates. The Pap smear has the lowest false positive rate, while DNA testing for HPV has the highest. False positive results increase the costs of screening, the burden of anxiety for women and morbidity from unnecessary diagnostic and treatment procedures. Oncogenic HPV strains produce oncoproteins, which are necessary for the development of cervical cancer in chronically infected women. A test for the detection of the specific E6 oncoproteins of HPV strains 16, 18 and 45 [4.16] is close to Government certification for use in China [4.17]. This approach shows considerable promise in reducing high false positive rates.

Certain standards of care are required after a positive screening result. For example, if the Pap smear is positive, a colposcopy is required for biopsy and, if this is positive, excision or cryotherapy of the abnormal area is usually needed. In resource poor settings, this series of procedures requires at least three visits and expertise in pathology and gynaecology, which are frequently not available.

VIA or VILI can be performed by nurses or midwives, and VIA has been shown to have a similar or higher sensitivity, but lower specificity, compared with the Pap smear for cervical intraepithelial neoplasia grade 2 (CIN 2), CIN 3 or invasive cancer [4.18]. Cryotherapy of cervical lesions detected by VIA or VILI can be carried out by health workers immediately, reducing the number of visits that the woman has to make. This has been termed the 'see and treat' approach, and has proven to be effective in resource poor settings [4.19].

Among women aged 30 or more, screening for HPV by DNA assays has a sensitivity of about 95% for detecting CIN 2 or later stages of pre-cancer and early cancer, making it more sensitive than cytology [4.9]. A randomized clinical trial that compared a single DNA, or Pap or VIA screening test followed by referral for colposcopy of women screening positive showed that the HPV DNA screening test was the only one that significantly reduced mortality when compared with the non-screened controls [4.4]. A single HPV test identifies almost all women who are chronically infected with oncogenic strains of the virus (i.e. those at risk of cervical cancer at the time of the test) [4.20]. Effective management of these women would be expected to have an impact on population mortality from cervical cancer.

The Pap test, when combined with a regular program of screening and appropriate follow-up, can reduce cervical cancer deaths by up to 80% [4.21]. VIA 'see and treat' leads to overtreatment, but minimizes or abolishes loss to follow-up for diagnosis and treatment, which VIA and refer involves and which can be a major obstacle to the impact of screening in poor settings [4.22]. It also depends on nurses to be 'over treaters', since this may be the women's only chance of secondary prevention of cervical cancer.

The USPSTF strongly recommends screening for cervical cancer in women who have been sexually active and have an intact cervix (i.e. the cervix has not

been surgically removed). They found good evidence from multiple observational studies that screening with cervical cytology (Pap smears) reduces the incidence of, and mortality from, cervical cancer. However, the USPSTF states that direct evidence to determine the optimal starting and stopping age and interval for screening is limited. Indirect evidence suggests most of the benefit can be obtained by beginning screening within three years of the onset of sexual activity or age 21 (whichever comes first) and screening at least every three years. The USPSTF concludes that the benefits of screening substantially outweigh potential harms. It recommends against routinely screening women older than age 65 for cervical cancer if they have had adequate recent screening with normal Pap smears and are not otherwise at high risk for cervical cancer [4.23].

Finally, the PEN (WHO) [4.14] comparison of cost effectiveness shows a one-time VIA (screening and treatment in one visit in a district hospital) for women 35–42 years of age has a cost of US $43 per year of life saved, compared with three visits for cytological examinations in district hospitals for women 35–48 years of age at US $331 per year of life saved.

## 4.5. CANCER OF THE PROSTATE

Teletherapy and brachytherapy are both used in the curative treatment of prostate cancer, and palliative teletherapy is the treatment of choice for painful bony metastases. There has been widespread screening for prostate cancer for at least two decades in developed countries using the PSA blood test with or without a digital rectal examination. The USPSTF currently recommends against using PSA for prostate cancer screening. It gave the service a D recommendation, which means there is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits, and the task force discourages use of the service [4.24].

The American Cancer Society (ACS) presents a somewhat more detailed recommendation. It recommends that men have an opportunity to make an informed decision with their health care provider about whether or not to be screened for prostate cancer [4.25]. According to the ACS recommendation, "[t]he decision should be made after getting information about the uncertainties, risks, and potential benefits of prostate cancer screening. Men should not be screened unless they have received this information." In addition:

— The discussion about screening should take place at age 50 for men who are at average risk of prostate cancer and are expected to live at least ten more years.

— This discussion should take place starting at age 45 for men at high risk of developing prostate cancer. This includes African Americans and men who have a first degree relative (father, brother or son) diagnosed with prostate cancer at an early age (i.e. younger than age 65).
— This discussion should take place at age 40 for men at even higher risk (those with several first degree relatives who had prostate cancer at an early age).
— After this discussion, those men who want to be screened should be tested with the PSA blood test. The digital rectal exam may also be done as a part of screening.
— If, after this discussion, a man is unable to decide if testing is right for him, the screening decision can be made by the health care provider, who should take into account the patient's general health preferences and values.
— Men who choose to be tested and who have a PSA of less than 2.5 ng/mL may only need to be retested every two years.
— Screening should be done yearly for men whose PSA level is 2.5 ng/mL or higher.
— Because prostate cancer grows slowly, those men without symptoms of prostate cancer who do not have a ten year life expectancy should not be offered testing since they are not likely to benefit. Overall health status, and not age alone, is important when making decisions about screening.
— Even after a decision about testing has been made, the discussion about the pros and cons of testing should be repeated as new information about the benefits and risks of testing becomes available. Further discussions are also needed to take into account changes in the patient's health, values and preferences.

The Cancer Council of Australia position is midway between the USPTF and ACS guidelines [4.26]. Canada's recommendations are also consistent, and state that "[p]rostate cancer screening should be offered to all men 50 years of age with at least a 10-year life expectancy" [4.27]. Annual screening has been the standard; however, two screening studies demonstrate that screening is beneficial every two to four years. If there is a higher risk of prostate cancer, such as family history of prostate cancer or if the patient is of African descent, screening should be offered at age 40 years. Furthermore, there may be benefit in offering a baseline PSA for men 40 to 49 years of age to establish future prostate cancer risk. Initial screening should include a digital rectal exam and PSA. PSA and PSA free/total ratio are currently the most reliable serum markers. Both markers offer a continuum of prostate cancer risk. No strict cut-off point should be used for all patients [4.27].

## 4.6. CANCER OF THE ORAL CAVITY

Teletherapy with or without chemotherapy is now preferred for the treatment of head and neck cancers, generally with primary surgical treatment used for accessible early cancers in sites like the oral cavity or the larynx, when feasible and preferred by the patient. The USPSTF concludes that the evidence is insufficient to recommend for or against routinely screening adults for oral cancer [4.28]. This is predominantly related to the relatively low incidence of oral cancer in the United States of America, even if screening is limited to adults who smoke. The Canadian Task Force on Preventive Health Care (CTFPHC) has taken a similar position. However, the British Columbia Cancer Agency has made the following recommendations for adult patients beginning at age 40 [4.29]:

— All new and general recall dental patients are to have a head, neck and oral soft tissue examination;
— Adjunct visual tools, such as toluidine blue staining and direct fluorescence visualization, are added.

In Sri Lanka and India, large studies of screening for oral cancer have proven the feasibility of screening by primary health care workers. In these areas, both betel nut chewing and reverse smoking (i.e. placing the burning end of the cigarette in the mouth) are high risk habits. The false positive rate ranged from 9 to 22%, and 1.3–4.2% of screened patients had lesions requiring follow-up by a specialist. Compliance rates with screening protocols have been a problem [4.30].

A randomized controlled trial of screening for oral pre-cancers and early cancers by visual inspection in Kerala, South India, showed a significant 34% reduction in mortality in high risk groups (i.e. users of alcohol, tobacco or both) [4.31].

As the evidence of a link between HPV infection and oropharyngeal and oral cancer has become stronger, there is reason to believe that in high risk populations, screening for oral cancer may become easier, and tests may become more sensitive and specific. However, these would still need to be linked to definitive follow-up and treatment, in order to see a decrease in incidence or mortality.

## 4.7. CANCER OF THE RECTUM

For colon cancer, radiation is seldom used after surgery for treating small areas of cancer that remain. However, for rectal cancer, radiation is often given

either before or after surgery to make the cancer more operable and/or prevent local recurrence [4.32]. The USPSTF recommends screening for colorectal cancer (CRC), using faecal occult blood testing (FOBT), sigmoidoscopy or colonoscopy, in adults, beginning at age 50 years and continuing until age 75 years. The risks and benefits of these screening methods vary. The USPSTF recommends against routine screening for colorectal cancer in adults aged 76 to 85 years [4.33]. There may be considerations that support colorectal cancer screening in an individual patient. The USPSTF recommends against screening for colorectal cancer in adults older than age 85 years. The WHO does not currently recommend either sigmoidoscopy or colonoscopy for screening. Regarding FOBT, WHO states:

> "It is clear that a major difficulty with screening using the FOBT is lack of specificity, especially if the test is rehydrated, which substantially increases the costs of programmes. Further, there seems to be a lack in sensitivity for detecting adenomas.
> "Taken together, the FOBT trials suggest that, after an interval of about 10 years, there could be a reduction of up to 20% in colorectal cancer mortality from biennial screening, and a greater reduction as a result of annual screening. Unless high compliance with the test can be achieved, however, the benefit that could be obtained in the general population would be much less, and not commensurate with the expense of the screening programme." [4.34]

Current population based FOBT screening programmes generally utilize immunochemical tests, which avoid the need for dietary restriction and rehydration that limited the older chemical test.

## 4.8. SUMMARY

WHO states that:

"The success of screening programmes depends on a number of fundamental principles:

- The target disease should be a common form of cancer, with high associated morbidity or mortality;
- Effective treatment, capable of reducing morbidity and mortality, should be available;
- Test procedures should be acceptable, safe, and relatively inexpensive." [4.35]

A national cancer control programme screening campaign should be organized to ensure that a large proportion of the target group is screened and that those individuals in whom abnormalities are detected receive appropriate diagnosis and therapy. Agreement needs to be reached on guidelines to be applied in the national cancer control programme concerning:

— The frequency of screening and ages at which screening should be performed.
— Quality control systems for the screening tests.
— Defined mechanisms for referral and treatment of abnormalities.
— An information system that can:
  • Send out invitations for initial screening;
  • Recall individuals for repeat screening;
  • Follow those with identified abnormalities;
  • Monitor and evaluate the overall programme [4.35].

Given these principles, screening for cancers which are responsive to radiotherapy should be limited to breast, cervical and rectal cancers. However, even published guidelines from developed countries must be interpreted with caution, because of differences in populations, age specific incidence, the availability of adequately trained personnel and of equipment and supplies, universal access to health care, education, economic factors, etc. Much of the evidence for effectiveness of screening for cancer has been based on trials or studies conducted among Caucasians, so applying these to racial or ethnic groups with a different natural history of the cancers (e.g. age at diagnosis, incidence rate, mortality rate, histological type) may make these recommendations inappropriate.

## 4.9. KEY POINTS

— Screening is the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly.
— Earlier detection of tumours may include those found among asymptomatic individuals (screening), but also among those with symptoms (early diagnosis). When initiating either a population based screening programme or an opportunistic programme (such as one offered at a health fair), both symptomatic and asymptomatic individuals will be present.
— WHO states that “screening programmes should be undertaken only when their effectiveness has been demonstrated, when resources (personnel,

equipment, etc.) are sufficient to cover nearly all of the target group, when facilities exist for confirming diagnoses and for treatment and follow-up of those with abnormal results, and when prevalence of the disease is high enough to justify the effort and costs of screening".

— Studies show that although clinical breast examination screening is a little less sensitive than mammography, it is also less resource demanding and much more cost effective.
— Visual inspection of the cervix with acetic acid is an attractive alternative to cytology based screening in low resource settings. Similarly, cryotherapy has been selected as the treatment option for the eligible test-positive cases.
— The United States Preventive Services Task Force currently recommends *against* using PSA for prostate cancer screening.
— The American Cancer Society recommends that men have an opportunity to make an informed decision with their health care provider about whether or not to be screened for prostate cancer.
— In high risk populations, screening for oral cancer may become easier, and tests may become more sensitive and specific.
— Taken together, the faecal occult blood testing trials suggest that, after an interval of about ten years, there could be a reduction of up to 20% in colorectal cancer mortality from biennial screening, and a greater reduction as a result of annual screening. However, unless high compliance with the test can be achieved, the benefit that could be obtained in the general population would be much less, and not commensurate with the expense of the screening programme.
— Given these principles, screening for cancers which are responsive to radiotherapy should be limited to breast, cervical and rectal cancers. However, even published guidelines from developed countries must be interpreted with caution because of differences in populations, age specific incidence, the availability of adequately trained personnel and of equipment and supplies, universal access to health care, education and economic factors.

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# Chapter 5

# ACCESS AND INEQUITIES IN RADIOTHERAPY

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## 5.1. INTRODUCTION

Cancer is the result of very complex interactions between environmental factors (e.g. inhalation of tobacco smoke, infectious diseases, unhealthy diets) and genetic susceptibility. The vast majority of cancers in adults are not genetically inherited, but rather are related to associated co-morbidities and exposure to carcinogenic substances.

Historically, the incidence of cancer has been higher in developed countries than in developing countries [5.1]. The recent demographic growth observed in the developing world as a consequence of the successful management of communicable diseases, which had caused substantial premature death, is inevitably making these populations more susceptible to cancer. In fact, of the estimated 14 million new cancer cases every year, 8 million are predicted to occur in the developing world [5.2].

Although early detection and optimal treatment have already proved to have a demonstrable effect on the decline of the cancer mortality rate in most developed countries [5.3, 5.4], diagnosis of cancer in developing countries is too frequently made during the advanced stages [5.5]. In countries with limited resources, cancer care can suffer from extreme limitations of human resources, physical capacity and equipment, leading to a mortality to incidence ratio about 19% higher than that in industrialized countries [5.2]. This difference is associated above all with elements of access, quality and efficiency of cancer care [5.6, 5.7].

The burden of the disease is shifting rapidly; thus, significant planning is required to prevent, detect earlier, treat and palliate cancer in developing countries. In order to address the complex issue of cancer control, the World Health Organization (WHO) has provided a framework for the development of national cancer control programmes (NCCPs) [5.8]. NCCPs constitute health approaches designed to tackle cancer through optimization, coordination and integration of the available resources in a systematic and comprehensive manner into evidence based strategies for prevention, early detection, treatment and palliation of cancer.

The IAEA, through its Programme of Action for Cancer Therapy (PACT), is committed to introducing, expanding and improving radiotherapy services as integral parts of comprehensive NCCPs in low and middle income countries (LMICs) by building partnerships and joining efforts with other international organizations and donors. Recently, the IAEA joined forces with WHO and implemented the WHO–IAEA Joint Programme on Cancer Control aimed at helping LMICs assess their specific cancer burden and target specific actions to combat cancer effectively within the comprehensive cancer control framework.

The establishment of an NCCP should include guidelines or recommendations for the management of the most common cancer types in any given country. These recommendations should link therapeutic approaches to their respective outcomes to break through the barriers to access cancer care and allocate resources efficiently and appropriately. This is particularly relevant in a period when roughly 56% of cancer patients worldwide live in the developing world and these countries possess only 5–10% of the global resources available to battle this epidemic and find immediate, sustainable solutions [5.9].

Worldwide, every year about 14 million people are diagnosed with cancer and 8.2 million die of this disease. The numbers place cancer as a global threat, and the burden of cancer is naturally reflected in health care budgets. The global cost of new cancer cases was estimated to be at least US $286 billion in 2009 [5.10]. In 2010, the estimated cost of cancer care in the United States of America was approximately US $124 billion [5.11]. Recently, it has been reported that accessibility of cancer care in high income countries is at a crossroads and the ability to deliver affordable care for most of these countries is becoming unsustainable due to the rise in costs [5.12]. The exploding cost of cancer care in recent years is generally related to the development of expensive anticancer agents, including molecularly targeted therapies, and the rapid expansion of demand for both drugs and imaging techniques.

The main components of cancer treatment are chemotherapy, surgery and radiotherapy. Chemotherapy, alone or combined with surgery and/or radiotherapy, is one of the most important components of modern cancer care and is responsible for curing 11% of those patients who achieve cancer cure [5.13]. Since the introduction of antineoplastic drugs around the middle of the last century, the use of cancer chemotherapy has been increasing. There are various types of tumours for which it is possible to achieve cures even in advanced stages (e.g. leukaemia, lymphomas, germinal cell tumours, paediatric tumours). There is another group in which antineoplastic adjuvant treatment significantly increases the overall survival rates or disease free survival rates obtained with surgery. This is the case for breast and colorectal cancers. Moreover, the use of chemotherapy can increase survival in many patients with advanced tumours such as lung, bladder, colon and breast tumours.

An important tool to assist in the formulation of a cost effective drugs policy for cancer was developed in 1985 when the WHO Expert Committee on the Selection and Use of Essential Medicines completed a list of the essential medicines in cancer therapy [5.14]. The WHO Model List of Essential Medicines (EML) includes medicines that ensure an increase in cancer survival at a relatively low cost in order to optimize the effectiveness and efficiency of chemotherapy and ensure equitable access to prioritized therapies, especially in areas where resources are scarce [5.15, 5.16]. Adding a new drug to clinical practice has always been associated with an overall increase in costs. Targeted cancer medicines such as imatinib for chronic myeloid leukemia (CML) and trastuzumab for HER2 positive breast cancer have shown an increase in the overall survival and disease free survival for those specific cancer types [5.17, 5.18]. Recently, WHO has evaluated the possible inclusion in the EML of imatinib for the treatment of children and adolescents with CML, but its inclusion has been delayed due to the low prevalence of CML, limited evidence of efficacy and long term safety issues for children, and the high cost [5.19]. The approval of targeted therapies by drug regulation agencies has yielded a significant investment in research and development of these therapies worldwide, and it is expected that they will eventually meet the key elements for inclusion in the EML.

The cost related to comprehensive chemotherapy includes not only the cost of anticancer medicines but also the requirement of both adequate diagnostic and hospital facilities, and qualified human resources. Additionally, patient compliance is influenced strongly by educational and socioeconomic factors, and its impact on accessibility also needs to be taken into account.

It is estimated that around 70% of patients with solid tumours undergo surgery [5.12]. In the absence of metastatic disease, surgery is often curative; of those cancer patients who are cured, it is estimated that 49% are cured by surgery [5.13]. However, as surgical procedures develop and become more sophisticated and less invasive, their cost grows proportionally. The high cost of new techniques (e.g. robot assisted surgery) also has an important impact on adequate and equitable provision of cancer care.

The increase in cost that all cancer treatment modalities experienced in the past decade, and its impact on patient decisions, should not be underestimated. It is clear that most patients continue to place a higher value on the medical aspects of treatment than on the financial aspects. Nevertheless, it should be recognized that there is a small minority who will elect not to receive anticancer treatment, with or without the endorsement and acknowledgment of their relatives, and will refuse to accept treatment that will burden their families with unmanageable debt.

Radiotherapy, chemotherapy and surgery represent the three major components of modern multidisciplinary care. It has been well established that

radiotherapy constitutes an essential modality in the management of cancer patients, either alone or in combination with other modalities, both for cure and palliation.

Radiotherapy saves lives by curing certain types of cancers and extending or improving the quality of a patient's life. It has been documented that about 50% of patients who are diagnosed with cancer worldwide would benefit from radiotherapy [5.20–5.22], and that 40% of the patients who are considered to be cured were cured by radiotherapy, either alone or combined with surgery or chemotherapy [5.13].

The expenditure on radiotherapy has been studied extensively in the developed world, and it is estimated that staff costs represent the dominant cost, while in LMICs the dominant cost would most likely be related to capital costs and maintenance of facilities and equipment [5.23].

Considering the initial capital investment in radiotherapy units and housing, as well as the highly specialized staff required to plan and deliver radiotherapy services, the provision of radiotherapy is often seen as being exceedingly expensive. But radiotherapy is, in fact, one of the most cost effective modalities of cancer therapy [5.24]; this is because most patients are treated as outpatients and the equipment has a high throughput and a long life.

Despite the evident and widely reported advantages of implementing a radiotherapy programme, radiotherapy is not accessible to up to 82% of the world's population living in the developing world; only 32% of the available teletherapy units are allocated to this part of the world. Conversely, developed countries, with 18% of the world's population, have 68% of the existing machines [5.2, 5.25].

The analysis of inequities related to radiotherapy resources is a complex issue, considering that the indicators for referring the needs can be approached from the availability of megavoltage (MV) and brachytherapy units to a more detailed study considering facilities, equipment, proper maintenance and the trained workforce required in a standard radiotherapy service, such as simulators, treatment planning systems, immobilization devices, radiation oncologists, medical physicists, biomedical engineers and radiotherapists (RTTs).

The availability of equipment, facilities and human resources alone does not determine the accessibility of radiotherapy. Other major factors, such as political commitment, public awareness of the benefits of radiotherapy and the stigma associated with treatment, need to be considered when addressing inequity in radiotherapy access and possible barriers to accessing adequate treatment [5.26, 5.27]. These factors can influence the acceptance of radiotherapy by patients and may lead to patient related delays in treatment. Other aspects, including geographical accessibility, the provision of accommodation for those forced to travel long distances for treatment, and the affordability of treatment for

both governments and individuals, also play a role in determining radiotherapy accessibility. Even though most of these factors have not been explored in developing countries, they are likely to be significant barriers to access to radiotherapy in low resource countries. Their deeper analysis and study of their impact on equal access to radiotherapy are, however, beyond the scope of this chapter.

The following sections will demonstrate the inequity in access to radiotherapy among different geographical regions and countries with distinct levels of economic development in terms of:

— Radiotherapy coverage (existing capacity and demand);
— Human resources coverage (existing capacity and demand);
— The role of radiotherapy in promoting gender equality.

Estimates of cancer incidence and mortality were taken from the GLOBOCAN 2012 project [5.2], developed by the International Agency for Research on Cancer (IARC), the WHO agency specializing in cancer research. The data derive from population based cancer registries. These may cover entire national populations, but more often cover subnational areas, and, particularly in developing countries, only major cities. Without enforcement and establishment of reliable national and regional cancer registries, the quality of information from most developing countries might not be of sufficient quality. However, the estimates of Globocan are still of unique importance, as they often remain the best available source of information on cancer incidence and projections.

The information regarding radiotherapy equipment and staff strength at the installations was taken from the IAEA's Directory of Radiotherapy Centres (DIRAC) in December 2013 [5.25]. The DIRAC database contains data collected since 1995 on radiotherapy resources worldwide, and it is updated continuously with the collaboration of radiotherapy centres and clinical institutions around the world.

## 5.2. RADIOTHERAPY COVERAGE

### 5.2.1. Current radiotherapy capacity

It is estimated that approximately 57% of cancer cases in the world arise in people living in LMICs. According to WHO, this proportion may increase to 70% in the next ten years. Worldwide distribution of radiotherapy units as a crucial element of access to radiation medicine is, however, not targeting these alarming numbers.

To show the inequity in access to radiotherapy, Fig. 5.1 compares different groups of countries in terms of distribution of cobalt units and linear accelerators (linacs), known as MV machines, and proportion of estimated new cancer cases. The grouping was based on the World Bank's classification of countries according to 2012 gross national income per capita [5.28].

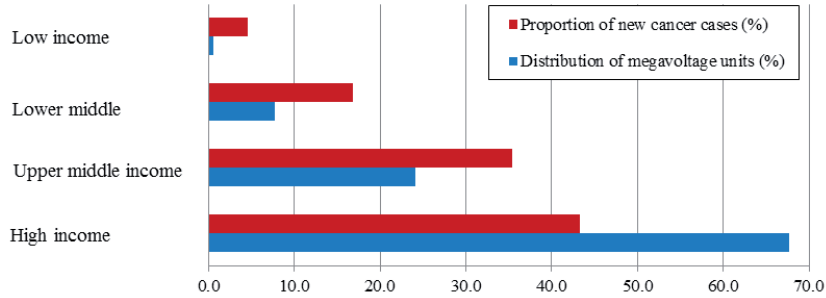


*FIG. 5.1. Comparison between the proportion of cancer incidence (red bars) and the distribution of MV units (blue bars) worldwide per income group [5.2, 5.25, 5.28].*

Furthermore, there is also a difference in the profile of existing radiotherapy equipment allocated to developed countries and to developing countries. Figure 5.2 shows that the most developed regions predominately have linacs, whereas in the rest of the world the number of cobalt machines represents approximately one third of the available MV units.

The reason for this difference lies mainly in the pricing of the radiotherapy machines and the cost of their maintenance. The approximate cost of cobalt machines and linacs is currently US $700 000 and US $2 million or more, respectively [5.29]. Moreover, cobalt units require the gamma ray emitting source to be replaced every five years on average, while linacs require continuous maintenance and quality assurance to maintain a safely calibrated radiation beam. Maintenance costs per year are estimated to range from US $1270 to US $35 680 for cobalt machines and from US $3000 to US $91 740 for linacs [5.30]. However, there has been a shift towards linacs throughout the world in terms of existing radiotherapy machines. The general trend observed in recent years shows that cobalt machines have been gradually replaced by linacs, with the number of linacs going from 5461 in 2006 to 10 766 in 2013 and the number of cobalt machines going from 2827 in 2006 to 2268 in 2013.

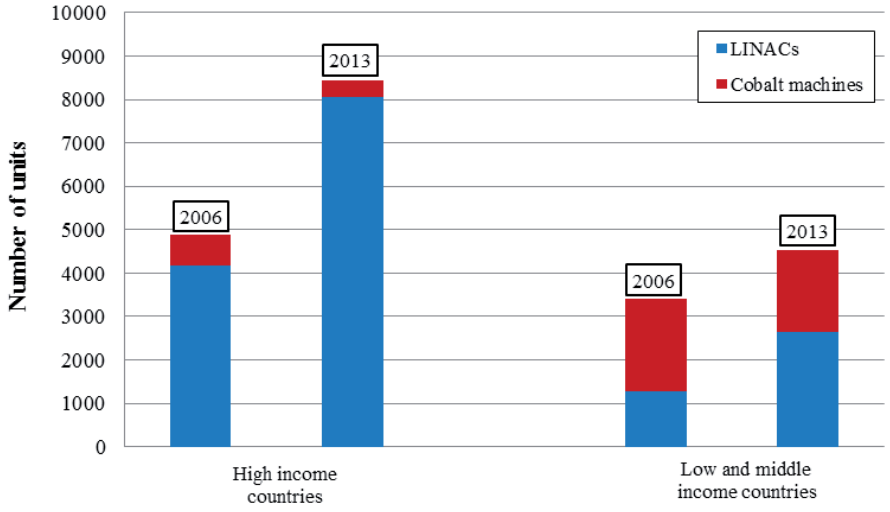


*FIG. 5.2. Distribution of MV units (linacs and cobalt machines) considering the level of economic development of countries. [5.2, 5.25, 5.28].*

Inequity in the availability of radiotherapy equipment can also be expressed considering the number of MV units per million inhabitants (MV/million). The current worldwide radiotherapy capacity status shows a tremendous disparity in terms of population coverage by radiotherapy equipment, ranging from an average of 7 MV/million in high income countries to 0.7 MV/million in LMICs, which means an average of one machine available per 1.3 million people in the poorest nations of the world.

Although this approach to evaluating the national coverage of the population in terms of access to radiotherapy is useful for most of the affluent countries, it cannot be applied to all regions and countries. As highlighted previously, the incidence of cancer in the developing world is growing at a higher rate. However, its crude rate is still about 30% of that reported for more developed countries [5.2]. Therefore, the demand for radiotherapy services should not be calculated on a population basis, but rather on the basis of cancer incidence.

Considering the number of available radiotherapy units per newly diagnosed cancer case as the main barrier to access to radiotherapy, most developed countries already have the equipment resources to theoretically cover the majority of cancer patients. Lately, in North America, there has been an expansion of approximately 60% in the number of radiotherapy units on a region-wide basis. However, the adequate number of MV units does not guarantee equal access to treatment in the developed world per se, and factors

such as affordability, centralization of the radiotherapy services and waiting times to commence treatment should be also considered.

Given the importance and the benefits of radiotherapy in cancer care, two types of concerns arise regarding adequate and equitable access to radiotherapy, depending on the extent of economic development of countries. On the one hand, the developed world faces a situation where there is inadequate provision of radiotherapy due mostly to long waiting times for treatment in some countries, and this is strongly reflected in the treatment outcomes [5.31, 5.32]. Among developed countries, and even within the same country, the proportion of patients receiving radiotherapy varies significantly; this is thought to be related to long waiting times to commence radiotherapy treatment.

On the other hand, in less developed countries the situation is that most of the population has fairly limited access to radiotherapy services, or no access at all, as the existing infrastructure is inadequate. The IAEA in 2010 reported that nearly 30 African and Asian countries have no radiotherapy services available [5.33]. Despite a 76% increase in the availability of radiotherapy between 1998 and 2010 in Africa [5.34], this region continues to have the lowest ratio of radiotherapy units to population.

Furthermore, a significant number of the limited radiotherapy facilities that do exist belong to the private sector, so the lower socioeconomic groups may not have access to them; even the access to public facilities in many countries is charged through social security fees, making it unavailable to the poorest sectors of the population.

It is evident that for the less developed regions, the provision of MV units per million population is far from the WHO recommended indicators [5.35]. The disparity is particularly noticeable in South and Southeast Asia and in Africa, particularly in sub-Saharan Africa. In reality, of the 131 radiotherapy units in sub-Saharan Africa, 75 are confined to one country (South Africa) and 56 are distributed across the rest of the region. This means that 57% of the current teletherapy capacity is covering approximately 6% of the population in sub-Saharan Africa, while the remaining units are spread throughout the region, with a population of over 800 million. The insufficient provision of radiotherapy will therefore lead to the unfortunate reality in most of these countries of patients having to endure cancer and eventually die of the disease without access to appropriate treatment.

### 5.2.2. Demand for radiotherapy units

Planning efficient and equitable treatment services for a defined population requires allocation of resources based on an estimation of demand versus the resources available. This is particularly important in regions where resources are

scarce, as the high initial capital expenditure of setting up radiotherapy services as well as the associated human resources and maintenance facilities needed to operate radiotherapy machines make this treatment modality prohibitively expensive for some LMICs.

Most of the studies estimating radiotherapy needs indicate that around 50% of the patients require radiotherapy at some point during the course of their illness. These studies have considered epidemiological data, evidence based clinical guidelines and/or treatment performed in high income countries such as Australia [5.20], Sweden [5.21] and the Netherlands [5.22]. Table 5.1 presents some examples of studies that aimed to determine the optimal radiotherapy utilization rate.

The model proposed by the Australian group has been used as a benchmark to calculate the optimal radiotherapy utilization rate in different countries [5.36]. The model combines population based cancer incidence data with radiotherapy decision trees to discover the frequency of every indication for radiotherapy. In Australia, it was estimated that 52.3% of cancer patients would benefit from radiotherapy at least once during the course of their illness and that 23% of those patients who received primary radiotherapy would require retreatment. This means that for every 1000 new cancer patients, 643 courses of treatment will be required.

Further, the model was applied to Africa and an estimate of 55% of new cancer cases had an indication for radiotherapy, ranging from 47% in Central Africa to 61% in Northern Africa [5.36]. These estimates relied on incidence data taken from GLOBOCAN, and thus no information on the staging of the disease and performance status was available. The patterns of cancer incidence have a strong influence on the need for radiotherapy in a specific country and the stage of the disease at diagnosis determines if radiotherapy is given with curative or palliative intent. In high income countries, over half of all cancer patients treated with radiotherapy, alone or combined with surgery and/or chemotherapy, are treated to achieve cures [5.21, 5.37], whereas in LMICs, radiotherapy resources are expected to be channelled to advanced and often incurable tumours for which radiotherapy has a higher rate of use. For this reason, the estimates provided in this model for LMICs in general, and Africa in particular, were seen as a minimum.

The Swedish [5.21], Dutch [5.22] and Brazilian [5.38] studies briefly described in Table 5.1 were based on government reports/databases on the use of various special medical techniques, including radiotherapy. Thus, the percentages do not refer to the prescription of radiotherapy, but rather to those patients who were in fact irradiated. Moreover, the Dutch study only includes patients treated with MV equipment, and for this reason the percentage of patients that would

TABLE 5.1. EXAMPLES OF STUDIES THAT ESTIMATED RADIOTHERAPY UTILIZATION RATE

| Country/ region | Income level | Estimate of radiotherapy utilization rate (%) | Data | | | Reference |
|---|---|---|---|---|---|---|
| | | | Epidemiological data | Indication for radiotherapy | Number of cases analysed | |
| Australia | High income | 52.3 | Australian population based data | Indications for radiotherapy were derived from treatment guidelines (before December 2003) | n.a. | [5.20] |
| Africa | n.a. | 55.0 | Globocan 2002 | Based on model developed by Delaney et al. [5.20] | n.a. | [5.36] |
| Brazil | Upper middle income | 42.7 | Authorization for high complexity procedures in the National Ambulatory Information System (2002–January 2004) | | 50 600 | [5.38] |
| Netherlands | High income | 47.48 | Netherlands Cancer Registry (1997) | Governmental report on the use of special medical techniques (1997) + Survey conducted in the 21 Dutch radiotherapy centres | 28 892 | [5.22] |
| Sweden | High income | 47.0 | Prospective survey of radiotherapy practice in 23 Swedish radiotherapy departments (2001) | | 4 171 | [5.21] |

benefit from radiotherapy was expected to be slightly higher, as some patients with skin cancer received orthovoltage irradiation.

The estimates calculated in this chapter aim to provide an approximation of the number of cases with an indication for radiotherapy. To compensate for possible underestimation of radiotherapy demand, it was estimated that 60% of the cancer patients would require radiotherapy at some point during the course of their illness.

By correlating the optimal radiotherapy utilization rate with the throughput of the MV units, an estimate of the real demand on radiotherapy facilities can be achieved. By comparing the demand with the existing capacity reported to DIRAC, projections on radiotherapy coverage in the countries with data available can be extrapolated. The IAEA suggests that an MV machine can treat between 400 and 600 new cancer cases per year [5.33]; for the purpose of this estimation, the performance of cobalt units and linacs was considered equivalent and it was considered that a machine can treat 500 new cancer patients per year (mean value of the range suggested). Figure 5.3 shows estimated radiotherapy coverage based on these parameters.

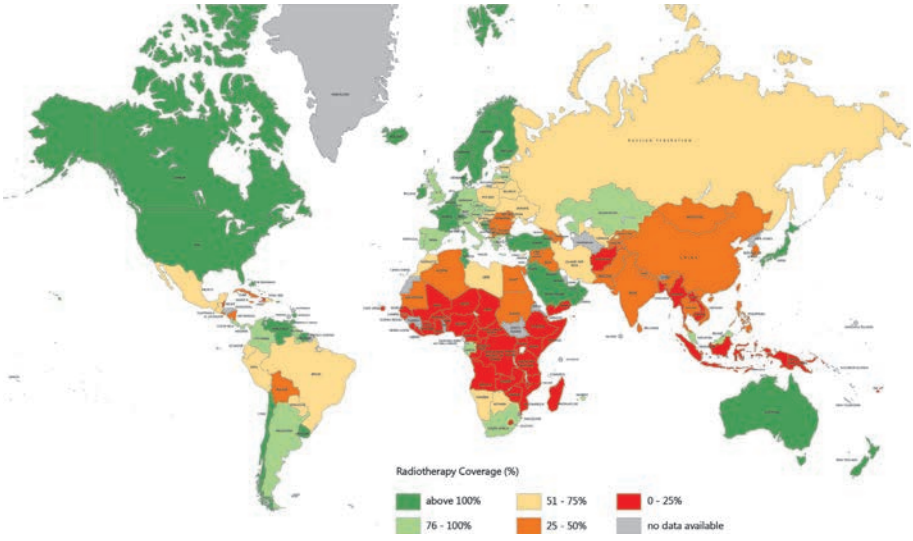


*FIG. 5.3. Estimate of the coverage of radiotherapy needs worldwide [5.2, 5.25].*

Africa and Southeast Asia face the largest shortages of teletherapy units and, therefore, have the lowest regional radiotherapy coverage indicators: 25.3% and 26.4%, respectively. When correlating the economic level of the countries with their radiotherapy coverage, nearly 70% of the LMICs with available

data are unable to cover more than 50% of the demand for MV units. On the other hand, nearly 80% of high income countries provide over 76% coverage of demand for radiotherapy units. By applying the aforementioned assumptions, it is also possible to estimate an overall shortfall of over 5000 MV units in LMICs.

Countries marked in dark green are those where the current number of machines is estimated to be higher than the number required to meet the assumptions. Most of those countries are high income nations where the majority of the patients present at diagnosis in an early stage of the disease, often with a need for longer duration and more complex courses of radiation. In 2003, a European project reviewed the existing guidelines for radiotherapy in 41 European countries and suggested the benchmark of one linac per 450 cancer patients [5.39]. This value might be slightly different in LMICs. Due especially to the significant number of advanced cancer cases at diagnosis and lower staffing costs, a machine performs shorter courses of treatment and could ideally operate for more hours than in high income countries.

Efforts are being made by the IAEA to close the gap between rich and poor countries in terms of the availability of radiotherapy treatment. In 2010, the IAEA established an Advisory Group on Increasing Access to Radiotherapy Technology in LMICs (AGaRT) under PACT aimed at reaching a mutual understanding between radiotherapy users and major radiotherapy equipment manufacturers and suppliers. The primary goal of AGaRT is to encourage the selection and provision of radiotherapy equipment packages that are affordable, sustainable and suitable for LMICs.

## 5.3. HUMAN RESOURCES COVERAGE — EXISTING CAPACITY AND DEMAND

The shortage of trained workers is seen as one of the most critical barriers to increasing access to health services, especially when a high level of technical expertise is required, as for high quality radiotherapy. Therefore, to make radiotherapy available to all patients who need it, human resources should be expanded while additional equipment is carefully acquired.

The IAEA, through its human health programme, provides a formula to estimate the medical workforce demand of the countries. It has been established that one radiation oncologist should treat 200–250 patients per year, and one medical physicist should treat 400 patients annually. To achieve effective radiotherapy, there is a need for two RTTs per MV unit treating up to 25 patients daily, or four RTTs per MV unit treating up to 50 patients [5.33].

Taking these numbers into consideration, an estimate of workforce demand and workforce coverage is presented in Table 5.2. There is currently a shortage of

TABLE 5.2. RADIOTHERAPY WORKFORCE COVERAGE

| Country income group | Radiation oncologists | | | Medical physicists | | |
|---|---|---|---|---|---|---|
| | Current staff | Staff needed | Coverage (%) | Current staff | Staff needed | Coverage (%) |
| High income | 10 619 | 16 259 | 65.3 | 5 991 | 9 033 | 66.3 |
| Upper middle income | 10 091 | 13 308 | 75.8 | 2 692 | 7 393 | 36.4 |
| Lower middle income | 1 710 | 6 326 | 27.0 | 718 | 3 515 | 20.4 |
| Low income | 117 | 1 675 | 7.0 | 50 | 931 | 5.4 |

over 15 000 radiation oncologists and over 11 000 medical physicists worldwide. The greatest shortage is in the LMICs, where the workforce coverage reaches the lowest levels.

## 5.4. GENDER EQUALITY — THE ROLE OF RADIOTHERAPY

Cancer types that affect women, namely cervical and most breast cancers, are more deadly in LMICs than in high income countries. As such, they constitute an urgent threat to women's health and a case study in health equity [5.40]. This disparity seems to be due to the lack of public knowledge, the absence of organized screening programmes (or inefficient programmes with low coverage of the target population) and lack of adequate treatment [5.41]. Radiotherapy is one of the major components of the treatment of these cancers, and therefore its adequate provision has a strong impact on the survival rate of these patients.

The advanced nature of the illness at diagnosis has a significant effect on the outcome of treatment. In developing countries, breast cancer represents nearly 20% of the cancer cases affecting women and it has been reported that between 50% and 80% of all women with breast cancer present with an advance stage of cancer at the first consultation [5.42]. According to evidence based estimations of the optimal utilization rate in high income countries, 83% of women diagnosed with breast cancer should benefit from radiotherapy during the course of their illness [5.43]. Furthermore, radiotherapy could improve the survival rates of 3000 cases and prevent about 11 000 additional local recurrences per 100 000 population of breast cancer patients for up to ten years if the entire population were treated optimally [5.44].

Controlling cervical cancer constitutes a health priority as it is estimated to be the cause of death of nearly 265 000 women every year [5.2]. Approximately 90% of those deaths occur in the developing world, making this disease one of the most serious threats to women in LMICs and a critical public health challenge for health systems. A comparison with more developed nations shows that the most likely reasons for this disparity in mortality are the lack of well distributed screening programmes, the high cost of human papillomavirus vaccination and the unavailability of efficient treatment [5.45].

According to WHO recommendations on cervical cancer management, brachytherapy in combination with external beam radiotherapy is recommended for the treatment of stage IB to IIIB/IVA cancer [5.46]. For the treatment of early stage invasive cancer cases, stages IB1 or lower, brachytherapy can also be used as the exclusive treatment.

Brachytherapy is a modality of radiotherapy where the radiation source is placed in close contact with the target tumour. Brachytherapy can be delivered in different dose rates by a team consisting of a radiation oncologist, a medical physicist and a radiotherapist in a specialized hospital with the appropriate equipment. Intracavitary brachytherapy is commonly administered with a low dose rate (LDR) or high dose rate (HDR) source with comparable effectiveness.

Brachytherapy plays a major role in the management of gynaecological cancers, particularly cervical cancer, and is used as a mandatory component of curative radiotherapy of cervical cancer in addition to external beam radiotherapy. The majority of radiation oncology facilities in the United States of America perform brachytherapy [5.47], and in Europe its indication has been increasing [5.48]. LDR systems have been gradually replaced worldwide by HDR afterloaders mostly due to the decision by manufacturers to no longer guarantee maintenance of their LDR afterloaders [5.49].

Although the global burden is significantly more pronounced in the developing world and brachytherapy is considered to be mandatory if the intent is to cure cervical cancer, countries with limited resources have less than 30% of the available brachytherapy equipment. Figure 5.4 clearly illustrates the unequal distribution of brachytherapy equipment compared to the incidence rates for cervical cancer.

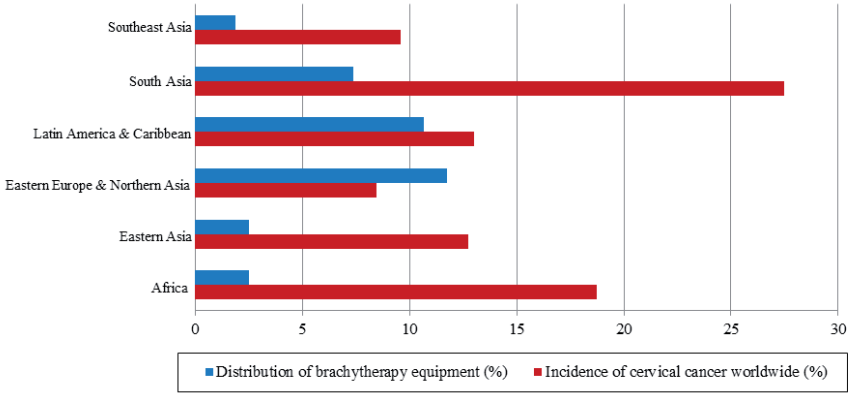


*FIG. 5.4. Disparity between distribution of brachytherapy equipment (blue bars) and incidence of cervical cancer (red bars) in different regions of the world (5.2, 5.25).*

To estimate the actual need for brachytherapy services, a model of optimal internal radiation has been proposed to determine brachytherapy needs. The estimation of the required number of brachytherapy devices has been made based on the following assumptions:

(a) Most of the brachytherapy equipment in the developing world will be skewed towards the management of gynaecological cancers.
(b) Due to the lack of effective screening programmes, nearly 60% of cervical cancers in LMICs will present at diagnosis in advanced stages, and therefore require a combination of teletherapy and brachytherapy, whereas in high income countries, only 30% of cancer cases would be diagnosed in such later stages [5.36].
(c) To treat 200 or more patients per year with brachytherapy, one HDR afterloader is needed (two or more if LDR is required) [5.50].

Based on this model, the regions where the current brachytherapy capacity is below demand are South Asia, Southeast Asia, Eastern Asia and Africa.

In many developing countries, cervical cancer represents a high proportion of all cancers treated with radiotherapy, while in most countries radiotherapy is indicated in more than 80% of all breast cancers [5.20]. Considering these facts, it is evident that inequities in the provision of radiotherapy affect women in particular, since women constitute a high proportion of the total number of radiotherapy patients.

## 5.5. KEY POINTS

— Worldwide, every year about 14 million people are diagnosed with cancer and 8.2 million die of this disease.
— Of the estimated 14 million new cancer cases that occur every year, 8 million (approximately 60%) are predicted to be in the developing world.
— National cancer control programmes constitute health approaches designed to tackle cancer through optimization, coordination and integration of the available resources in a systematic and comprehensive manner into evidence based strategies for prevention, early detection, treatment and palliation of cancer.
— Recently, the IAEA joined forces with WHO to assist Member States under the WHO–IAEA Joint Programme.

— The exploding cost of cancer care in recent years is generally related to the development of expensive anticancer agents, including molecularly targeted therapies, and the rapid expansion of demand for both drugs and imaging techniques.
— The expenditure on radiotherapy has been studied extensively in the developed world, and it is estimated that staff costs represent the dominant cost, while in low and middle income countries (LMICs) the dominant cost would most likely be related to capital costs and the maintenance of facilities and equipment.
— Radiotherapy is far from being accessible to 82% of the world's population living in the developing world; only 32% of the available equipment is allocated to this part of the world. Conversely, developed countries, with 18% of the world's population, have 68% of the megavoltage machines worldwide.
— The general trend observed in recent years shows that cobalt machines have been gradually replaced by linacs.
— The IAEA has recently reported that nearly 30 African and Asian countries have no radiotherapy services available.
— A radiotherapy machine is required for every 400–600 new radiotherapy patients per year.
— Africa and Southeast Asia face the largest shortages of teletherapy units and, therefore, have the lowest regional radiotherapy coverage indicators: 25.3% and 26.4%, respectively. On the other hand, nearly 80% of high income countries provide over 76% coverage of demand for radiotherapy units.
— It is estimated that there is an overall shortfall of over 5000 megavoltage units in LMICs.
— The shortage of trained workers is seen as one of the most critical barriers to increasing access to health services, especially since a high level of technical expertise is required for high quality radiotherapy. Therefore, to make radiotherapy available to all patients who need it, human resources need to be expanded while additional equipment is carefully acquired.
— Cancer types that only affect women, namely cervical and most breast cancers, are more deadly in LMICs than in high income countries, constitute an urgent threat to women's health and as such are a case study in health equity.

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# Part III

# THE SCIENCE AND TECHNOLOGY OF RADIOTHERAPY

# Chapter 6

# WHY RADIOTHERAPY WORKS

**S. Tashiro, I. Nishibuchi, J. Wondergem**

## 6.1. BACKGROUND

The history of radiotherapy began in 1895, when Röntgen discovered X rays, and in the following year, radiation was used for medical treatment. In the early days, the development of radiotherapy was based extensively on empiricism. Radiotherapists worked closely with radiation biologists in attempting to describe and understand the phenomena produced by ionizing radiation in the clinic and in biological systems [6.1]. During the ensuing 120 years, radiotherapy has been improved significantly and, in addition to radiation biology, medical physics has played an important role in the design and development of equipment, quality assurance and dosimetry.

Over recent decades, advances have been made in the field of molecular biology. Currently available techniques enable us to elucidate the molecular mechanisms of cellular response to ionizing irradiation, and it is anticipated that the role and contributions of radiation biology in radiotherapy will remain relevant.

This chapter describes the clinically important biological points, including knowledge from current molecular biology.

## 6.2. MECHANISM OF CELL KILL BY IONIZING RADIATION

### 6.2.1. Types of ionizing radiation

Ionization is the process of removing one or more electrons from atoms by incident radiation, leaving behind electrically charged particles (an electron and a positively charged ion) which may subsequently produce significant biological effects in the irradiated material [6.2]. Ionizing radiation may be divided into directly ionizing and indirectly ionizing radiation according to its biological effects. Most of the particulate types of radiation (protons, neutrons, carbon ions) are directly ionizing, i.e. individual particles with adequate kinetic energy can directly disrupt the atomic structure of the absorbing medium through which they pass, producing chemical and biological damage. In contrast, electromagnetic

radiation, namely X and γ rays, is indirectly ionizing because the rays do not produce chemical and biological damage themselves, but produce secondary electrons (charged particles) after energy absorption in matter.

### 6.2.2. Interaction of ionizing radiation with biological matter

Biological effects of radiation arise when ionizing radiation interacts with an organism or tissue, leaving some energy behind. The process by which electromagnetic photons are absorbed in matter depends on their energy and the atomic number of the absorbing material. Photons passing through matter transfer their energy through the following three main processes: photoelectric absorption; Compton scattering; and pair production. The photoelectric effect is the dominant energy transfer mechanism for X and γ ray photons having energies below 50 keV, but it is much less important for higher energies. The principal absorption mechanism for X and γ rays in the intermediate energy range from 100 keV to 10 MeV (therapeutic radiation range) is Compton scattering.

### 6.2.3. Radiation chemistry: Direct and indirect effects

The physical interaction of ionizing radiation with matter leads to loss of radiation energy, ionization and free radicals. These radicals react rapidly ($10^{-10}$ s) with neighbouring molecules and produce secondary DNA or lipid radicals. Free radicals are fragments of molecules having unpaired electrons. They have high reactivity with cellular molecules and, therefore, a short life. Free radicals are generated in great number by ionizing radiation due to the process of energy absorption and breakage of chemical bonds in molecules. These radicals play a major role in radiation effects on biological tissues and organisms.

The absorption of energy depends on the abundance of material in the radiation path. When ionizing radiation energy is deposited in a macromolecule associated with observable biological effects such as DNA, it is called a direct effect of radiation. Alternatively, photons may be absorbed in the water of an organism causing excitation and ionization in the water molecules. Water is the predominant molecule in living organisms (about 80% of the mass of a living cell is water). Therefore, a major proportion of radiation energy deposited will be absorbed in cellular water. A complex series of chemical changes occur in water after exposure to ionizing radiation. This process is called water radiolysis. About two thirds of the biological damage by low linear energy transfer (LET) radiation or sparsely ionizing radiation such as X rays or electrons is due to indirect action. Several lines of evidence indicate that the biological effects of radiation are mainly derived from damage to chromosomal DNA, a critical target of ionizing radiation in the human body [6.3–6.5]. Cancer cells whose DNA is

damaged beyond repair stop dividing or die. When the damaged cells die, they are broken down and eliminated by the body's natural processes.

### 6.2.4. DNA damage and repair

Ionizing radiation induces several types of DNA damage, such as base damage, single strand breaks (SSBs), double strand breaks (DSBs) and cross-links [6.3, 6.4]. Since cells have repair pathways corresponding to each type of radiation induced DNA damage, they are able to recover from the radiation induced damage. Persistent or unrepaired DSBs may determine the anti-tumour effects of ionizing radiation by inducing apoptosis, necrosis, mitotic catastrophe or permanent growth arrest. About 40 DSBs/cell are generated by irradiation with 1 Gy. In theory, if only one DSB remains in an important gene, the cell might be sterilized or even die. Therefore, the efficiency of DSB repair capacity of a cell is a very important factor in radiotherapy. Eukaryotic cells repair DNA DSBs mainly by either non-homologous end joining (NHEJ) or homologous recombination (HR).

The NHEJ pathway directly rejoins the two broken DNA ends. After the induction of DSBs, the Ku70/80 heterodimer recognizes the DSB sites, and DNA-PKcs are subsequently recruited and activated [6.3, 6.4, 6.6]. The activated DNA-PKcs phosphorylate themselves and other proteins involved in repair or damage signalling. The DNA ends are then processed by nucleases, such as Artemis and WRN, and DNA polymerases, such as pol λ and pol μ. In the final step, the broken ends are ligated together by the XRCC4/DNA ligase IV/XLF complex. NHEJ does not require the homologous DNA sequence, so it is available regardless of the cell cycle stage. However, during the end processing, the sequence information at the ligated site is lost, so NHEJ is an error-prone mechanism of repair.

HR is a repair pathway that utilizes the undamaged homologous DNA sequence, usually from the sister chromatid, as the template [6.3, 6.4, 6.7]. The initial step of HR involves the creation of single stranded regions by the MRN complex (Mre11-Rad50-Nbs1) and CTBP1 (C-terminal-binding protein 1). The single stranded DNA formed around the breaks is immediately coated with 'replication protein A' (RPA). Subsequently, HR proteins, including RAD51, RAD52 and BRCA1/2, are recruited to form a nucleoprotein filament. RAD51 is the central protein in HR, since it mediates the search for homologous DNA and the strand invasion. Afterwards, DNA synthesis is performed with DNA polymerases. HR is error free repair, because it utilizes DNA with the same sequence as the basis for repair. However, it can only function in late S/G2 phases of the cell cycle, when sister chromatids are available as templates.

The radiation induced reorganization of damaged chromatin, such as post-translational modifications and histone exchange, has recently been shown to play important roles in DNA repair. The phosphorylation of H2AX (γH2AX), a histone variant, is one of the best characterized radiation induced modifications of histones, and occurs within 5–30 min after the induction of DSBs. γH2AX forms nuclear foci, called γH2AX foci, at damaged sites and serves as a scaffold for the recruited repair proteins (Fig. 6.1). The number of γH2AX foci has been shown to correspond to the number of DSBs. The kinetics of γH2AX focus formation is widely used to analyse the induction of DNA damage, the ability of DSB repair and the radiosensitivity of cells [6.3, 6.4, 6.8].

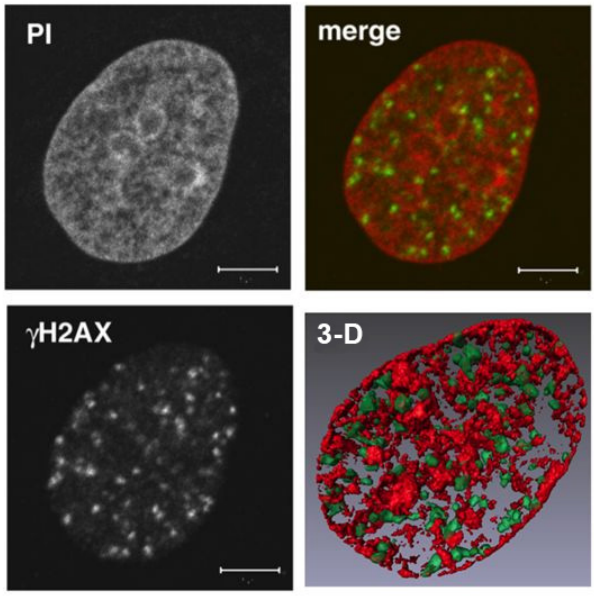


*FIG. 6.1. Radiation induced focus formation of γH2AX. Immunofluorescence staining of a human fibroblast cell line at 30 min after 8 Gy irradiation. γH2AX (γH2AX) and DNA (PI) are shown in green and red, respectively, in the merged (merge) and 3-D reconstructed (3-D) images. Scale bars = 10 μm.*

### 6.2.5. Cell death

In the context of radiation biology and cancer therapy, 'cell death' is defined as "the permanent loss of reproductive capacity", except for terminally differentiated non-proliferating cells, such as muscle and nerve cells [6.3].

Previously, cell death was separated into only two types in the field of radiation biology, 'interphase death' and 'mitotic death', based on the period after radiation. Interphase death is defined as the death of irradiated cells before they reach mitosis. On the other hand, mitotic death is defined as the death of irradiated cells after they execute one or more cell divisions.

However, recent progress in cell death research has shown that cells can die in many different ways after irradiation, such as by apoptosis, autophagy, necrosis, mitotic catastrophe and senescence-like growth arrest [6.3, 6.4, 6.9]. *Apoptosis*, a form of rapid cell death after irradiation, is characterized by chromatin condensation, nuclear fragmentation and compartmentalization by densely staining globules. *Autophagy* is a process in which cellular components are self-digested through the lysosome machinery. Autophagy was originally considered as an important mechanism for cellular maintenance, through the exchange of damaged and newly synthesized proteins. Recently, it has been shown that autophagy is also involved in cell death induced by radiation. *Necrosis* is a type of cell death characterized by an increase in cell volume, with the swelling of organelles such as mitochondria, plasma membrane rupture, and the subsequent loss of intracellular contents. *Mitotic catastrophe* is a mode of cell death occurring from the inappropriate completion of cell division due to unrepaired or misrepaired DNA damage, and can be accompanied by morphological alterations such as micronucleation and multinucleation. *Senescence-like growth arrest* is defined as the permanent arrest of cell division in G1 phase with active metabolism. Senescence has been considered a tumour suppressing mechanism that prevents excessive cell growth after the accumulation of genomic mutations by radiation. However, many details of the molecular mechanisms of radiation induced cell death remain to be clarified.

## 6.3. RADIOSENSITIVITY

Radiosensitivity varies greatly, depending on the cell type, the tumour type, the exposed tissue or organ and, to a lesser extent, individual differences. In addition, cellular radiosensitivity is also dependent on the type of radiation (i.e. low or high LET radiation), the duration of exposure, number and size (dose) of fractions, and the cellular environment. One of the rationales for radiotherapy is based on the difference in the radiosensitivities between normal and cancer cells. In order to increase the tumour cure rate and minimize the adverse effects, such as early and late normal tissue reactions, various approaches related to biological and physical aspects of the treatment are still under exploration. Several factors, such as the differentiation grade of the cells (i.e. are the exposed cells stem cells or terminally differentiated cells?), the cell cycle phase (in which

cell cycle phase are the cells when they are exposed?), the growth rate (what is the size of the growth fraction, what are the growth rates?), and oxygen levels/concentration during radiation, have been shown to affect the radiosensitivity of tumours and normal tissues.

### 6.3.1. Law of Bergonie–Tribondeau

In 1906, Bergonie and Tribondeau realized that cells are more sensitive to radiation when they:

(a) Are rapidly dividing;
(b) Are undifferentiated;
(c) Have a long mitotic future.

Today, it is recognized that this law has many exceptions. However, it is still useful to roughly estimate the 'radiation response' of tumours and organs.

### 6.3.2. The oxygen effect

The sensitivity of cells to ionizing radiation is strongly dependent on the $O_2$ (oxygen) levels. In general, cells irradiated under (normal) oxygenated conditions are two- to threefold more radiosensitive than cells irradiated under hypoxic or anoxic conditions [6.3]. The ratio of the radiation dose required for the same biological effect in the absence of oxygen versus in its presence is called the oxygen enhancement ratio (OER):

OER = radiation dose in hypoxia/radiation dose in air

For the oxygen effect to be observed, oxygen must be present either during irradiation or within microseconds after irradiation. The mechanism of the oxygen effect is referred to as the oxygen fixation hypothesis. As described in Section 6.2.3, two thirds of the biological damage produced by low LET radiation, such as X rays, is due to indirect action mediated by free radicals. Since these free radicals react rapidly with oxygen to form organic peroxides, the impact of indirect action is increased in the presence of molecular oxygen. One means strongly suggested for reducing hypoxia induced radioresistance is to irradiate hypoxic tumours with high LET radiation. Hypoxia in tumours can be achieved by two quite different mechanisms, called 'chronic hypoxia' and 'acute hypoxia' [6.3, 6.4, 6.10]. Since oxygen can only diffuse over a limited distance, increasing the distance between the tumour cell and the vasculature can lead to chronic hypoxia. In acute hypoxia, cells are exposed to hypoxia for minutes to

hours, and are then reoxygenated. Therefore, this type of hypoxia is also referred to as 'cycling hypoxia'. Acute hypoxia results from altered blood flow, caused by the transient closing of tumour blood vessels due to abnormal anatomical structures.

Recently, it was revealed that the hypoxic response of cells is transcriptionally regulated by hypoxia inducible factor (HIF-1), which mediates enhanced radioresistance [6.10].

### 6.3.3. Cell cycle

In dividing/proliferating cells, the radiosensitivity of exposed cells varies considerably throughout the cell cycle. In general, cells in the very late G2 phase and mitosis are the most radiosensitive, while those in the late S and early G2 phases are the most radioresistant [6.11]. The reason for the radioresistance in the late S and early G2 phases is considered to be DSB repair, occurring mainly by homologous recombination, an accurate DNA repair system for DSBs that is activated only during those phases.

## 6.4. FRACTIONATED RADIOTHERAPY

It is generally accepted that for conventional radiotherapy, the overall patient outcome is improved by fractionating radiation treatments [6.2]. Many of the underlying biological effects occurring during fractionated radiation treatment have been identified, and the improvement may be explained in terms of the biological response of the tumour and the surrounding tissues.

The most important factors mediating the efficacy of fractionated radiotherapy based on radiation biology concepts were summarized by Withers [6.12] as the 'four R's': repair, redistribution, reoxygenation, and repopulation. In recent years 'radiosensitivity' has been added to make 'five R's', in order to allow for differing radiosensitivity among normal cells and among tumour cells in different individuals (see Section 6.3).

### 6.4.1. Repair/recovery

As mentioned above, cells have the ability to repair the damage caused by radiation. If a given radiation dose is split into two fractions, separated by up to a few hours, then the cell survival increases. This effect is referred to as 'repair of sublethal damage' or 'Elkind recovery' (Fig. 6.2) [6.13]. Cell death correlates well with chromosomal abnormalities, as a consequence of the inaccurate rejoining of more than two DSBs. At first, the repair of sublethal damage was

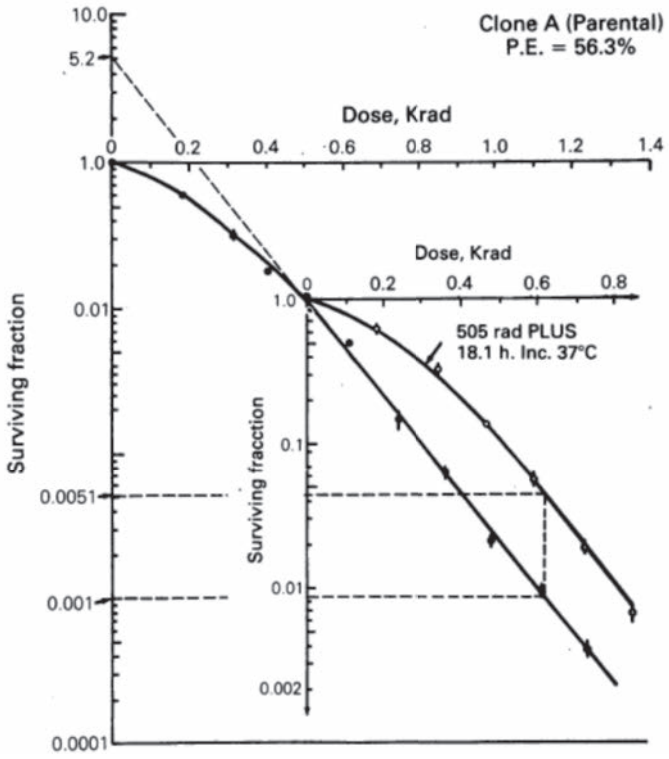


*FIG. 6.2. Fractionation survival curves of Chinese hamster ovary cells exposed to a second dose of 50 kV X rays 18.1 h after the first dose [6.13].*

thought to be due to HR, but subsequently the involvement of NHEJ was also suggested [6.14, 6.15]. Therefore, although the molecular mechanism underlying the sublethal damage recovery is still unclear, the extent of sublethal damage is considered to be nearly proportional to the number of DSBs. It is generally accepted that normal cells are capable of recovering more successfully from sublethal damage than tumour cells. Thus, normal tissues can be protected by fractionated radiotherapy without decreasing the antitumour effect.

### 6.4.2. Redistribution/reassortment

Cells have a checkpoint system as a control mechanism to verify whether each phase of the cell cycle has been accurately completed before progression to the next stage. When cells are irradiated, the G2/M checkpoint is activated to arrest the progress of damaged cells in G2 [6.3, 6.4]. The surviving cells in the radioresistant late S phase move to and accumulate in the radiosensitive

G2/M phase. Therefore, if the next irradiation is performed during the period of G2 arrest, then the effectiveness of cell killing by radiation is increased.

### 6.4.3. Reoxygenation

The response of tumours to large single doses of radiation is dominated by the presence of hypoxic cells within them, even if only a very small fraction of the tumour stem cells are hypoxic [6.2]. Immediately after a dose of radiation, the proportion of the surviving cells that is hypoxic will be elevated. However, with time, some of the surviving hypoxic cells may gain access to oxygen and hence become reoxygenated and more sensitive to a subsequent radiation exposure. Reoxygenation can result in a substantial increase in the sensitivity of tumours during fractionated treatment. Reoxygenation has been shown to occur in almost all rodent tumours studied, but both the extent and the timing of this reoxygenation are variable. Reoxygenation may result from increased or redistributed blood flow, reduced oxygen utilization by radiation damaged cells, or rapid removal of radiation damaged cells so that the hypoxic cells become closer to functional blood vessels. Measurements of the $pO_2$ in human tumours (using Eppendorf oxygen electrodes) during fractionated radiotherapy have demonstrated improved oxygen status in some tumours. Although there is no direct evidence for reoxygenation of surviving hypoxic cells in human tumours, it is probable that it is a major reason why fractionating treatment leads to an improvement in therapeutic ratio (compared with single large doses) in clinical radiotherapy [6.3, 6.4]. Currently, several strategies to overcome tumour hypoxia are under investigation to further improve radiotherapy treatments, such as:

(a) Enhancing $O_2$ delivery and/or micro-circulation using 'new' hypoxic cell sensitizers and cytotoxins (i.e. mitomycin-C and tirapazamine, nimorazole);
(b) Hypoxia mediated gene therapy approaches exploiting the fact that HIF-1 is expressed in almost all tumours;
(c) Bioreductive and/or endogenous markers that may be useful in discerning patients who should benefit from hypoxia targeted treatment approaches (individualization of therapy);
(d) Use of high LET radiation (i.e. neutrons and charged particle therapy).

### 6.4.4. Repopulation

In rapidly growing cells, an increase in the number of surviving cells resulting from cell division, or repopulation, might occur during fractionated radiotherapy because of proliferation and/or reduction of cell loss. The proliferation rate of tumour cells can be increased in the late phase of treatment

and become even faster than that before irradiation, in a phenomenon called 'accelerated repopulation' [6.16]. Therefore, an extension of the overall treatment time leads to a decrease in the local control rate [6.17]. The mechanism of repopulation has not been elucidated completely. Recently, the involvement of cancer stem cells has been suggested in repopulation after radiation.

## 6.5. THE ROLE OF RADIATION BIOLOGY IN THE FUTURE DEVELOPMENT OF RADIOTHERAPY

Many molecular targeting drugs are now being used in cancer therapy. Molecular targets are often differentially expressed in tumours and normal tissues, offering a potential therapeutic gain. An example is the epidermal growth factor receptor (EGFR) expression on the membrane of the tumour cell. Inhibition of these receptors (i.e. using radiotherapy combined with cetuximab) might lead to therapeutic gain [6.18]. Bonner et al. [6.19] published the five year survival data from a phase III randomized trial giving radiotherapy plus cetuximab for locoregionally advanced head and neck cancer. Their results showed that adding cetuximab to primary radiotherapy increased overall survival in patients with locoregionally advanced squamous cell carcinoma of the head and neck with acceptable side effects. Studies using temozolamide and radiotherapy for glioblastoma also showed a positive effect [6.20]. Another approach is targeting the vasculature of tumours (the architecture of tumour blood vessels is different from blood vessels seen in normal tissues) by combining radiotherapy with anti-angiogenic agents [6.21]. Various clinical trials using these types of drugs or approaches are now ongoing with the expectation of improved treatment outcomes in combination with radiotherapy. In the near future, the biological effects of radiation will be further clarified at the molecular level and useful biomarkers for the prediction of an individual's radiosensitivity will be discovered, thus enabling personalized radiotherapy. Furthermore, the development of radiosensitizing and radioprotective agents that act specifically on tumours or normal tissues would be a great breakthrough for radiotherapy.

Another promising approach is to attenuate radiation induced damage to normal tissues based on the underlying radiopathology of the damaged organs/tissues. Many preclinical studies are underway using anti-inflammatory drugs (glucocorticoids and NSAIDs) and drugs that interfere with pathways leading to fibrosis such as ACE (angiotensin converting enzyme) inhibitors (captopril) and AII type-1 and type-2 antagonists [6.22]. To date, the beneficial effects of these drugs are only minimal. Since radiation induced organ failure is often due to reduced functioning of the tissue stem cells, replenishment of the depleted stem cell compartment should allow regeneration of irradiated tissues.

As a result of new scientific knowledge and biotechnological developments, it has become apparent that stem cell therapy may rescue damaged or diseased organs. Currently, a wide variety of stem cell therapies are being investigated for their potential to treat radiation induced damage to normal tissue [6.23–6.33]. A successful replacement of stem cells and subsequent amelioration or reduction of radiation induced complications may open the road to completely new strategies in radiotherapy (see Chapter 30).

During the last decade, considerable improvement has been made regarding the availability, sensitivity and reliability of predictive tests. Individualization of the treatment based on extensive knowledge of the genetics of cancer patients and tumours (specific information on intrinsic radiosensitivity, hypoxia, repopulation and metastatic potential) would offer 'the ultimate tool' for radiation oncologists to successfully treat cancer patients in the future.

## 6.6. KEY POINTS

— Ionizing radiation induces several types of DNA damage, such as base damage, single strand breaks, double strand breaks and cross-links.
— Cancer cells whose DNA is damaged beyond repair stop dividing or die.
— In the context of radiation biology and cancer therapy, 'cell death' is defined as the permanent loss of the cell's reproductive capacity.
— Cells irradiated under oxygenated conditions are two- to threefold more radiosensitive than cells irradiated under hypoxic or anoxic conditions ('oxygen effect').
— The most important factors mediating the efficacy of fractionated radiotherapy based on radiation biology concepts can be summarized as the 'five R's': repair, redistribution, reoxygenation, repopulation and radiosensitivity.
— An extension of the overall treatment time leads to a decrease in the local tumour control rate.
— Adding cetuximab (an epidermal growth factor receptor inhibitor) to definitive radiotherapy increases overall survival in patients with locoregionally advanced squamous cell carcinoma of the head and neck with acceptable toxicity.
— Radiation biology and molecular biology will continue to be key to the development of effective radiotherapy strategies to treat cancer in the future.

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# Chapter 7

# REGULATORY PREREQUISITES TO CANCER DIAGNOSIS AND TREATMENT

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The government plays a central role in the establishment of regulations and in regulating the use of radiation in medicine [7.1]. These regulations will need to be satisfied before introducing radiotherapy into a country. Meeting regulatory requirements goes a long way toward satisfying the radiation protection and safety aspects of establishing a radiotherapy programme. While the range of regulatory requirements varies from country to country, the IAEA has established, through its safety standards programme, the essential components of a regulatory infrastructure required for radiation protection and safety.

## 7.1. GOALS OF REGULATIONS FOR THE USE OF IONIZING RADIATION IN MEDICINE

Regulations for the use of ionizing radiation in medicine are established within the governmental, legal and regulatory framework for safety. The objective is to protect public health and safety by preventing the availability of unsafe practices and equipment [7.1]. Radiation should only be considered when it is effective and potentially beneficial for the diagnosis or treatment of the patient. Needless or excessive exposures are not justified, and patients should be guaranteed that the treatment given is reliable and that the individuals administering the radiation are adequately trained.

Safety is the primary regulatory goal. A country's regulatory infrastructure needs to be in place in order to balance safety, effectiveness, the need for medical radiation practices and access to therapy. Regulations must be in place to facilitate informed and rational decision making, and to protect against unwise choices [7.2].

## 7.2. REGULATORY INFRASTRUCTURE

### 7.2.1. National authority

The safety requirements established in IAEA Safety Standards Series No. GSR Part 1 (Rev. 1), Governmental, Legal and Regulatory Framework for Safety [7.3], require governments to implement a framework for safety by establishing laws and adopting policies pertaining to radiation safety. Governments should authorize regulatory bodies, give them the funding and authorization to develop rules to carry out relevant laws and policies, and ensure that the regulatory body is effectively independent in its safety related decision making.

### 7.2.2. Roles and responsibilities of the regulatory body

A single regulatory body is rarely responsible for all radiation safety related activities. Coordination is critical to ensure there are no gaps or overlaps in regulatory authority. Memoranda of understanding, regular meetings and communication/coordination should be used to achieve a comprehensive working regulatory environment. Regulatory authority over the use of radiation in medicine may be the responsibility of one ministry or may be shared between several ministries. Regulatory authority may be shared among several levels of government, such as federal, state, provincial, regional and local governments. An example could be that patient protection would be the responsibility of the ministry of health, while regulation of the possession of radioactive material would be the responsibility of the ministry of the environment, and educational requirements and worker safety would be the responsibility of the ministry of labour. Some governments may have a department of radiation protection which would be responsible for all aspects of radiation protection and safety. Regulatory authority may be shared between different levels of government, for example importing of sources would be controlled by the federal government, but the qualification of medical personnel may be the responsibility of the local health authority. However, the government should ensure that all radiation safety related responsibilities are assigned to a relevant authority in order to ensure that there is no gap in responsibilities in relation to radiation safety related activities. Potential registrants and licensees should be aware of the situation within their country.

GSR Part 1 (Rev. 1) [7.3] addresses 12 requirements for the regulatory control of radiation devices:

(1) Establishing a national policy and strategy for safety;

(2) Establishing a framework for safety;
(3) Establishing a regulatory body;
(4) Ensuring the independence of the regulatory body;
(5) Assigning the prime responsibility for safety;
(6) Stipulating compliance with regulations and responsibility for safety;
(7) Coordinating other authorities with responsibilities for safety;
(8) Making provision for emergency preparedness and response;
(9) Establishing an effective system for protective actions to reduce existing or unregulated radiation risks;
(10) Making provision for the decommissioning and management of radioactive waste;
(11) Making provision for building and maintaining the competence for safety;
(12) Ensuring that there are adequate arrangements for the interface of safety with security and the provision of technical services.

The adoption of these requirements varies from country to country. In low and middle income countries (LMICs), few or none of these requirements may be in place, making the import of radiation generating devices or sources difficult and potentially unsafe. Potential registrants or licensees may need to assist in promoting the development of these regulatory requirements.

## 7.3. RADIATION PROTECTION AND SAFETY OF RADIATION SOURCES: THE INTERNATIONAL BASIC SAFETY STANDARDS

The second set of safety requirements to be considered by registrants and licensees as a prerequisite to obtaining and using medical radiation equipment is that established in IAEA Safety Standards Series No. GSR Part 3, Radiation Protection and Safety of Radiation Sources: International Basic Safety Standards (the BSS) [7.4]. The BSS complement GSR Part 1 and outline the essential safety standards for both the government and the registrants or licensees for radiation protection and safety. They were established to protect people and the environment from harmful effects of ionizing radiation.

The requirements can be seen as defining the government's responsibilities, the government's requirements to promulgate regulations that require activities to be performed by registrants or licensees of radiation devices used in medicine, and the requirements for registrants or licensees to comply with these regulations.

### 7.3.1. Responsibilities of the government

Ultimately, the government is responsible, either through its actions or through the actions of others, via regulations, inspection and enforcement, to ensure the safety of the public and the environment. An active regulatory programme that performs all of these activities (authorization, inspection and enforcement) is essential to ensure the safe use of radiation in medicine. Most governments have some general regulatory requirements and some specific requirements that should be considered prior to establishing radiotherapy in a country. The government is responsible for establishing and maintaining the legal and regulatory framework (regulatory body), establishing regulations and guides, enabling inspections and enforcement of the regulations, and issuing guidelines for radiation protection and safety.

### 7.3.2. Responsibilities of the regulatory body

The regulatory body should adopt regulations that are commensurate with the characteristics of the practice or the source within a practice, and with the magnitude and likelihood of the exposures. These regulatory requirements are placed on the registrant or licensees. The requirements will vary from location to location, and are usually based on the complexity and risk of exposure of people and the environment. For planned exposures in medicine (diagnostic and therapeutic), the registrant or licensee should be prepared to comply with regulations concerning general radiation safety as well as specific regulations concerning the safe use of radiation in medicine. Some of the issues that should be considered by the regulatory body when promulgating regulations include:

— Notification and authorization;
— Review and assessment of facilities and activities;
— Inspection of facilities and activities;
— Enforcement of regulatory requirements;
— The regulatory function relevant to emergency exposure situations and existing exposure situations;
— Provision of information to, and consultations with, parties affected by its decisions and, as appropriate, the public and interested parties.

### 7.3.3. Responsibilities of the registrant or licensee

Registrants and licensees will need to establish and implement technical and organizational measures for the types of activities they are performing. They may need to establish a radiation protection or safety committee and appoint a

radiation protection officer who is qualified to perform tasks associated with radiation protection and safety. Some of the duties of a radiation protection officer are to: communicate with the regulatory body to inform it of, and to gain authorization for, the possession and use of radiation devices; develop or coordinate the development of operating procedures; arrange for protection and safety; perform periodic reviews; maintain records; and inform management of these activities. Some of the activities that could be assigned to the radiation protection officer are testing and performing or overseeing maintenance of the equipment, surveying restricted areas, record keeping, and acting as a point of contact for reporting accidents and incidents to the regulatory body. The radiation protection officer may also be part of the management team or may be a consultant with contractual obligations to respond on behalf of the registrant or licensee.

## 7.4. GENERAL REQUIREMENTS OF THE INTERNATIONAL BASIC SAFETY STANDARDS

With any use of ionizing radiation, there are protection and safety requirements. Registrants or licensees should be familiar with these as well as the specific requirements for medical exposure. Registrants or licensees will be expected to comply with all of the requirements. As stated previously, more than one regulatory body may have jurisdiction over radiation protection and safety. Each country will be unique in the regulatory process, and registrants or licensees are encouraged to contact the appropriate regulatory body for the specific requirements in their country.

Some of the more common general requirements are discussed below. In the next section, the suggested activities to meet regulatory requirements for medical exposure are described.

### 7.4.1. Justification

The introduction of a new source of radiation that can change the likelihood of exposures has to be justified to ensure that the detriments of possession and use of the device are outweighed by the individual and societal benefits. Justification of medical exposure operates at three levels. Level 1 deals with the use of radiation in medicine in general. In practice, this is accepted as doing more good than harm, and its justification is taken for granted. Level 2 deals with the specified procedures used for a specific objective. The aim at this level is to judge whether the procedure will improve diagnosis or provide necessary information about those exposed. The responsibility to assess this lies with the health

authority in conjunction with appropriate professional bodies. Level 3 deals with the application of the procedure to an individual. The particular application should be judged to do more good than harm for the individual patient and should be carried out in consultation between the radiological medical practitioner and the referring medical practitioner.

### 7.4.2. Radiation protection and optimization

The dose to the patient should be sufficient to provide the information necessary to make a diagnosis or treat a patient, yet it should not exceed the amount of radiation needed. In therapy, too low a radiation dose can be just as detrimental as an overexposure. The consequences could be the loss of cancer control.

### 7.4.3. Dose constraints and diagnostic reference levels

Dose constraints and diagnostic reference levels are used for optimization of protection and safety. Dose constraints are used for controlling occupational and public exposure, but not as dose limits. Non-compliance with the constraint should lead to an investigation and follow-up actions.

The regulatory body develops diagnostic reference levels after consultation with the relevant professional bodies. These diagnostic reference levels take into consideration the need for adequate image quality and are based on wide scale surveys or published values that are appropriate for the local circumstances. Registrants and licensees should be familiar with the diagnostic reference levels established in their country. There are no guidelines for therapeutic applications, and radiation oncologists should rely on recommendations of professional organizations that have established dose ranges for treatment based on scientific evidence [7.5, 7.6].

### 7.4.4. Safety requirements for manufacturers

The regulatory body must approve imaging and therapy equipment before it can be installed and used in the country. Manufacturers will need to submit the protection and safety standards, engineering performance reviews, quality standards and functional specifications, and information on the display and operational systems. The regulatory body should consider equipment that meets the standards of the International Electrotechnical Commission (IEC) and International Organization for Standardization (ISO) [7.7, 7.8]. Some countries may base approval of equipment on certification provided by other countries that have established standards. Two of these are the United Kingdom's Medicines

and Healthcare Products Regulatory Agency (MHRA) medical device approval process and the US Food and Drug Administration (FDA). MHRA is responsible for safeguarding public health by making sure that medical devices work and are acceptably safe. This includes providing information about the benefits and risks of medicines and medical devices to key stakeholders, including the public, patients, healthcare professionals, researchers and industry. Successful manufacturers are identified with a seal of approval called an 'accreditation mark'. The FDA has a similar medical device approval process [7.9].

### 7.4.5. Safety and security of radiation devices

Today, security has become an important consideration in addition to safety in the use of radioactive sources in medicine. However, safety and security must be designed such that security measures do not compromise the safe use of the device and vice versa. Prior to possession and use of radioactive sources, a safety and security assessment should be completed by the registrant or licensee and reviewed by the regulatory body. The safety and security assessment is essential prior to ordering a source.

Safety assessments are required at different stages of equipment acquisition and use, such as initial siting design, manufacturing, construction, assembly, commissioning, use, maintenance, annual checks and decommissioning. The level of assessment is commensurate with the use and risk of the radiation devices. For therapy equipment, more safety checks are needed prior to patient use and should be repeated throughout the life of the device.

For some uses of radiation in medicine, the safety assessment must be performed prior to use. The purchase and installation of a linear accelerator or treatment planning system used in radiotherapy are examples of when such assessments must be performed. The registrant or licensee will need to perform a safety assessment as part of the design process to make sure that the planned shielding is adequate for the protection of workers, the public and the environment. A second safety assessment would then be performed to validate the adequacy of the actual shielding. This assessment would require surveys of the area surrounding the treatment room and calculations of exposure based on, for example, hours of operation. In addition, an independent verification of critical radiotherapy equipment parameters such as output should be performed prior to use. Treatment planning systems require similar safety assessment and validation of accuracy of the data. The transfer of data from the radiotherapy equipment to the treatment planning system requires another safety assessment and validation, with independent calculations, measurements and in vivo dosimetry also to be considered. The regulatory body may also perform an inspection of the facility to verify compliance [7.10].

Registrants and licensees should be prepared and have the resources to monitor the activities of the facility and equipment. This will require the purchase of quality control and radiation detection equipment. The equipment will need to be maintained and calibrated as required by the regulatory body. The registrant or licensee should also adhere to the manufacturer's recommendations for safety activities, considering that warranties and service contracts may be contingent on following the manufacturer's recommendations. Staff performing these activities will need to be trained in the use and maintenance of the equipment. Calibration and monitoring equipment can be expensive for sophisticated treatment units and should always be considered in the purchase of the radiotherapy equipment.

The registrant or licensee must maintain records of assessments. If the assessment identifies opportunities to optimize dose to the patient, public or workers, then procedures should be amended and reported to staff and the regulatory authorities.

For radioactive sources, a security assessment should be performed to prevent unauthorized access to and removal of sources. A security assessment should include the registrant's or licensee's equipment, training and procedures to prevent, delay and respond to unauthorized access to or removal of sources.

### 7.4.6. Prevention and mitigation of accidents

There have been several reported accidents with newly acquired radiotherapy equipment. To prevent future accidents, registrants or licensees should prepare a safety analysis that begins with facility siting and design, or when retrofitting existing structures with new equipment. For example, retrofitting a cobalt-60 teletherapy room with a linear accelerator may require additional shielding in the walls and ceiling, or it may require that access to the space adjacent to the external wall or ceiling be restricted and secured from unauthorized access. Weight limitations may also prevent additional shielding material from being added to the structure [7.11].

The sophistication of treatment equipment requires data transfer between the imaging units, treatment planning system, treatment unit, and records and verification system. Greater effort should be made to ensure that data transfer is correct at each stage of the process and that the data are verified as being accurate. Independent verification is essential to ensure that equipment is calibrated correctly and data transfer is correct [7.12].

There are many measures that can be taken by the registrant or licensee to minimize the possibility of medical errors. These may be required by regulations or recommended by professional organizations. Some of these are described in the BSS [7.4], such as providing information and training to workers; developing and maintaining adequate operating procedures and inventory procedures; reviewing

and maintaining occupational worker reports; and performing daily, monthly, annual and after servicing tests on equipment, including mechanical, hardware and software checks. A strong quality assurance programme is necessary for the prevention of medical errors.

An example of an accident that could have been prevented concerned the replacement of a cobalt-60 source in an existing unit. After several months, nursing staff reported increased skin reactions after treatment. A physicist reviewed output tables and original calibration and reported that the data were correct. During an intercomparison by a national medical physics board, it was noted that the calibration of the machine was wrong and that patients were receiving 25% more radiation than prescribed. Two hundred seven patients were treated incorrectly. The error in output values would have been discovered prior to patient treatment if there had been an independent verification of the machine's output prior to its use for treatment [7.11].

There have been numerous reported errors in the calibration of radiotherapy equipment. In order to reduce these types of errors, the BSS require independent regular audits to review quality assurance programmes. In addition, the IAEA has developed a web based learning system for sharing information on radiotherapy incidents and near misses. The Safety in Radiation Oncology (SAFRON) event reporting system allows registrants and licensees to review and contribute information on incidents and near misses [7.13].

## 7.5. REQUIREMENTS FOR PLANNED EXPOSURE SITUATIONS

Tables 7.1–7.3 provide a snapshot of the types of activities and records that need to be maintained by the registrant or licensees to meet the BSS. Registrants or licensee need to take these requirements into account when deciding to offer radiotherapy. The tables are not all-inclusive, but do provide guidance on the administrative and financial resources needed to maintain an adequate radiation protection and safety programme. The registrant or licensee should seek specific guidance from the regulatory authority to ensure that they have met all the specific requirements for their country. In the absence of such regulatory requirements, these tables may provide some general guidance for meeting the protection and safety standards for the safe use of radiation in medicine. In evolving regulatory bodies where specific regulations are not in place, users are encouraged to adhere to the activities listed. To obtain more guidance on the specific items, the IAEA and many professional organizations have prepared reports. For example, Safety Reports Series No. 38, Applying Radiation Safety Standards in Radiotherapy, may be useful in assisting registrants and licensees in these activities [7.14].

*Text cont. on p. 125*

TABLE 7.1. OCCUPATIONAL EXPOSURE: LIST OF REQUIRED REGULATORY AND REGISTRANT OR LICENSEE ACTIVITIES

| BSS reference | Regulatory requirement | Types of activities |
|---|---|---|
| Requirement 19 | Establish and enforce dose limits for workers. | Provide personnel monitoring to workers. |
| Requirement 20 | Establish and enforce dose limits for workers. | Maintain worker dose records and monitor the dose to ensure compliance. |
| Requirement 21 | Establish responsibilities for employers, registrants and licensees. | Provide monitoring and safety equipment (aprons and shields) to workers. Provide health surveillance and services to workers. |
| Requirement 22 | Evaluate through inspections compliance of workers. | Establish policies and procedures requiring workers to wear monitoring and safety equipment. Establish a safety culture within the organization. |
| Requirement 23 | Evaluate through inspection that workers are compliant and that a safety culture exists. | Maintain personnel exposure records including records from previous employees. Establish internal investigation levels and actions to be taken by workers and managers when investigation levels are exceeded. |
| Requirement 24 | Require registrant and licensees to maintain a radiation protection programme by establishing organizational, procedural and technical arrangements. | Establish controlled areas; restrict access; provide signage to identify the controlled areas; monitor for radiation levels and contamination; conduct surveys; establish procedures; provide personal protective, radiation detection and decontamination equipment and supplies [7.15]. |
| Requirement 25 | Require registrant or licensees to monitor occupational exposure and worker health surveillance. | Provide personnel monitoring equipment such as film badges, dosimeters or thermoluminescent dosimeters. Maintain workers occupational exposure including past history records. Allow workers access to their occupational exposure records. |

TABLE 7.1. OCCUPATIONAL EXPOSURE: LIST OF REQUIRED REGULATORY AND REGISTRANT OR LICENSEE ACTIVITIES (cont.)

| BSS reference | Regulatory requirement | Types of activities |
|---|---|---|
| Requirement 26 | Require registrants and licensees to provide instruction information and training to workers. | Establish a training plan for workers, including initial training and refresher training. Records should include course material, a methodology to assess worker comprehension of the information (test) and documentation of worker completion of the training. |
| Requirement 27 | Require registrants and licensees to prohibit workers from receiving benefits as a substitute for radiation protect and safety. | Establish ALARA (as low as reasonably achievable) procedures for workers demonstrating that the registrant or licensee prohibits radiation exposure in exchange for benefits. Establish a safety culture within the facility. |
| Requirement 28 | Regulatory bodies should have regulations in place for minors and for workers who are pregnant or breast-feeding. Prohibit through regulations persons under the age of 16 from being radiation workers. | Provide education and information to workers who perform tasks in areas where exposure can occur. Provide monitoring equipment to pregnant workers to monitor dose to embryo/foetus. Monitor for the duration of the pregnancy and maintain these records. |

TABLE 7.2. PUBLIC EXPOSURE: LIST OF REQUIRED REGULATORY AND REGISTRANT OR LICENSEE ACTIVITIES

| BSS reference | Regulatory requirement | Types of activities |
|---|---|---|
| Requirement 29 | Adopt international dose limits for the public and the environment and establish responsibilities for registrants or licensees. | Perform initial surveys, verification surveys. Develop procedures to prevent exposure to the public or environment and maintain compliance with international dose limits. |
| Requirement 30 | Provide protection and safety to members of the public. | Prepare shielding diagrams and calculations for all areas where radiation sources will be used and stored.<br>Survey areas after installation to ensure that public spaces are below regulatory thresholds.<br>Provide appropriate signage and notification to the public of restricted areas and prohibit access.<br>Perform follow-up surveys as required by regulations and after major structural changes and equipment modifications to demonstrate that public dose thresholds are not exceeded.<br>Develop a plan to ensure that disused sources are safely and securely stored from unauthorized access.<br>If using unsealed radioactive sources, have procedures in place to protect the public and the environment from exceeding exposure limits.<br>Maintain a certificate or record authenticating that the device has been approved by the regulatory body. Maintain records of upgrades and equipment modifications. |

TABLE 7.2. PUBLIC EXPOSURE: LIST OF REQUIRED REGULATORY AND REGISTRANT OR LICENSEE ACTIVITIES (cont.)

| BSS reference | Regulatory requirement | Types of activities |
|---|---|---|
| Requirement 31 | Establish standards for the discharge of radioactive waste. | Minimize amount of waste generated, provide secured storage location for waste, maintain inventory and disposal pathways information for all radioactive waste. |
| Requirement 32 | Establish regulations for environmental monitoring and reporting. | Have equipment, personnel and procedures to conduct surveys of the environment and documents for reporting survey results to regulatory body. |

TABLE 7.3. MEDICAL EXPOSURE: LIST OF REQUIRED REGULATORY AND REGISTRANT OR LICENSEE ACTIVITIES

| BSS reference | Regulatory requirement | Types of activities |
|---|---|---|
| Requirement 34 | Develop regulations requiring responsibilities, diagnostic reference levels, dose constraints and criteria and guidelines for release of patients. | Ensure that qualified personnel are performing medical procedures. Develop procedures to comply with diagnostic reference levels, dose constraints and release of patients after radiotherapy. Develop procedures for exposure to caregivers and research subjects (if applicable). |
| Requirement 35 | Develop regulations on minimum education and training for health professionals using radiation in medicine. | Maintain records of health professionals' education and training for inspection. Develop training procedure based on regulatory requirements and needs of the facility. |
| Requirement 36 | Develop regulations requiring referral for medical exposure, patient protection and notification to patient of radiation exposure. | Develop procedures that require authorization from a medical practitioner for medical exposure. Maintain records of all orders, written directives or prescriptions for radiation procedures. |
| Requirement 37 | Develop regulations requiring registrants and licensees to have procedures in place justifying medical radiation exposure. | Develop procedures for authorizing consultation between the radiological medical practitioner and the referring medical practitioner on the appropriateness of the test, urgency of the test and risk to the patient from the test. |

TABLE 7.3. MEDICAL EXPOSURE: LIST OF REQUIRED REGULATORY AND REGISTRANT OR LICENSEE ACTIVITIES (cont.)

| BSS reference | Regulatory requirement | Types of activities |
|---|---|---|
| Requirement 38 | Develop regulations requiring radiological medical practitioners to optimize medical exposure. Develop regulations concerning calibration and dosimetry of patients, diagnostic reference levels, dose constraints and quality assurance for medical exposure. | Perform acceptance and commissioning activities on new equipment, including software. Perform daily, monthly and annual quality assurance checks of equipment as required by regulatory body or recommended by manufacturer or professional organizations. Repeat activities after service or repair, if appropriate. Provide independent audit of quality assurance for medical exposure. Support radiotherapy exposure using treatment planning systems to develop plans that target treatment to the prescribed volume and minimize exposure outside the target [7.16, 7.17].<br>For radiopharmaceutical therapy, ensure that the correct radiopharmaceutical, activity and tagging agent are used. |
| Requirement 39 | Establish through regulations requirements for medical exposure for pregnant and breast-feeding women. | Provide signage instructing patients to inform staff if they are pregnant, suspect pregnancy or are breast-feeding. Develop procedures requiring negative pregnancy test prior to radiotherapy for women of childbearing age and education for women of childbearing age to abstain from exposure that could cause pregnancy during treatment. Procedures should also include educating breast-feeding patients to discuss alternatives if breast milk may be contaminated from the radiotherapy. |
| Requirement 40 | Establish regulations to ensure public protection from exposure from patients who are released after radionuclide therapy or implantation of sealed sources. | Develop procedures that prevent unauthorized release of patients after therapy as required by regulations. Provide oral and written instructions to patients on radiation risk and risk to the public and family members. |

TABLE 7.3. MEDICAL EXPOSURE: LIST OF REQUIRED REGULATORY AND REGISTRANT OR LICENSEE ACTIVITIES (cont.)

| BSS reference | Regulatory requirement | Types of activities |
|---|---|---|
| Requirement 41 | Establish regulations that minimize unintended and accidental medical exposures. Require registrants and licensees to investigate and report such an event and to implement corrective actions. | Develop procedures to address unintended and accidental medical exposures, including notification of an event, investigation and determination of the estimated dose to the patient(s) and corrective actions. Procedure should include instructions on establishing reporting requirements to the patient, management, referring physician and the regulatory body [7.18]. If the event is caused by equipment failure, the equipment should be evaluated, repaired and calibrated prior to continued use. |
| Requirement 42 | Establish regulations for reviews and record retention. | Registrants or licensees should maintain and review records as required by the regulations and as described in relation to the requirements listed above. The regulations should specify the retention time for each required record. In situations where the retention time is not specified, the registrant or licensee should establish a conservative time, based on the need for long term access to the record. |

## 7.6. SPECIAL CONSIDERATIONS FOR DEVELOPING COUNTRIES

Developing countries face extraordinary challenges in providing radiotherapy. The lack of a regulatory framework can prevent radioactive devices from being shipped to them. Similarly, the lack of a safety programme can lead to poor protection of the patient and potential harm. An adequate regulatory infrastructure and safety programme are thus essential. For countries that have made good progress in the development of an infrastructure and safety programme, there might be an increase in access to radiotherapy.

Qualified personnel to operate the equipment are an essential requirement in providing radiotherapy. There may be some opportunities for regional training, but rarely can the level of training needed for safely operating the equipment be acquired within the facility.

The cost of radiotherapy should be considered for the lifetime of the device and not just the startup cost. A budget should include preventive maintenance and disposal of the unit at the end of its life. As the device ages, the maintenance and repair costs will increase. Registrants and licensees should be aware of the operational costs as well as the costs of the radiotherapy equipment.

Registrants and licensees should also consider the eventual disposal of radioactive sources. At the time of acquisition, it should be possible to negotiate the transfer of the source back to the manufacturer at the end of its useful life. For other radiation devices, activation parts (target) may need to be disposed of as radioactive waste.

## 7.7. CONCLUSIONS

Cancer has no boundaries, and low and middle income countries need adequate radiotherapy services. Potential registrants and licensees and government should work together to find common solutions to improving the regulatory infrastructure and safety programme to ensure that everyone has access to cancer treatment. The IAEA has several programmes that can assist in developing the appropriate regulatory infrastructure, acquiring the equipment and training personnel in the safe and effective use of radiation in medicine.

## 7.8. KEY POINTS

— The IAEA has established, through its safety standards, the essential components of a required regulatory infrastructure for radiation protection and safety.

— Safety is the primary regulatory goal. Regulations must be in place to facilitate informed and rational decision making, and to protect against making unwise choices.
— The IAEA safety standards assign to governments the responsibility of implementing a framework for safety by establishing laws and adopting policy pertaining to radiation safety.
— The second set of safety requirements to be considered by registrants and licensees as a prerequisite to obtaining and using medical radiation equipment is that established in Radiation Protection and Safety of Radiation Sources: International Basic Safety Standards (the BSS).
— Ultimately, the government is responsible, either through its actions or through the actions of others, via regulations, inspection and enforcement, to ensure the safety of the public and the environment.
— It is the government's responsibility to establish and maintain the legal and regulatory framework (regulatory body), establish regulations and guides, enable inspections, enforce the regulations and issue guidelines for radiation protection and safety.
— Registrants and licensees will need to establish and implement technical and organizational measures for the types of activities they are performing. They may need to establish a radiation protection or safety committee and appoint a radiation protection officer who is qualified to perform tasks associated with radiation protection and safety.
— Each country will be unique in the regulatory process, and registrants or licensees are encouraged to contact the appropriate regulatory body for the specific requirements in their country.
— The regulatory body must approve imaging and therapy equipment before it can be installed and used in the country.
— There are no regulatory guidelines for therapeutic patient applications in radiotherapy, and radiation oncologists should rely on recommendations of professional organizations that have established dose ranges for treatment based on scientific evidence.
— There have been numerous reported errors in the calibration of radiotherapy equipment. In order to reduce these types of errors, the BSS require independent regular audits to review quality assurance programmes.
— The Safety in Radiation Oncology (SAFRON) event reporting system allows registrants and licensees to review and contribute information on incidents and near misses.
— Developing countries face extraordinary challenges in providing radiotherapy services. An adequate regulatory infrastructure and safety programme are essential.

— The cost of radiotherapy should be considered over the lifetime of the device, not just the startup cost. A budget should include preventive maintenance and disposal of the unit at the end of its life.
— Qualified personnel in adequate numbers to operate the equipment are essential to providing radiotherapy services.

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# Chapter 8

# EQUIPMENT, QUALITY ASSURANCE AND QUALITY CONTROL

**D. Van Der Merwe**

## 8.1. INTRODUCTION

Radiotherapy equipment evolves continuously owing to its technological nature. Modern technology enables electronic integration and exchange of patient administrative, diagnostic, imaging and treatment data using Digital Imaging and Communications in Medicine (DICOM) protocols [8.1] across secure networks. This standard is updated continuously as technology matures and new applications and Internet standards are developed. The typical clinical workflow defines the logic with which such data are organized and networked. Figure 8.1 gives an example of how the DICOM standard can be used to transfer information between different stakeholders in a health system.


*FIG. 8.1. How the DICOM standard can expedite the transmission of data between stakeholders in a typical clinical setting (image courtesy of NEMA).*

Radiation oncology deals with the application of radiation to a wide range of malignant diseases over many different sites and stages. Non-malignant lesions can also be treated using radiotherapy. As a result, there is no universal or generic treatment type or technique, and multidisciplinary approaches

(surgery and medical oncology) may affect the urgency or timing of radiotherapy treatment. Figure 8.2 shows the position of radiotherapy within a wider cancer management matrix represented by its need for regulatory and multidisciplinary support infrastructure.

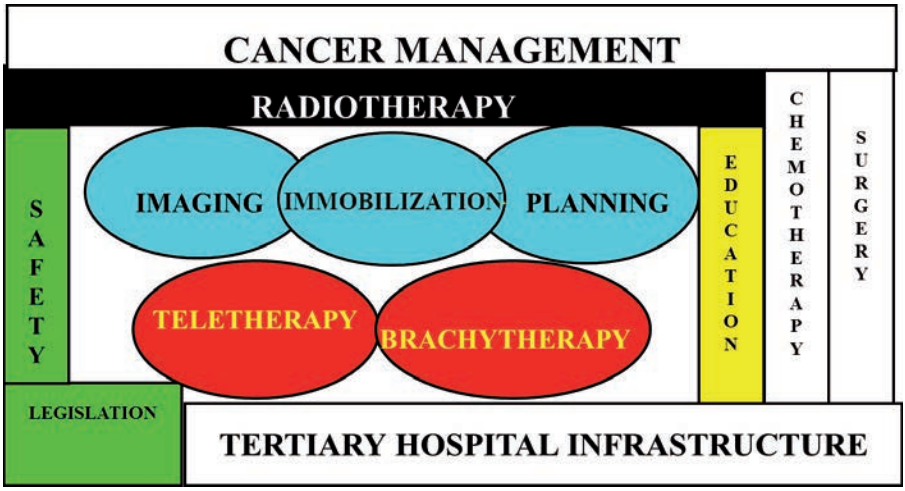


*FIG. 8.2. The components of radiotherapy within a tertiary cancer management system.*

Highly qualified, competent teams of clinical (radiation oncologists), medical physics and radiation technology professionals are necessary to provide a safe and effective service [8.2]. Given the inequitable access to radiotherapy services worldwide [8.3], radiotherapy professionals are tasked with providing the optimal solution within the prevailing national resources and conditions. In addition, the local socioeconomic conditions also affect the incidence of disease. As a result, there is a large variation in the level of technology and the treatment techniques that are employed internationally. This chapter will focus on the most traditional techniques, known as two dimensional (2-D) and three dimensional (3-D) radiotherapy. Advanced techniques such as intensity modulated radiation therapy (IMRT) and image guided radiation therapy (IGRT) are covered in Chapter 10.

## 8.2. EQUIPMENT

Once the decision has been made to administer radiotherapy, the process of treatment planning, a preparatory phase leading to the actual treatment delivery, is initiated. Following a definitive diagnosis, the treatment planning process

establishes the most effective modality and beam arrangement, or combinations thereof, for irradiating the target. Localizing the target and identifying surrounding high risk structures is a prerequisite to this endeavour so that the radiation can be focused on the target volume and high risk normal structures are avoided as much as possible. Target and risk volume definition can be achieved clinically by visualization or palpation, using planar X ray fluoroscopy and radiography, or from cross-sectional imaging procedures like ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET). Images produced with X rays (e.g. CT) indirectly provide a measure of the electron density of the tissue, which is represented visually using a grey scale. Figure 8.3 shows a typical image from a pelvic CT scan being used for treatment planning purposes. Electron density data are important to the radiotherapy planning process because this information is used to predict and model the physical interaction of the photon and electron treatment beams in the patient. The other imaging modalities assist in the localization and determination of the extent of the disease, mainly because they provide better soft tissue contrast or additional metabolic or physiological information.

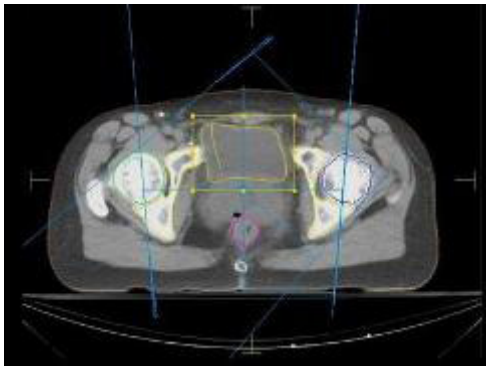

*FIG. 8.3. A CT slice from a pelvic scan used for radiotherapy treatment planning.*

Many skin conditions, for instance, can be seen with the naked eye, and low or medium energy X ray units or megavoltage electron beams can be used to treat these lesions, including their clinical target volume, which includes microscopic spread. For these cases, no other imaging or immobilization and positioning aids and devices are necessary. The location and shape of these fields are simply drawn or referenced to identifiable anatomical features. Figure 8.4 shows a typical patient set-up for treatment of a skin lesion on an orthovoltage unit capable of delivering low and medium energy X ray beams.

*FIG. 8.4. A medical radiation technologist positions an orthovoltage machine in preparation for treatment of a skin lesion (image courtesy of Xstrahl).*

Since the ultimate aim is to be able to treat patients with multiple fractions in any area of the body, reproducible patient positioning and immobilization are important. A range of immobilization devices are available and complex individualized devices are needed when targets are situated very close to critical structures, e.g. in the head and neck volume. Figure 8.5 shows head and neck and whole body immobilization and positioning devices that can be used to position patients reproducibly during a course of radiotherapy.

Once the patient positioning has been approved and documented, the treatment planning process proceeds with clear definition of all the treatment and organ at risk volumes, placement of the treatment fields and calculation of the radiation dose. Simpler treatment techniques can generally be planned from planar images and axial contours using manual calculations and standard isodose atlases. This is known as 2-D treatment planning. Treatment field borders are often described using surface anatomical landmarks. Figure 8.6 shows a conventional fluoroscopic simulator used for planar imaging in 2-D treatment planning. These units are mechanically designed to simulate the physical capabilities of most isocentric teletherapy treatment units. Fluoroscopy is used to localize the treatment field and radiographic records are made of the final, approved portals.

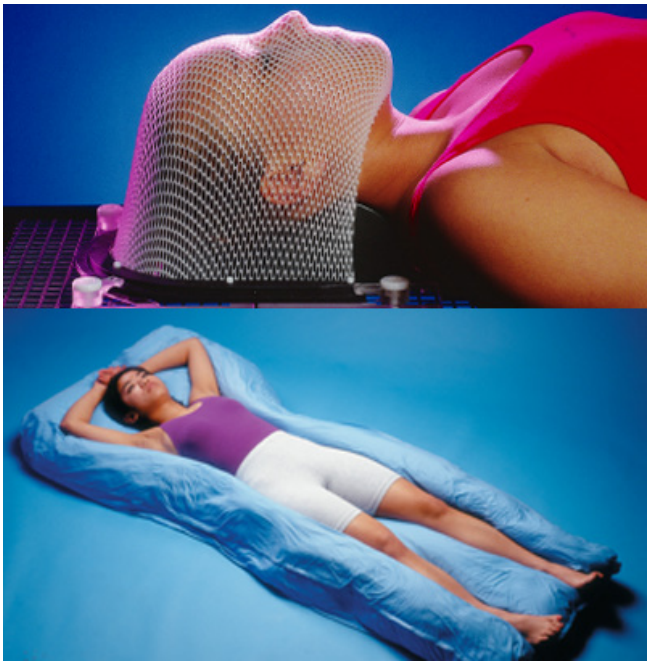

*FIG. 8.5. Immobilization devices used to ensure reproducibility of patient position for a course of radiotherapy (images courtesy of CIVCO).*

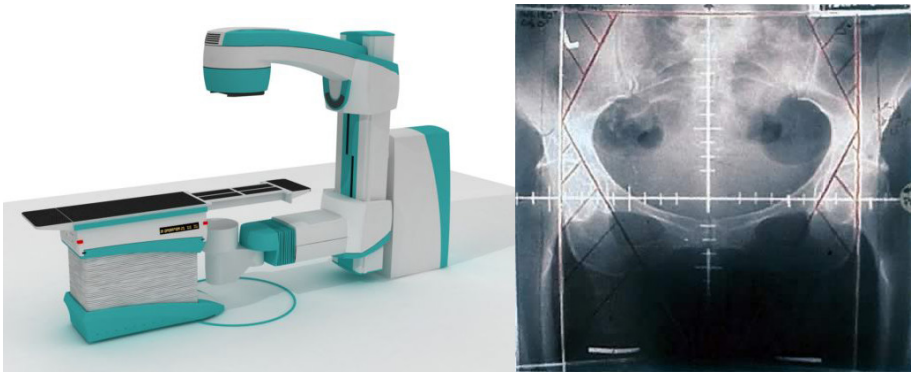

*FIG. 8.6. A radiotherapy simulator used for field localization in 2-D treatment planning. The simulator radiograph shows the radiopaque field centre and borders superimposed on the radiological anatomy (images courtesy of UJP PRAHA and Global Library of Women's Medicine).*

If dose escalation is to be achieved and critical structures are to be preserved in some disease sites, more advanced techniques are required. CT based

three dimensional conformal radiotherapy (3-D CRT) is often considered the standard treatment technique. This implies that the patient anatomy is known in three dimensions and can be referenced to the isocentre of the treatment unit. Computerized treatment planning systems (TPSs) capable of generating isodose distributions are necessary to perform CRT. Extensive beam data libraries of all available treatment units need to be commissioned by the medical physicists in order to perform 3-D CRT [8.4]. This process includes validation of the data exchange with the imaging and treatment hubs as well as parameters providing the physical capabilities and radiation beam characteristics of each treatment modality. Figure 8.7 shows a typical 3-D CRT based TPS workstation. Graphics of reconstructed images of a patient overlaid with shaded isodose distributions are visible on the screen.

*FIG. 8.7. A TPS workstation showing reconstructed images of the patient's anatomy, radiotherapy beam portals, isodoses and plan evaluation tools (images courtesy of Elekta).*

Since TPSs are technology dependent, they have also undergone significant improvements over time, and the algorithms used to produce volumetric dose distributions have therefore become more complex [8.5]. Figure 8.8 shows the difference obtained in the isodose distribution when different algorithms are invoked. Such differences are bigger in regions of high inhomogeneity, like the chest.

Ongoing efforts are being made to use Monte Carlo calculations routinely to produce clinical dose distributions based on the fundamental principles of radiation transport. Highly advanced techniques which employ on-line adaptive treatment techniques call for real time treatment planning solutions.

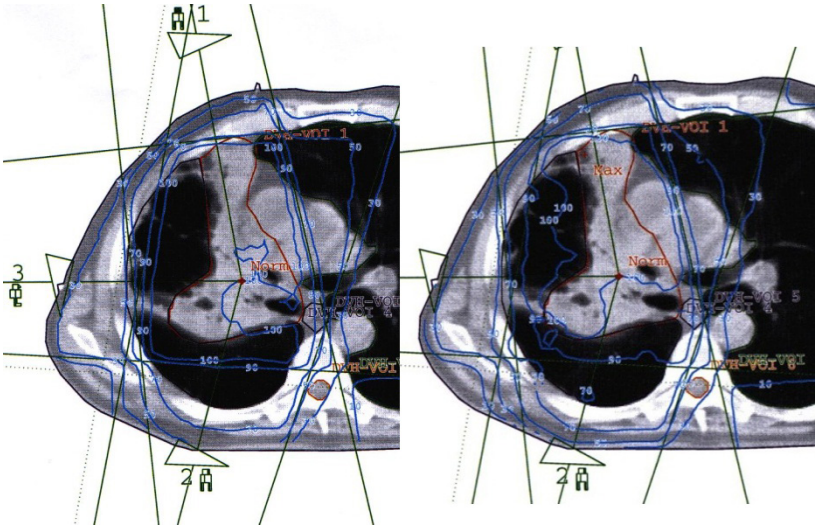

*FIG. 8.8. Isodose distributions with the same beam arrangement and normalization level but using different TPS algorithms (the distribution predicted by a pencil beam algorithm is shown on the left, whereas the result from a collapsed cone algorithm is shown on the right).*

Most modern radiotherapy departments are equipped with isocentric treatment machines for teletherapy (cobalt units and/or linear accelerators providing a range of megavoltage energies). Individual beam modifiers are used to optimize the dose delivered from each portal. Most beam modifiers are coded to provide unique identifiers that ensure their correct use, position and orientation (e.g. wedges and missing tissue compensators). Teletherapy units are often equipped with multileaf collimators to provide the composite field shape. Alternatively, shielding blocks can be manufactured and placed into the beam in order to shape or block part of a field.

Portal imaging is required to confirm that the treatment plan has been communicated and interpreted correctly at the treatment delivery station. Many different techniques are employed including non-ionizing, kilovoltage and megavoltage sources using planar and tomographic techniques. Confirmation is needed that both the field shape relative to the treatment unit isocentre and placement of the field relative to the patient's anatomy are correct. Thus, convergence of two reference systems (equipment and patient) is confirmed prior to commencing treatment. TPSs generally produce digitally reconstructed radiographs of field portals and these are used to confirm patient set-up. Figure 8.9 shows a modern cobalt teletherapy unit and linear accelerator, both set up to perform portal imaging.

*FIG. 8.9. A modern cobalt teletherapy unit and a radiotherapy linear accelerator. Portal imaging using film on the cobalt unit shown here and, similarly, an electronic device on the accelerator, are used to verify patient and target volume position relative to the equipment isocentre, prior to treatment. The accelerator is also fitted with an orthogonal X ray imaging system (images courtesy of the IAEA Programme of Action for Cancer Therapy and Varian).*

Data transfer from TPSs to treatment delivery units and subsequent download of the correct parameters for each treatment field and fraction is achieved using an integrated record and verify system (RVS). RVSs also track dose points and can therefore be used to alert medical radiation technologists to changes in treatments which have multiple phases. In addition, RVSs can be expanded to schedule, monitor workload and expedite workflow. Figure 8.10 shows the data flow of an RVS between the different radiotherapy workstations.

Brachytherapy is a modality providing highly localized treatment and is often used in conjunction with teletherapy. Brachytherapy is available over a range of dose rates using different radioactive or electronic sources. Applications can be contact (intracavitary, endoluminal, surface or endovascular) or interstitial. Most permanent and high dose rate afterloading applications are performed with on-line imaging and access to the TPS because optimization of the positions and dwell times of the source are required for each application. Imaging systems are often dedicated to the brachytherapy suite to prevent or minimize patient transfer and applicator movement during a procedure. Figure 8.11 shows a selection of applicators used to guide the sources near or in the target volume and also shows an imaging and treatment planning snapshot of a typical gynaecological application.

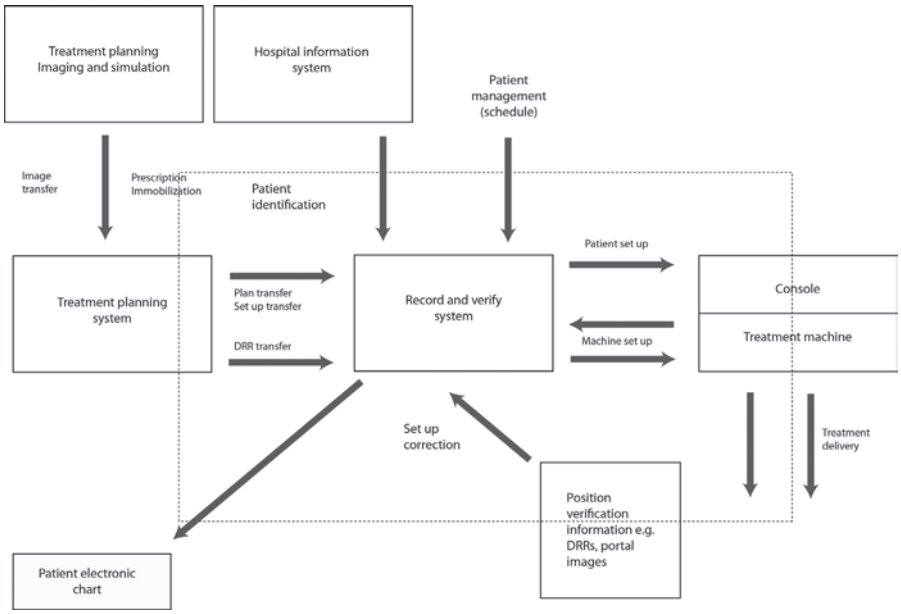


*FIG. 8.10. Information data flow through an RVS server linked to the various workstations in a radiation oncology department [8.6].*

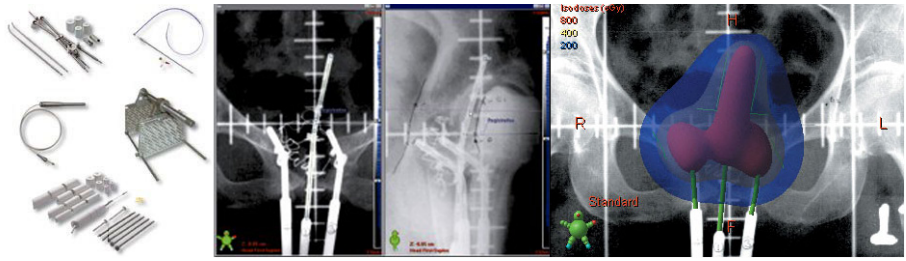


*FIG. 8.11. A selection of different brachytherapy applicators; an orthogonal image set from a high dose rate brachytherapy intracavitary procedure with its associated treatment plan on the right (image courtesy of Varian).*

## 8.3. QA/QC

It is clear that the specification of all radiotherapy equipment not only requires forethought in terms of application, infrastructure and resources [8.7], but also consideration of workflow and connectivity via DICOM standards [8.1]. The latter is reinforced when compliance with the International Electrotechnical Commission (IEC) guidelines is required [8.8–8.15]. The safety and quality of

radiotherapy equipment is grounded in the medical physics service, which has a major role and responsibility in the physical and technical supervision of equipment specifications covering: acceptance, commissioning, operation and maintenance of equipment, and quality management (see Chapter 16). In addition, clinical competence and continuing education to enhance multidisciplinary collaboration in the ongoing development of treatment protocols and techniques are essential [8.16, 8.17].

In order to provide high quality medical physics services, a range of supplementary equipment is required to ensure the mechanical, safety and dosimetric performance of all modalities. The regular calibration and verification of these instruments is vital for international traceability. The process starts with verifying that the facility itself is safe in terms of public and occupational exposure. The mechanical integrity of the unit and all its safety and interlock systems are then tested. A description of the physical aspects of a medical physics quality assurance programme and the details of a quality control and safety programme are described in such IAEA publications as Setting Up a Radiotherapy Programme: Clinical, Medical Physics, Radiation Protection and Safety Aspects [8.18]. The baseline data for these procedures are established post-installation during the acceptance testing of the equipment. Figure 8.12 shows a medical physicist preparing to conduct a constancy check on a linear accelerator.

*FIG. 8.12. A medical physicist positioning a check device on the treatment couch of a linear accelerator in order to carry out a quality control check of the beam (image courtesy of PTW).*

The output of all types of radiotherapy treatment equipment should be calibrated to a known absorbed dose in water according to international dosimetry protocols such as those described in Technical Reports Series No. 398 and IAEA-TECDOC-1079 [8.19, 8.20]. In order to perform this calibration, reference equipment is used; an example of an absolute dosimetry system needed for the calibration of high energy external beam radiotherapy photon beams is shown in Fig. 8.13.

*FIG. 8.13. A water phantom and an absolute dosimetry system (ionization chamber and electrometer) that is used to determine the reference output of megavoltage photon beams from a teletherapy treatment unit. Such systems are calibrated by a dosimetry standards laboratory that has been accredited to provide an internationally traceable coefficient (image courtesy of PTW).*

In order to provide a data set that can be applied to any clinical situation under which patients are to be treated, all permutations of energy, treatment depth and field shape have to be characterized relative to the absolute dosimetry normalization point. In addition, all beam modifiers and patient accessories need to be characterized. Figure 8.14 shows a set of different dosimeters that can be used during this process. These devices are generally waterproof and used as radiation detectors in automatic beam acquisition systems, which are large water phantoms that are placed under the beam in order to generate dose profiles (see Fig. 8.14).

In addition, all imaging and networking equipment is also subject to quality assurance. Similarly, acceptance testing, commissioning and ongoing quality control are required to achieve this.

A quality system in radiotherapy should include regular internal and external auditing of the infrastructure, clinical and equipment procedures, and education programmes [8.21].


*FIG. 8.14. Waterproof detectors (left) are used to measure relative dose profiles in computer controlled beam acquisition systems, which are large water phantoms (right) (images courtesy of PTW).*

## 8.4. KEY POINTS

— Highly qualified, competent teams of clinical, medical physics and radiation technology professionals are necessary to provide a safe and effective service.
— Since the ultimate aim is to be able to treat patients with multiple fractions in any area of the body, reproducible patient positioning and immobilization are important.
— Computed tomography based three dimensional conformal radiotherapy is often considered the standard treatment technique.
— Treatment planning systems have undergone significant improvements over time and the algorithms used to produce volumetric dose distributions have become more complex.
— The safety and quality of radiotherapy is grounded in the medical physics service, which has a major role and responsibility in the physical and technical supervision of equipment specifications covering: acceptance, commissioning, operation and maintenance of equipment, and quality management.
— Clinical competence and continuing education to enhance multidisciplinary collaboration in the ongoing development of treatment protocols and techniques are essential.

— In order to provide quality medical physics services, a range of supplementary equipment is required to ensure the mechanical, safety and dosimetric performance of all modalities. The regular calibration and verification of these instruments is vital for international traceability.
— The baseline data for dosimetry procedures are established post-installation during acceptance testing of the equipment.
— The output of all types of radiotherapy treatment equipment should be calibrated to a known absorbed dose in water according to international dosimetry protocols such those described in Technical Reports Series No. 398 and IAEA-TECDOC-1079.
— A quality system in radiotherapy should include regular internal and external auditing of the infrastructure, clinical and equipment procedures, and education programmes.

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# Chapter 9

# RECENT DEVELOPMENTS IN THE TECHNOLOGY OF RADIATION ONCOLOGY

**E. Rosenblatt, E. Zubizarreta**

## 9.1. INTRODUCTION

The accurate targeting of tumours with maximum preservation of normal tissues has long been the foremost goal of radiotherapy practice [9.1]. Over the last two decades, the ability to achieve this goal has improved greatly. This achievement has been made possible by advances in imaging technology, specifically the development of computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and fusion PET–CT [9.2]. Developments in imaging coupled with advances in computer technology have fundamentally changed the processes of tumour targeting and radiotherapy planning. The ability to display anatomical information in an infinite selection of views has led to the emergence of three dimensional conformal radiotherapy (3-D CRT), a modality in which the volume treated conforms closely to the shape of the tumour volume.

During the past decade, there have been significant advances in radiotherapy technology. This chapter presents an overview of recent developments in radiotherapy technology.

## 9.2. RECENT TECHNOLOGICAL ADVANCES

### 9.2.1. Intensity modulated radiation therapy

Intensity modulated radiation therapy (IMRT) is a sophisticated type of 3-D CRT that assigns non-uniform intensities to tiny subdivisions of beams called beamlets. The ability to optimally manipulate the intensities of individual rays within each beam permits greatly increased control over the overall radiation fluence (i.e. the total number of photons/particles crossing over a given volume per unit time). This in turn allows for the custom design of optimal dose distributions. Improved dose distributions may lead to improved tumour control and reduced toxicity in normal tissue [9.3].

When a tumour is not well separated from the surrounding organs at risk and/or has a concave or irregular shape, there may be no practical combination of uniform intensity beams that will safely treat the tumour and spare the healthy organs. In such instances, adding IMRT to beam shaping allows for much tighter conformity to targets. IMRT requires the setting of the relative intensities of tens of thousands of individual beamlets in an intensity modulated treatment plan. This task cannot be accomplished manually and requires the use of a multileaf collimator (MLC) [9.4] and specialized computer assisted optimization methods. IMRT is proving to be a very useful tool to approach difficult problems which could not be solved dosimetrically in the pre-IMRT era.

A debate entitled "IMRT: Are you ready for it?" took place during the International Conference on Advances in Radiation Oncology (ICARO), organized by the IAEA in April 2009 [9.5] The debate brought together panel members who represented various views from different regions of the world. Health economics was identified as a key driver in the adoption of IMRT as a treatment modality in some countries. Nevertheless, there is still a lack of randomized trials that clearly demonstrate the clinical benefits of IMRT in many tumour sites, other than improved dose distribution and a reduction in toxicity in some situations. Unexpected toxicities and recurrences have also been reported [9.2].

Advanced radiation treatment technologies such as IMRT require improved patient immobilization and image guidance techniques. There is debate as to whether image guidance is always required with IMRT to ensure accurate delivery. Whether image guidance is necessary each day is also debated. It may be necessary in specific cases, such as when immobilization is not optimal or when hypofractionation is used. Other techniques to control organ motion during treatment, such as respiratory gating and breath hold techniques, may be necessary when reduced target volumes are considered.

Since IMRT sometimes uses additional treatment fields from different directions, its use may increase the volume of normal tissue receiving low doses, increasing the integral dose, which might lead to a higher risk of secondary cancers. This is particularly worrisome in the case of paediatric patients. With the introduction of any advanced technology such as IMRT and image guided radiation therapy (IGRT), data should be collected prospectively, to allow a thorough evaluation of cost effectiveness and cost–benefit analysis.

Experts advise caution in the widespread implementation of such new technologies [9.5]. If the identification of target tissues is uncertain when margins around target volumes are tight, the likelihood of geographical misses or underdosing of the target increases.

### 9.2.2. Image guided radiation therapy

IGRT can be defined as increasing the precision of radiotherapy by frequently imaging the target and/or healthy tissues just before each radiotherapy session and acting on these images to adapt the treatment. There are several image guidance options available: non-integrated CT scan, integrated X ray (kV) imaging, active implanted markers, ultrasound, single slice CT, conventional CT and integrated cone beam CT [9.6].

Safety margins are used to account for geometrical uncertainties during radiotherapy (patient movements, internal organ movements). In many cases, these margins include part of the organs at risk, thereby limiting dose escalation. The aim of IGRT is to improve accuracy by imaging tumours and critical structures just before irradiation [9.6]. The availability of high quality imaging systems and automatic image registration has led to many new clinical applications, such as high precision hypofractionated treatments of brain metastases and solitary lung tumours with on-line tumour position corrections (Fig. 9.1).

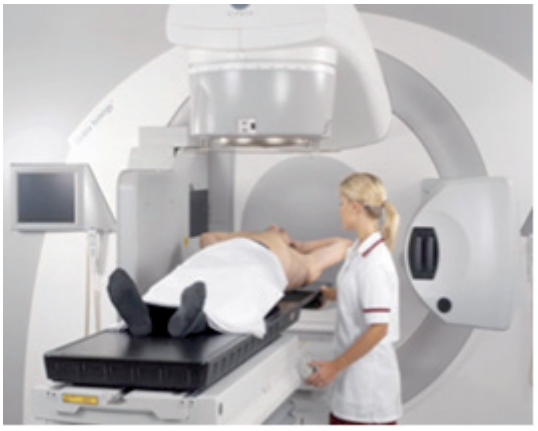

*FIG. 9.1. Image guided radiation therapy (IGRT) integrated imaging system based on kilovoltage cone beam CT (image courtesy of Elekta).*

### 9.2.3. Helical tomotherapy

Helical tomotherapy is a modality of IMRT in which the radiation is delivered slice by slice (hence the use of the Greek prefix *tomo-*, which means ‘slice’). This method of delivery differs from other forms of external beam radiotherapy in which the entire tumour volume is irradiated at one time [9.7] (Fig. 9.2).


*FIG. 9.2. Helical tomotherapy unit (image courtesy of Accuray).*

Radiotherapy has developed with a strong reliance on homogeneity of dose throughout the tumour. Helical tomotherapy embodies the *sequential* delivery of radiation to different parts of the tumour, which raises two important issues. First, this method, known as 'field matching', brings with it the possibility of a less than perfect match between two adjacent fields with a resultant 'hot spot' and/or 'cold spot' within the tumour. The second issue is that if the patient or tumour moves during this sequential delivery, then, again, a hot or cold spot may result. The first problem can be overcome, or at least minimized, by careful construction of the beam delivery system. The second requires close attention to the position of the target throughout treatment delivery. Generally, dose homogeneity is lower in IMRT than in 3-D CRT, which may account for the relative lack of concern regarding the field matching issue.

### 9.2.4. Volumetric modulated arc therapy

Volumetric modulated arc therapy (V-MAT) is a technique that delivers a precisely sculpted 3-D dose distribution with a single 360 degree rotation of the linear accelerator gantry [9.8]. It is made possible by a treatment planning algorithm that simultaneously changes three parameters during treatment:

(1) Rotation speed of the gantry;
(2) Shape of the treatment aperture using the movement of MLC leaves;
(3) Delivery dose rate.

V-MAT differs from other techniques, such as helical tomotherapy or intensity modulated arc therapy (IMAT), in that it delivers doses to the whole volume, rather than slice by slice. The treatment planning algorithm contributes to the treatment precision, helping to spare normal healthy tissue.

### 9.2.5. Stereotactic radiotherapy

Stereotactic radiotherapy (also called 'radiosurgery', although there is no surgery involved) consists of the delivery of a relatively high dose of radiation to a small volume, using a precise stereotactic localization technique. The stereotactic component of the technique refers to immobilization or fixation of the patient with a rigid head frame system that establishes a patient specific coordinate system for the entire treatment process [9.9]. This modality is usually applied in the treatment of intracranial tumours. After placement of the head frame, typically by use of four pins that penetrate the scalp and impinge the outer table of the skull, an imaging study (CT, MRI) is performed to localize the target volume relative to the head frame coordinates.

Stereotactic radiotherapy can be delivered using a gamma knife device (Fig. 9.3). This machine uses 201 small $^{60}$Co sources collimated to converge in a small volume where the lesion is located. The gamma knife is a radiotherapy device specifically designed to treat intracranial lesions.


*FIG. 9.3. A modern gamma knife unit (image courtesy of Elekta).*

A linear accelerator (linac) can be modified to perform stereotactic radiotherapy (Fig. 9.4). The linac is modified to accept a tertiary collimator assembly to accurately position circular collimators to form small circular fields 4–40 mm in diameter. The peripheral dose is spread over a large volume by using radiation paths that follow arcs. Stereotactic radiotherapy remains a popular and growing modality, and its delivery technique continues to improve.

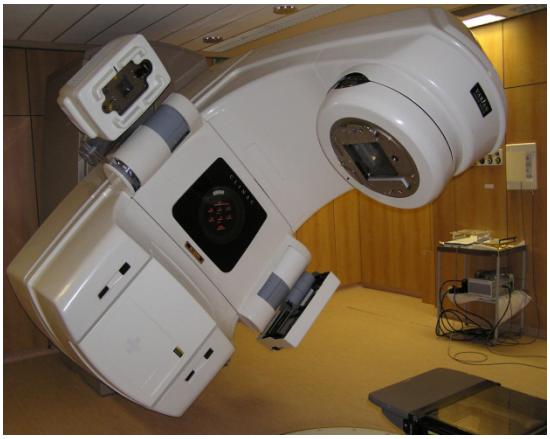

*FIG. 9.4. A linac commonly used in radiosurgery (image courtesy of Varian Medical Systems).*

Common clinical situations treated with stereotactic radiotherapy include small intracranial tumours in general, pituitary adenomas, small meningiomas, acoustic neuroma, craniopharyngioma, pineal tumours, brain metastasis or non-malignant conditions such as arteriovenous malformations. Stereotactic body radiotherapy (SBRT) is being used to treat localized lung and liver tumours.

### 9.2.6. Robotic radiotherapy

Robotic radiotherapy is a frameless robotic radiosurgery system (Fig. 9.5). The two main elements of robotic radiotherapy are the radiation produced from a small linac and a robotic arm that allows the energy to be directed at any part of the body from any direction.

The robotic radiotherapy system is a method of delivering radiotherapy with the intention of targeting treatment more accurately than can be achieved with standard radiotherapy. It is not widely available, although the number of centres offering the treatment around the world has grown in recent years to over 150, particularly in North America, East Asia and Europe. The robotic radiotherapy system is used for treating malignant tumours, benign tumours and other medical conditions.


*FIG. 9.5. A CyberKnife® robotic radiotherapy unit.*

### 9.2.7. The fourth dimension: Time and movement

Radiation oncologists face particular problems in regions of the body where organs and tumours move during treatment. Movement of the target due to respiration or for any other reason during treatment increases the risk of it being missed or underdosed, while increasing the planned dose to healthy tissues. As the delivery of the radiation dose becomes more and more precise, movement of organs and tumours becomes a significant factor influencing the accuracy of the dose delivery. This is particularly dramatic for chest located tumours, since they move during breathing. However, tumours located in the larynx, abdomen (liver), prostate, bladder, and in the pelvis in general also move during and between treatment applications.

Through the development of respiratory gated radiotherapy, tumour motion can now be taken into account very precisely [9.10]. In computer driven respiratory gated radiotherapy, a small plastic box with reflective markers is placed on the patient's abdomen. The reflecting markers move during breathing, and a digital camera hooked to a central processing unit monitors these movements in real time. A computer program analyses the movements and triggers the treatment beam synchronized with the respiratory cycle. With this technique it is also possible to choose the respiratory phase; depending on its location, the tumour can be irradiated during inspiration or expiration. Therefore, the tumour will always be encompassed by the radiation beam while avoiding the excessive exposure of critical organs.

### 9.2.8. PET in radiotherapy treatment planning

Recent years have seen an increasing trend in the use of PET and PET–CT imaging in oncology. Along with diagnosis, staging, relapse detection and follow-up, one of the main applications of PET–CT is the assessment of treatment response and treatment planning. PET provides molecular information about the tumour microenvironment ('functional imaging') in addition to anatomical imaging. Therefore, it would be highly beneficial to integrate PET data into radiotherapy treatment planning. The use of functional imaging to better delineate the treatment target is a good example of individualized treatment. In fact, instead of using a previously established field or set of fields, the radiation dose is shaped based on the tumour for each individual patient [9.11]. PET–CT radiotherapy treatment planning is an evolving strategy which presents some obstacles that need to be addressed. This is currently the topic of intensive research work.

### 9.2.9. Particle therapy: Proton beam and heavy ions

The advance of technology in recent decades has also led to the increasing use of particle therapy in the field of radiation oncology. Increasing attention has been focused on the application of proton beam therapy. According to data from the Particle Therapy Co-operative Group, as of January 2017, there were 61 proton therapy centres in operation worldwide, and more than 131 000 patients had been treated with this modality. The number of operating proton centres is projected to increase in the future.

The advantage of particle therapy, including proton therapy, is that the particle beam can provide a more favourable dose distribution compared with photon beam (X ray) radiotherapy. A particle beam deposits its energy at a certain depth as a sharp energy peak, called a Bragg peak, releasing a much lower dose before, and almost none after, the Bragg peak. Thus, by manipulating this characteristic (modulating the Bragg peak), particle therapy can yield a better dose distribution than photon therapy, providing the therapeutic dose to the tumour while minimizing unnecessary dose to the healthy tissues [9.12–9.14].

One of the main issues surrounding the application of proton therapy is the paucity of evidence of clinical benefit from comparative controlled clinical trials. While the superiority of the dose distribution of proton therapy has been clearly shown in physical studies, the clinical evidence comes mostly from phase II studies or retrospective series.

Cost effectiveness is another concern currently surrounding proton beam therapy. The implementation of proton therapy requires a sophisticated facility with accelerators such as cyclotrons or synchrotrons. In order to include proton

therapy as a part of standard cancer treatment modalities, socioeconomic cost–benefit analysis would be required [9.15].

The main issues surrounding the application of proton and carbon ion radiotherapy (Fig. 9.6) are similar, namely the lack of evidence from randomized controlled clinical trials and the high cost. While conducting randomized controlled studies may be difficult for such highly specialized treatment, objective analysis of outcome data, such those from matched-pair controlled studies, is warranted to assess the true benefit of particle therapy. The cost of implementing carbon ion therapy is higher than that for proton therapy. While the effort to downsize the scale and cost of carbon ion therapy facilities is ongoing, a cost−benefit analysis would be necessary when considering the significant initial capital investment required to implement this modality at present.

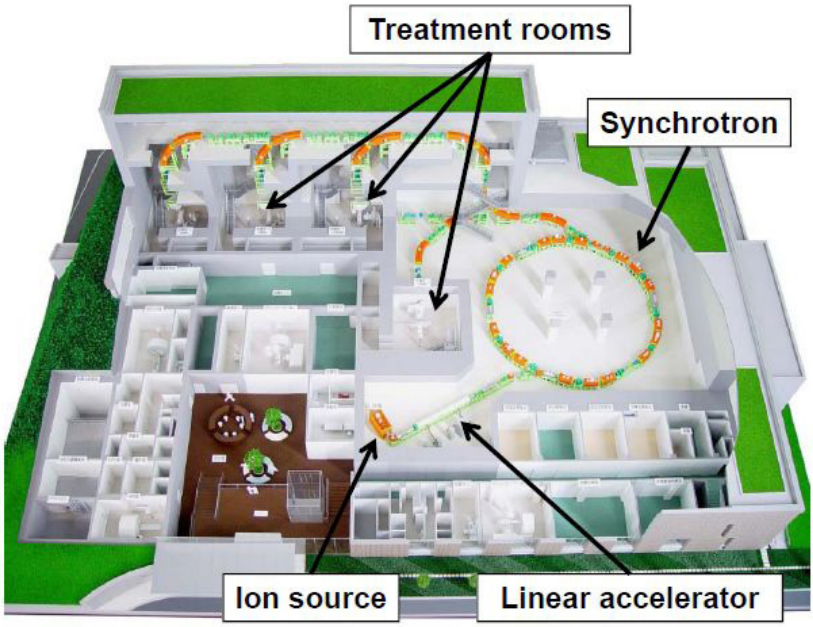


*FIG. 9.6. Schematic diagram of a carbon ion therapy facility (image courtesy of Gunma University Heavy Ion Medical Center).*

### 9.2.10. Introduction of advanced technologies: The radiation oncologist's perspective

The implementation of advanced radiotherapy technologies tends to distance the physician from the patient, a trend that needs to be consciously counterbalanced through a more personal and holistic approach. In addition, such technologies make it more and more difficult for the treating staff to intuitively understand the relationship between the radiation fields and the patient's anatomy. Whereas with 3-D CRT, the physician can rely on port films to assess the irradiated volume, with IMRT the physician must rely on tools such as computer simulations and dose volume histograms. Users of advanced technologies should be cautioned not to become too dependent upon the technology itself. It is also recommended that advanced technologies such as IMRT/IGRT not be acquired until physicians and other radiotherapy staff are fully experienced with treatment planning techniques in 3-D CRT over a number of years.

Modern 3-D approaches including IMRT introduce new requirements in terms of the understanding of axial imaging and tumour/organ delineation. The recent literature points to an uncertainty level at this stage known as 'inter-observer variation'. Efforts continue aimed at harmonizing the criteria with which tumours, organs and anatomical structures are contoured by the radiation oncologist as well as how volumes are defined [9.16, 9.17].

### 9.2.11. Introduction of advanced technologies: The medical physics perspective

The introduction of IMRT and stereotactic radiotherapy procedures brings with it special physics problems. For example, it is required that calibrations be performed in small fields, where dosimetry is challenging and no harmonized dosimetry protocol exists. Use of the correct type of dosimeter is critical and errors in measurement can be substantial. Several new treatment machines provide radiation beams that do not comply with the reference field dimensions given in existing dosimetry protocols, complicating the accurate determination of dose for small and non-standard beams.

The introduction of highly precise collimators (and their use in IMRT), small fields, robotics, stereotactic delivery, V-MAT and image guidance has brought new challenges for commissioning and quality assurance (QA). Existing QA guidelines are often inadequate for these new technologies. New QA procedures are needed and are currently under development.

In the meantime, the existing paradigm of commissioning followed by frequent QA should continue, with attention paid to the capabilities offered by

the new technologies. Risk management tools should be adapted from other industries, to help focus QA procedures where they can be most effective [9.18].

### 9.2.12. Brachytherapy

Brachytherapy is the administration of radiotherapy by placing radioactive sources adjacent to or into tumours or body cavities. With this mode of therapy, a high radiation dose can be delivered locally to the tumour with rapid dose fall-off in the surrounding normal tissues. In the past, brachytherapy was carried out mostly with radium or radon sources. Currently, use of artificially produced radionuclides such as $^{137}$Cs, $^{192}$Ir, $^{198}$Au, $^{125}$I and $^{103}$Pd is well established.

According to the International Commission on Radiation Units and Measurements (ICRU) [9.19] definition, high dose rate (HDR) brachytherapy means more than 12 Gy/h, although the usual dose rate delivered in current practices is about 100–300 Gy/h. The use of HDR (Fig. 9.7) has the advantage that the treatments can be performed in a few minutes, allowing them to be administered on an outpatient basis, with minimal risk of applicator movement and minimum patient discomfort. Remote controlled afterloading brachytherapy devices eliminate the hazards of radiation exposure.

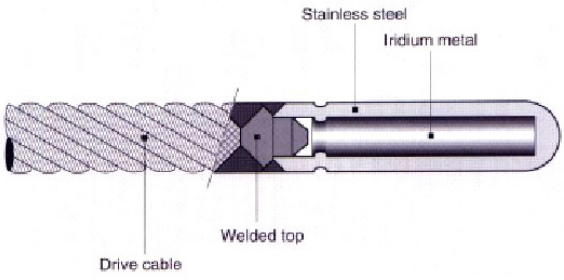


*FIG. 9.7. An HDR brachytherapy microsource (image courtesy of Elekta).*

Brachytherapy is essential for the curative treatment of cancer of the uterine cervix. In this particular setting, IMRT cannot replace brachytherapy as a curative treatment component. Brachytherapy has also become very popular in the management of prostate cancer, with two decades of experience and very encouraging results.

A recent development in the field of HDR brachytherapy consists of the miniaturization of $^{60}$Co sources into microsources the same size as HDR $^{192}$Ir sources. These new systems have the same versatility as all modern afterloading HDR systems, but with the added advantage of using an isotope

with a half-life of 5.27 years. This permits replacement of the source every five years instead of every three–four months, as is the case with $^{192}$Ir. The savings in terms of resources, time, and source import and replacement procedures is significant [9.20].

Currently, image based treatment planning for gynaecological brachytherapy takes full advantage of modern imaging techniques (CT, MRI) to visualize the tumour, the applicators and the organs at risk, and to prescribe the doses accurately to predefined volumes and with dose volume constraints [9.21, 9.22].

### 9.2.13. Introduction of new technologies in developing countries

The potential or actual use of new advanced technologies in developing countries raises questions about cost, efficacy and ethics. The increased capital and operating costs and the economic burden of increased QA is a challenge [9.5, 9.23]. Stereotactic radiosurgery, SBRT, proton and other charged particle therapies using single or hypofractionation regimens have the advantage of saving time, but require well qualified personnel and excellent QA/quality control (QC) programmes, as there is little chance of adjustment once the treatment has been initiated.

The major concerns regarding the introduction of technically advanced equipment and techniques in developing countries are [9.24]:

(a) Appropriate resources and qualified and trained staff for the accurate delivery of high therapeutic radiation doses;
(b) Infrastructure requirements capable of handling this technology most efficiently and effectively;
(c) Types and stages of cancers to be treated;
(d) Development of commissioning and QA/QC protocols;
(e) Institutional resources and clinical backup to deal with increased downtime for the more complex technologies.

Needs for technologically advanced radiation oncology in developing countries must be considered in the context of the need for other essential infrastructure in order to allow a smooth, incremental and safe progression to advanced radiotherapy services.

An important theme echoed by experts from developing countries is the global shortage of skilled professionals [9.3, 9.5, 9.25]. It is noted that, while short term and local solutions have been devised, there is a need for a long term strategy to establish training programmes and produce trainers and educators who could increase the availability of adequately trained staff in the radiotherapy

disciplines. Training must be adapted to both the working environment and the available technology; little benefit is derived by a trainee or the trainee's institution when the education addresses a technology that is not available in his or her own country.

There is clearly a role for collaboration at the national and regional levels to support education networks. The role of the IAEA in education and training through national and regional training courses and development of teaching materials and syllabi has been recognized by other international/professional organizations as well as by radiotherapy professionals in its Member States.

## 9.3. SUMMARY

Recent technological developments in radiation oncology have brought with them improved dose distributions and reduced toxicity in selected tumour sites. Improved dose distributions and reduced toxicity in turn may mean potentially higher chances of local tumour control and improved cure rates. These, coupled with increased revenues, make these techniques very popular among radiation oncologists and hospital administrators. The clinical scientific evidence regarding local tumour control and overall cancer survival is generally inconclusive at this time.

More clinical trials are necessary to demonstrate the benefits of advanced technologies before they are adopted for widespread use. A new and unproven technology should not be universally adopted *as a replacement* for established, proven technologies. Countries with limited resources should avoid the risk that hasty implementation of new technologies would limit patients' access to well established methods of treatment.

## 9.4. KEY POINTS

— Intensity modulated radiation therapy (IMRT) is a sophisticated form of three dimensional conformal radiotherapy that assigns non-uniform intensities (fluences) to tiny subdivisions of beams called beamlets.
— Image guided radiation therapy (IGRT) can be defined as increasing the precision of radiotherapy by frequently imaging the target and/or healthy tissues just before treatment and acting on these images to adapt the treatment.
— Helical tomotherapy is a modality of IMRT in which the radiation is delivered slice by slice. This method of delivery differs from other forms of

external beam radiotherapy in which the entire tumour volume is irradiated at one time.

— Volumetric modulated arc therapy (V-MAT) is a technique that delivers a precisely sculpted 3-D dose distribution with a single 360 degree rotation of the linear accelerator (linac) gantry.
— Stereotactic radiotherapy consists of the delivery of a relatively high dose of radiation to a small volume using a precise stereotactic localization technique.
— Robotic radiotherapy is implemented using a frameless robotic radiosurgery system. The two main elements of robotic radiotherapy are the radiation produced from a small linac and a robotic arm that allows the radiation beam to be directed at any part of the body from any direction.
— The advance of technology in recent decades has also led to the increasing use of particle therapy in the field of radiation oncology. Greater attention has been focused on the application of proton beam and carbon ion beam therapy.
— As the delivery of the radiation dose becomes more and more precise, movement of organs and tumours becomes a significant factor influencing the accuracy of the dose delivery. Through the development of respiratory gated radiotherapy, tumour motion can now be taken into account very precisely.
— A recent development in the field of high dose rate (HDR) brachytherapy consists of the miniaturization of $^{60}$Co sources into microsources the same size as HDR $^{192}$Ir sources.
— More clinical trials are necessary to demonstrate the benefits of advanced technologies before they are adopted for widespread use.
— With the introduction of any advanced technology such as IMRT and IGRT, data should be collected prospectively, to allow a thorough evaluation of the cost effectiveness and a cost–benefit analysis.

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# Chapter 10

# INTENSITY MODULATED RADIATION THERAPY AND IMAGE GUIDED RADIATION THERAPY: AN OVERVIEW

**A.C. Bernhardt**

## 10.1. HISTORICAL DEVELOPMENT

Ionizing radiation has been related to medicine since its discovery (see Milestones in Cancer Radiotherapy and Imaging). The ability to visualize the inside of the body by contrasting soft and bone tissues was the first capability of X rays exploited and was the beginning of a path that has brought medical imaging to the heights it occupies today. The harmful side of X rays was only discovered by chance, by Henri Becquerel, and subsequently tested by Pierre Curie, who carried out the first experiment on himself.

The use of radiotherapy to treat malignant diseases offered a good alternative to surgery, resulting in a rush during which almost all patients wanted to be treated with it. But the disadvantages were slowly becoming apparent, showing the hazards of ionizing radiation. Minor and major complications were reported, and the ability to induce tumours was recognized. Since then, radiation oncology has become the art of balancing between destroying the tumour and protecting healthy tissues. More than a hundred years of retrieving information and experience from patients has helped build a medical specialty that represents one of the most important modalities to treat, relieve and control cancer.

It was recognized early on that higher radiation doses were needed to achieve tumour control, but complications with healthy tissue ensued which were only partly resolved by the use of radiotherapy fractionation. Combining radiotherapy with surgery and chemotherapy was feasible and served as an effective strategy to solve this problem.

Medical physics in the early years was confined to verifying both that the equipment was delivering the calculated dose and the calibrations. Dose calculations in the patient were difficult to carry out; looking back, they were, at the most, reasonable approximations of what can be done today. Homogeneous and flat radiation beams were indicators of good treatment. Cobalt-60 machines were introduced in the 1950s, providing a better way to irradiate deep seated targets. Wedge filters and compensators (Ellis) were used to overcome anatomical diameter differences. Parallel opposed fields or orthogonal fields could help concentrate the dose on targets while attempting to avoid healthy tissues. Targets

were defined on plain X ray films or guessed from surgery reports. Linear accelerators (linacs) became widely available in the 1960s and with them, the need for measuring and controlling the delivered dose. Radiotherapy using electron beams was also available, opening a new and challenging way to deliver radiation.

The introduction of computers in the 1980s changed everything in radiation oncology, making detailed iterative mathematical calculations possible, providing information on the patient's actual anatomy and allowing the performance of reliable patient dosimetry. Dose calculations could now be performed in a volume instead of only in one point, and this major advance led to three dimensional conformal radiotherapy (3-D CRT) in the early 1990s. This completely new approach required additional work. The possibility of determining the target, the lymphatic pathways involved and the neighbouring organs that could be affected demanded new knowledge and skills from the radiation oncologist. Calibration of the equipment and the commissioning of treatment planning systems (TPSs) became more important. Quality assurance (QA) demanded much more machine and staff time than did the older techniques.

Recently, 3-D CRT has made its way into routine radiation oncology, showing that either radiation toxicity could be reduced while keeping the same dose levels or the dose could be increased while maintaining the toxicity levels already known. The workload of physics departments grew, and QA became a major part of their duties. At the same time, there were significant strides in medical imaging with the introduction of computed tomography (CT) scans and magnetic resonance imaging (MRI). Integration of these methods into TPSs was rapidly achieved. This was followed by functional imaging, with positron emission tomography–computed tomography (PET–CT) and MRI spectroscopy or MRI diffusion, allowing better definition of targets even in areas where no suspected lesion could be seen.

The use of various beam arrangements was considered in order to cover volumes better and to save more healthy tissue. However, there were still some difficulties irradiating targets close to sensitive structures such as the brain and spinal cord. This new technology enabled the implementation of more personalized treatments. In the process, the long supported paradigm that a beam arrangement should deliver a homogeneous dose to the target was challenged. Why not treat the tumour by using several different beam apertures in the same angle and modulate the 'intensity' (fluence) of that beam?

As a result, intensity modulated radiation therapy (IMRT) was introduced in the new millennium. Steep dose changes could then be planned, allowing the target dose to be raised to new levels by keeping the dose in the organs at risk (OAR) as low as possible. This was only possible because tools became available to verify the calculated plans on high performance phantoms or

chamber arrangements. Multileaf collimators (MLCs) became available and made the delivery of complex treatments feasible within an acceptable time span. The positioning and immobilization of patients improved, becoming accurate to within millimetres. This was very soon recognized as an important prerequisite to delivering IMRT treatments. With the dose delivery reaching a precision of the order of a few millimetres, patient and organ movements now became a critical issue. The movement of organs (and tumours), which was not a critical issue in the two dimensional (2-D) radiotherapy era, became critical when a very accurate system was delivering a very precisely defined high dose, but to the wrong volume. Onboard imaging, together with the use of new fiducial markers placed within the target, became routine and the image guided radiation therapy (IGRT) concept was born. However, where do all these advances lead us?

## 10.2. INTENSITY MODULATED RADIATION THERAPY

The ability to build sharp dose differences between the target tissues and OAR using IMRT is very appealing, but this can also be done appropriately with 3-D CRT. A major improvement is the possibility of shaping doses into invaginations of the target. Concave dose distributions are desirable when critical structures are very close to or protrude into the target volume. Implementation of this treatment modality is not simple and requires a completely new staff approach [10.1]. There are various techniques to implement IMRT, but most agree that this is not just a simple new modality that can be added to the therapeutic arsenal, but rather a completely new philosophy [10.2]. 'Intensity' (fluence) modulation can be based on the use of an MLC or on compensating filters [10.2]. MLC based IMRT can be delivered using multiple segments in a field, which creates the desired intensity variation. This is known as 'step-and-shoot' IMRT. Another way is to have the leaves moving across the field at various speeds or rates, known as the 'sliding window' technique.

In 3-D CRT, fields are conformed to the targets' irregular shapes; this can be visualized using a tool called a 'beam's eye view', providing a possible solution to the TPS known as forward planning. In IMRT, the solution is found by an 'inverse planning' approach. There are thousands of different possible beam arrangement solutions to fulfil a specified treatment objective, with a variety of different dose distributions to the OAR. To try them all until the best fitted one is found would be a very cumbersome and almost impossible task without the aid of a computer program. Therefore, this task is carried out by the planning software using an inverse planning approach. The planner establishes the dose range goals and dose constraints at the different planned volumes and OAR. The

software, ranking these plans by cost functions, then produces the 'best' possible plan solution [10.3].

IMRT demands a high level of precision and accuracy that starts with the proper selection of the patient with a clear indication for IMRT. It is not necessarily a modality reserved only for curative treatments, but the patients must be able to support long immobilization times and should be cooperative [10.1]. The radiation oncologist must not only define the target volume, but also clearly define all OAR and communicate the goals of the treatment, clearly establishing the priorities and dose constraints [10.1, 10.2, 10.4]. The physicist's tasks have increased significantly, since QA and quality control (QC), dose verification and reporting are different and more demanding than is required for 3-D CRT [10.2]. MLC QA demands a high level of accuracy in leaf positions, leaf gap, leaf speed and dose leakage between leaves [10.1, 10.2, 10.4]. All these parameters must be considered in the final selected plan. An IMRT treatment often requires a large number of beams, each of them with many parameters and several beamlets, which makes it almost impossible to handle or transfer manually from the TPS to the linac. This means IMRT, at least with MLCs, should rely on a record and verify system (RVS) [10.4]. The TPS should run using a known algorithm, and the staff must be aware of it and be familiar with its limitations [10.1]. Patient positioning and immobilization are some of the most important aspects of the process [10.1, 10.5]. Positioning must not only be reproducible but very accurate, and organ immobilization systems or devices are often required.

Patient imaging also demands a high degree of accuracy. In addition to the anatomical area to be treated, the required volume must be determined in case non-coplanar beams are deemed necessary. Multiple modality images may be required, and they must be fused in the TPS to ensure a correct delineation. Once the patients' images are in the TPS, all structures must be accurately delineated, namely the targets, OAR and non-target regions. Sometimes, regions located far from the treatment volume must be specified to avoid overdosing. Delineation and contouring of targets and organs have become a new and important component in the training of radiation oncologists. The fact that different specialists will draw different volumes for the same patient is well known (inter-observer variations), and the development of atlases for this purpose is recommended [10.6].

The desired doses and dose constraints must be clearly communicated, because the inverse calculation will produce many possible solutions, some better and some worse, until the goal is achieved. Special attention must be paid to the fact that too many beams or too many segments can protract the fraction too long, leading to immobilization difficulties [10.5], monitor units that are too high [10.1] and potential inaccuracies. The guiding concept should be 'as good as reasonably achievable' (AGARA), as stated by Galvin et al. [10.1]. TPSs

will produce various possible solutions. The choice of the optimal one for the individual patient is made by the radiotherapy team.

Verification of the plan is of paramount importance; all steps in the process must be recorded thoroughly and an independent dose calculation method should be used to verify the doses [10.1, 10.2]. Dose comparisons among centres in order to validate the entire process are encouraged [10.1, 10.3].

## 10.3. IMAGE GUIDED RADIATION THERAPY

Bony anatomy is easily seen with an X ray, as opposed to soft tissue. In the past, this property was widely exploited as a set-up verification method, assuming that the bony anatomy could be a good reference for the planned treatment volume. Sometimes other fiducial markers were placed to help define the target volume, such as metal clips in the surgical tumour bed [10.7].

With technological advances and better target definition has come the need for more accurate patient positioning, allowing more precise dose delivery. The IGRT concept requires that images be taken in the treatment room and compared with previously defined reference images. The patient is then moved to the congruent position before the treatment is delivered [10.8]. This enhances the treatment precision and enables dose escalation, which is sometimes referred to as ‘adaptive radiotherapy’ [10.1].

There are many ways of performing IGRT, depending on the imaging method used. This can be kilovolt or megavolt imaging using fiducial markers, ultrasound, or kilovolt or megavolt scan images, allowing for different levels of precision. It is very important to be aware of the capability of the method that is being implemented and the particular constraints it can impose, such as operator ability in the case of ultrasound imaging. Depending on the target, there will be some imaging modalities that may or may not fit the requirements. Therefore, the IGRT imaging modality must be chosen depending on the clinical objective. If the aim is to correct only for interfraction displacements (set-up differences), the modalities can be different from the ones chosen for intrafraction movements, such as for stereotactic body radiotherapy. The use of fiducial markers placed in soft tissues can be very helpful in defining the target’s position, but little or no information will be available regarding changes in the target’s size or shape [10.8]. It is the radiation oncologist’s responsibility to know what to expect from an IGRT imaging modality and to decide whether or not the observed displacements are acceptable. Sometimes, different modalities must be combined to ensure the correct visualization of the target position.

Special attention must be paid to the commissioning and acceptance of the IGRT imaging modality as well as to staff training in these concepts. Regular

calibrations are mandatory; it is important to record displacements for a given patient and to ensure correct communication between the IGRT imaging source and the linac. All these must be part of the regular QA programme. Clear guidelines should be developed and be made available in each centre, establishing the threshold for patient displacement and action levels allowed to each staff member [10.8].

## 10.4. CLINICAL OUTCOMES

There are still too few randomized controlled trials comparing IMRT with other radiotherapy techniques to confirm what has been shown by case control studies [10.9]. Therefore, clinical trials are encouraged in order to demonstrate whether these new efforts are worthwhile [10.6].

The implementation of an IMRT programme requires a significant effort and represents an important change for the whole radiotherapy department. The implied costs are considerable. As a result, a major debate about the real impact of the new technologies arose very early on to clarify whether these investments are worth their cost.

Earlier studies showed the potential impact of IMRT in reducing radiation side effects in head and neck cancer patients, including xerostomia, which has a huge negative impact on a patient's quality of life [10.9]. This by itself could justify the implementation of an IMRT treatment programme.

Other publications showed encouraging results in the treatment of prostate cancer, a very common cancer recognized as a dose dependent tumour susceptible to control by dose escalation [10.10, 10.11]. Almost all authors recommended a thorough and careful implementation of IMRT and a careful evaluation of results. An article in the journal Medical Physics [10.12] argued that IMRT may be used excessively in the United States of America because of its higher reimbursement rates compared with other treatment techniques.

What is the situation almost a decade later? The role of head and neck IMRT in salivary gland treatment is well established [10.9, 10.13, 10.14], but whether this has a real impact on the patient's quality of life is still a point of debate [10.9, 10.15]. The use of IMRT demands a significant effort and a clear understanding of each step of the process — it is more labour intensive and expensive than other methods [10.16]. Set-up reproducibility is very important and IGRT is not always used with IMRT, leading to difficulty in achieving the established goals in the radiation oncology community [10.16]. There is still room for improvement, including learning how to better define targets and learning from the pathophysiology of saliva secretion and swallowing functions.

The discussion on whether or not IMRT should be used in prostate cancer is ongoing. Data still do not support the use of IMRT over 3-D CRT [10.17], and there are significant cost differences involved [10.18, 10.19]. In the early stages, prostate cancer control rates achieved by good quality 3-D CRT or other means, such as brachytherapy or radical prostatectomy, are almost equivalent [10.20]. De Crevoisier et al. [10.21] showed the importance of IGRT when IMRT is used for prostate cancer. This study showed that when prostate cancer patients who had rectal distension in the planning CT were treated without daily image guided prostate localization, they suffered from decreased biochemical and local control and had more rectal toxicity. This clearly highlights the relevance of IGRT when performing IMRT for prostate cancer treatment.

Breast cancer patients often require radiotherapy treatment. The traditional opposed tangential, wedged fields have been used since the 1980s, allowing better sparing of lung tissue, but sometimes the dose distribution is not as good as is desired. Treatment of large breasts, the left breast (due to the presence of the heart in the high dose volume) or patients who also require elective lymph node irradiation represents a challenge to dosimetrists. Breast IMRT studies have shown that the use of these techniques can reduce the acute and late complications of breast irradiation [10.9]. In the context of breast IMRT, concern has been expressed regarding the need to clearly establish if multiple subfields can or cannot be considered IMRT [10.22].

## 10.5. DISCUSSION

No one can doubt that the clinical introduction of IMRT more than ten years ago has provided major benefits to patients. Anyone who has compared the uncertainties of 2-D radiotherapy to 3-D CRT and to IMRT can see how much progress has been made. However, this progress has been difficult to document in published research. This may be because of the difficulty of reflecting in publications the subjective changes in treatment quality and patient quality of life. Or perhaps because too many started too early, using an immature technology, swayed by the potential clinical (or economic) benefits, prescribing IMRT for cancers or anatomical sites that did not require or benefit from it, the actual outcomes were blurred. The implementation speed of IMRT in the United States of America was (or still is) completely different than in Europe, where the average use is lower.

An interesting question that should be answered is: What is IMRT? There are several definitions based on who is defining the technique. For example, for some authors, the use of inverse planning is required for an approach to qualify as IMRT [10.3]. For others, IMRT can have no more than a certain number of fields

in the same axes [10.9]. Class solutions or geometrical solutions used to treat almost all patients in a given anatomical region (e.g. prostate cancer) would not qualify as IMRT using the inverse planning requirement. In an attempt to find the best way to treat prostate cancer, a comparison of different available approaches and methods has been published. Using the same data set, a total of 34 different techniques and planning systems were evaluated; the four best ranked plans all involved forward planning IMRT [10.23].

Peters et al. [10.24] reported on the clinical impact of QC and protocol compliance in patients with advanced head and neck cancers treated in the TROG 02.02 trial. They showed that noncompliance with the radiotherapy plans had a major negative impact on the treatment results. The patient group with the compliant plans had a two year overall survival rate of 70%, compared with 50% for those patients with major deviations from the requested radiotherapy. This trial enrolled over 818 patients in 81 different centres, and the treatment was either standard head and neck radiotherapy or forward planning 3-D CRT, but no IMRT treatments were included. The authors also showed that the centres enrolling more patients (over 20) had a better compliance rate than those centres enrolling fewer than five patients. Interestingly, the authors concluded that the effect of a good radiotherapy technique overrides the effect of the added chemotherapy drugs, which in many cases add an important economic burden to the treatment. Although one could argue that the IMRT techniques for head and neck cancers could overcome the technical problems, the lack of significant improvement in overall survival and quality of life in head and neck cancer patients treated with IMRT could be explained by a similar 'non-compliance' effect.

Prostate cancer has progressed from being a 'radioresistant' tumour to a radiosensitive one in recent decades. The impact of dose escalation has been proved, and the quest to deliver even higher doses to the prostate gland continues. There is still no 'winning' treatment in the race between urologists and radiation oncologists for local control. Both groups have achieved comparable rates of biochemical (PSA) disease free patients at five or more years of follow-up despite the T stage.

Why is this? If we consider that a cancer can only be cured if all cancer clonogenic cells are eradicated, then the logical explanation is that we are not eliminating all these clonogenic cells with our current techniques. An important clonogenic cell hiding place is the lymph nodes, and this might be the reason why we cannot achieve better disease control. An important proportion of prostate sentinel lymph nodes are located outside the obturator and external iliac regions, thus not following an expected drainage pattern [10.25]. These regions are often not included in standard radiotherapy fields.

While better technology is available, and while it is ideal to be able to use it to benefit patients, completely new hazards are emerging with it. The New York

Times reported a radiotherapy accident that occurred in New York in relation to the use of these new technologies [10.26, 10.27].

There is a debate [10.28] regarding the issue of informatics in radiotherapy. Computerized treatment planning is an important field that provides significant benefits, but it can also be a source of great difficulties. Vendors often upgrade computer planning and operating systems, and sometimes the new releases do not allow previously installed programs, or parts of them, to run as expected. Modern radiotherapy departments are often part of a hospital network, sharing useful information, but also computer viruses. Many medical software vendors do not recommend the use of networks, but this is hardly practical in this day and age. Who is, or should be, responsible for the RVS software, networks and computers in a radiation oncology department?

On the other hand, the knowledge acquired from implementing these complex techniques has expanded the possibilities of 3-D CRT, making more challenging treatments feasible. TPS software and algorithms are more precise than in the past. Different image modality integration in the TPS for a more precise contouring of target volumes and the now better known dose tolerances to OAR facilitate a more robust and accurate 3-D CRT. The better and faster MLCs, with good QA programmes, allow more accurate shielding of healthy organs. Implementation of RVS software to connect the TPS with, and to control, the linacs also facilitates the use of more beams and treatment techniques, which would not be possible without this computerized control. In many cases, the use of the electron beam is no longer required to protect OAR (in head and neck or breast cancer), allowing the treatment of more cases in less expensive single energy linacs.

IGRT also has improved the aiming ability, which, together with a better understanding of different diseases, permits higher dose schemes to be prescribed. Today, IMRT treatment should probably not be started without the pertinent IGRT capabilities [10.21]. This does not mean that IMRT treatment can only be conducted with the aid of a cone beam CT system or similar system. Head and neck IMRT can be conducted using portal imaging and by referring to the bony anatomy, and the prostate can be treated with portals and fiducial markers or other methods, but a regular, and in most cases daily, position control of the target before treatment should be required for IMRT.

There is no doubt that modern technologies such as IMRT and IGRT have brought radiation oncology to a higher level, but we should be aware that there are very important issues to be resolved [10.6]. The IAEA has issued a publication to assist centres in moving along the path from 2-D radiotherapy to 3-D CRT, and from there to the more complex IMRT [10.3]. Whether or not this suggested path has been followed by the centres in the implementation of this more complex treatment technique is an open question. It is the responsibility of

each State to implement the needed controls and rules in order to ensure that the radiotherapy centres are complying with the recommendations of international bodies, including the IAEA, ensuring that patients are receiving high quality therapy.

Better imaging, better understanding of disease through cancer biology and radiobiology, and more robust and reproducible treatment techniques are of paramount importance if we are to achieve better cancer control by radiation. It is our responsibility to offer our patients the best, not the fanciest, treatment available.

## 10.6. KEY POINTS

— Intensity modulated radiation therapy (IMRT) treats the target volume by using several different beam apertures in the same angle and modulates the 'intensity' (photon fluence) of that beam.
— A major advantage of IMRT is the possibility of shaping doses into invaginations of the target. Concave dose distributions are desirable when critical structures are very close to or protrude into the target volume.
— The image guided radiation therapy (IGRT) concept requires that images be taken in the treatment room and compared with previously defined reference images. The patient is then moved to the congruent position before the treatment is delivered.
— Position control of the target by IGRT before treatment should be mandatory for IMRT.
— The implementation of an IMRT programme requires significant effort and investment of resources, and represents an important change for the entire radiotherapy department.
— Modern technologies such as IMRT and IGRT have brought radiation oncology to a higher level, but there are still very important issues to be resolved.

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# Chapter 11

# PROTON THERAPY: RATIONALE, CLINICAL OUTCOMES AND FUTURE DIRECTIONS

**G. Suneja, Z. Tochner**

## 11.1. INTRODUCTION

A central tenet of radiotherapy delivery is to maximize the tumour control probability (TCP) while minimizing the normal tissue complication probability (NTCP). Balancing TCP and NTCP, thereby creating a favourable therapeutic ratio, is particularly challenging for tumours located in close proximity to critical normal structures uninvolved with tumours [11.1]. Proton therapy is a type of non-invasive radiation which uses charged particles instead of X rays to more precisely deposit radiation dose as compared with traditional external beam radiotherapy. Proton therapy has the capacity to minimize entrance and exit dose, decrease integral body dose, and save normal tissues, organs at risk or previously irradiated tissue [11.2]. Therefore, proton therapy may deliver biologically equivalent doses of radiation with more precision and less treatment toxicity than conventional photon radiation. In this chapter, a summary is presented of the rationale, clinical outcomes and future applications of proton therapy.

## 11.2. HISTORY OF PROTON THERAPY

Robert Wilson, a physicist, became the first to describe the favourable dose distribution profile of protons in 1946 when he proposed that accelerated protons could be used for cancer therapy [11.3]. The first clinical use of protons was in the United States of America in the 1950s for pituitary hormone suppression in metastatic breast cancer patients [11.3–11.5]. By the late 1950s, high energy proton beams were being studied in animals for lesions of the hypothalamus, cerebral cortex, spinal cord and cerebral hemispheres [11.6, 11.7]. In the 1970s, proton therapy was used for uveal melanoma and base of skull tumours, and initial results were reported by the four existing centres at that time in France, Japan and the United States of America. Since that time, proton therapy has been used in the treatment of numerous cancers, including prostate cancer, head and neck cancers, and numerous paediatric malignancies. According to the Particle Therapy Co-operative Group (PTCOG), nearly 84 000 patients worldwide have

been treated with proton therapy. There are currently 71 particle therapy centres in clinical use around the world, with more under construction and projected to open by 2020 (see Fig. 11.1) [11.8].

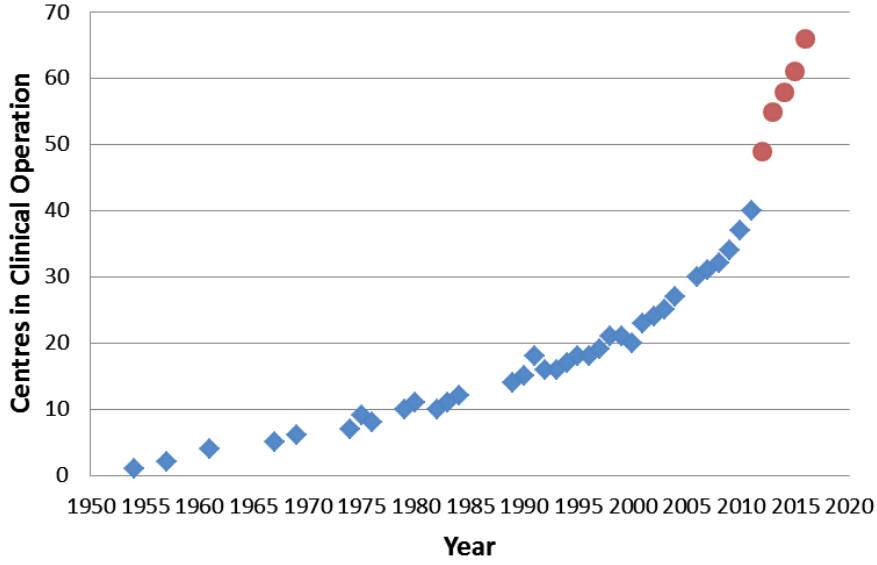


*FIG. 11.1. Trajectory of proton facility development. Blue dots represent facilities currently in operation, red dots represent facilities expected to open in the future.*

## 11.3. PHYSICAL PROPERTIES OF PROTON THERAPY

### 11.3.1. Dose distribution

Radiation works by causing ionization reactions in the nucleus of tumour cells, leading to irreparable DNA damage. Photons (i.e. traditional X ray based radiation) deposit high doses of radiation on the surface of the body, and absorbed dose decreases exponentially as the photon traverses to greater depth in tissue. Photons also deposit dose as they enter and exit the body. Protons, on the other hand, deposit little energy on the surface of the body. Because of their high velocity, protons produce more dense ionizations near the end of their path in tissue. The energy deposited at a given depth is inversely proportional to the square of the velocity of the particle. This release of energy (or dense ionization) is called a Bragg peak. In front of the Bragg peak the radiation dose is low, and beyond the Bragg peak the dose falls to zero over a very short distance. Varying the initial energy of the proton beam will result in a different depth at which

maximal energy deposition occurs. In order to cover an entire tumour volume, proton beams of different energies must be superimposed to create a spread-out Bragg peak (SOBP) that will cover the entire depth of the tumour. A comparison of photon and proton beam profile characteristics is seen in Fig. 11.2. The advantages of the improved proton dose distribution can be used either to treat tumours at high doses but maintain a similar normal tissue toxicity profile, or to treat tumours at the standard dose but lower the normal tissue toxicity profile as compared with photon radiation.

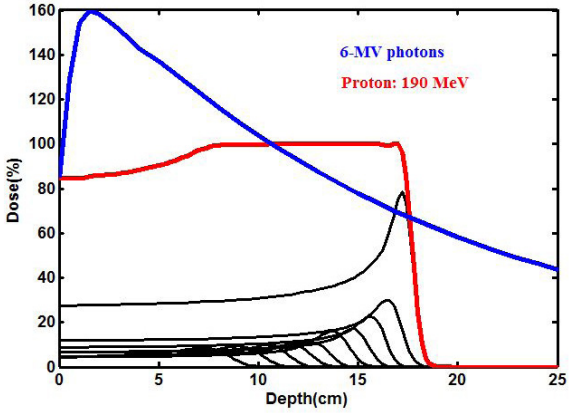


*FIG. 11.2. Schematic of Bragg peak and spread out Bragg peak (SOBP). Blue: 6 MV photon beam, black: proton beams of various energies with Bragg peaks, red: SOBP.*

### 11.3.2. Radiobiological effects

Relative biological effectiveness (RBE) is defined as the ratio of X ray dose producing a biological effect to particle dose required to produce the same effect. Heavy ions have a high linear energy transfer (LET), meaning the number of ionizations created is greater per unit of tissue traversed. Unlike heavy charged particles, which have a high RBE, and are therefore more effective at killing cells, protons have an RBE of 1.1, although the range varies from 0.7 to 1.6 over the SOBP [11.9, 11.10]. Protons and photons are generally regarded as having equal efficacy of tumour cell kill.

### 11.3.3. Dosimetric studies

Numerous dosimetric and treatment planning studies have compared dose distributions of conformal photon plans and proton therapy plans for many

tumour sites [11.2–11.15]. In general, they have found coverage of the planning target volume to be similar or slightly better with protons, but dose to critical avoidance structures and total integral dose are much lower with protons. In contrast to intensity modulated radiation therapy (IMRT), a highly conformal photon technique, proton therapy is associated with smaller volumes of normal tissue irradiation (see Fig. 11.3). Proponents of proton therapy have advocated for incorporation of proton therapy into routine clinical practice based on the large reduction in normal tissue dose seen in these planning studies, while others have raised the question of whether the improved dose profile will translate into a clinical benefit. Prospective randomized clinical evidence is limited. However, many prospective non-randomized and retrospective studies have been published, and the body of literature is growing rapidly as more proton centres are opened worldwide.

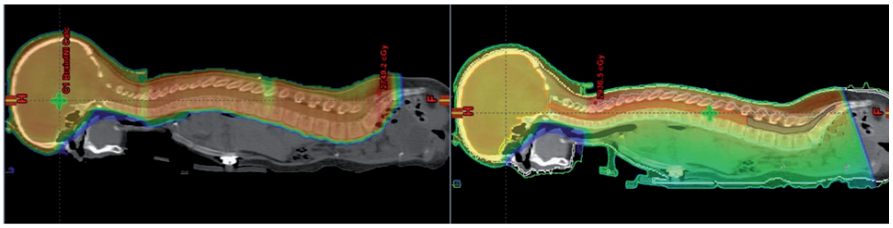


*FIG. 11.3. Comparison of proton versus photon treatment plan for craniospinal irradiation (CSI). In the case of proton CSI, significant irradiation of the contents of the thoracic and abdominal cavities is avoided.*

## 11.4. CLINICAL EVIDENCE AND OUTCOMES

### 11.4.1. Skull base and brain tumours

Chordomas and chondrosarcomas are rare, indolent tumours with a natural history of poor local control and invasion of surrounding structures. Safe maximal resection followed by radiotherapy is the treatment of choice. However, even with multimodality treatment, local recurrence continues to be a common pattern of failure. With conventional photon radiation, dose is limited by the tolerance of the brain stem or spinal cord. In contrast, proton therapy has been used to increase the dose delivered to the tumour while sparing dose to adjacent critical normal structures. Prospective randomized trials comparing photons and protons have not been conducted. However, retrospective data demonstrate a high

probability of local control with proton therapy, in the range of 45–80% local control at five years for chordoma and 98% at five years for chondrosarcoma [11.14, 11.16–11.22]. One prospective study of 100 patients treated with combined modality treatment (photons plus protons) to a dose of 67 cobalt gray equivalents (CGE) showed a three year local control rate of 71% for chordoma and 85% for chondrosarcoma [11.23]. Clinical data for proton therapy in skull base tumours demonstrate superior outcomes compared with conformal photon therapy.

Similarly, dose limiting toxicity is seen in parenchymal brain tumours located close to critical structures such as the optic nerve, optic chiasm, pituitary gland, hippocampus, temporal lobes, brain stem and spinal cord. The effect of treatment toxicity is even greater with benign and low grade tumours, such as meningioma, that have a high chance of cure. Even with highly conformal techniques such as IMRT, late neurocognitive deficits can be seen months to years after radiotherapy. One retrospective study evaluating the use of combined photon/proton therapy for atypical meningiomas after surgical resection showed a local control rate of 61% and two year overall survival of 95% [11.24]. In other series treating low grade meningiomas with protons alone or after surgery, local control rates of 92–100% were reported with minimal severe toxicity [11.25–11.27]. A small phase I/II study of 20 patients with resected grade 2 and 3 glioma treated with 68–80 CGE of proton therapy showed local control and overall survival rates comparable to outcomes reported in patients treated with photons in the past [11.28]. The possibility of safely escalating radiation dose for malignant brain tumours may exist with proton therapy.

### 11.4.2. Ocular tumours

Ocular melanoma can be a locally aggressive and potentially fatal disease. Enucleation was previously the favoured approach for local control. However, in recent years, organ preservation with radiotherapy and other ablative techniques have emerged as a reasonable alternative to surgical resection. Doses of 50–70 CGE in five fractions yield local control rates of 95% and eye preservation rates of 90% [11.29–11.32]. Proton therapy is especially effective for large, posterior tumours that are difficult to reach with conventional techniques such as brachytherapy. The existing evidence suggests high rates of organ preservation and disease control with proton therapy.

### 11.4.3. Prostate cancer

Prostate cancer is among the most common male cancers in the world, and detection of early stage, low risk cancer is particularly high in countries where

screening prostate-specific antigen (PSA) is readily available. Options for the treatment of localized prostate cancer include surgery or radiotherapy with or without hormone therapy. When available, the preferable method of radiation treatment for most men is IMRT to reduce genitourinary and gastrointestinal toxicity. Two prospective randomized clinical trials have investigated the role of proton therapy in the treatment of prostate cancer. The first was a trial of 202 men with stage T3–T4 prostate cancer comparing 75.6 Gy delivered with photons (50.4 Gy) followed by proton boost (25.2 CGE) to 67.2 Gy delivered with photons. While the proton boost did not improve overall survival, local control was improved in the subset of patients with high tumour grade [11.33]. The second trial compared 70.2 CGE delivered with photons to 79.2 Gy delivered with photons and protons in 393 men with T1b–T2 disease and PSA <15 ng/mL. The rate of biochemical failure was 32.4% for the lower dose (photon only) arm and 16.2% for the higher dose (proton boost) arm [11.34]. Other phase I/II and retrospective studies using proton therapy alone or in combination with photon therapy show favourable local control outcome and toxicity profile [11.35–11.39]. No randomized clinical data comparing protons alone to photons alone currently exist. The greatest benefits of proton therapy for localized prostate cancer include dose escalation and reduction in mean integral dose to the normal tissues of the pelvis, which may translate into fewer secondary malignancies following treatment for prostate cancer.

### 11.4.4. Lung cancer

Lung cancer is not only common but also highly lethal, with universally poor long term survival. The standard of care for early stage non-small cell lung cancer is surgical resection. However, excellent local control results have been achieved with stereotactic body radiotherapy in medically inoperable patients [11.40, 11.41]. Two prospective non-randomized trials have examined the use of hypofractionated proton therapy at a dose of 50–60 CGE in ten fractions. In the study in the United States of America, three year local control was 74% and three year overall survival was 72% [11.42]. In the Japanese study, two year local control was 60% and two year overall survival was 80% [11.43]. More recently, a study of 18 patients with early stage non-small cell lung cancer treated with proton therapy of 87.5 CGE in 35 fractions showed a two year local control rate of nearly 90%, and a two year overall survival of 70% [11.44]. Additionally, two retrospective studies demonstrated local control rates in the 80% range for patients with early stage disease treated with proton therapy [11.45, 11.46].

The standard of care for locally advanced non-small cell lung cancer is concurrent chemotherapy and radiation, occasionally before or after surgical resection. The recently published results of a phase II study of proton therapy

with concurrent chemotherapy for unresectable stage III non-small cell lung cancer show very promising results, with median survival of 29 months and minimal toxicity [11.47]. Proton therapy may offer significant advantages over photon therapy for the treatment of lung cancers because of the reduction of the low dose bath created by photons as they exit the lung. This may decrease the incidence of acute esophagitis and pneumonitis, and may completely save the uninvolved lung from receiving excess radiation dose. However, lung motion and lung density changes during respiration present challenges in proton treatment planning and dose verification.

### 11.4.5. Hepatocellular carcinoma

Radiotherapy has been used in the treatment of unresectable hepatocellular carcinoma. However, treatment with photon therapy is limited by excess dose to surrounding liver parenchyma in patients with already compromised liver function. Several retrospective studies and prospective non-randomized trials demonstrate favourable results with proton therapy. Retrospective data from Japan using 60–76 CGE showed five year local control rates of 85% with five year overall survival of around 25% [11.48, 11.49]. The low survival rate was partially explained by coexisting liver cirrhosis in many individuals with hepatocellular carcinoma. The three prospective non-randomized studies used proton doses between 63 and 76 CGE, and showed local control rates of 60–88% [11.50–11.52]. Local control rates were higher with higher doses of proton radiation, suggesting that dose escalation may be beneficial in hepatocellular carcinoma. The use of proton therapy for other gastrointestinal cancers has been limited. However, there may be a role for its use in the future in unresectable pancreatic and oesophageal cancers.

### 11.4.6. Head and neck cancers

Cancer of the head and neck is challenging to treat due to the presence of a large number of critical normal structures in a small, confined space. Both acute toxicity and long term treatment related morbidity from surgery and radiation are high. Proton therapy has been investigated for the treatment of head and neck cancers, particularly nasal cavity, paranasal sinus, and nasopharyngeal tumours, which are generally not amenable to surgical resection. Two retrospective studies using combined photon/proton treatment plans with doses of 75–76 CGE demonstrated five year local control rates of 84% for oropharyngeal cancer and 74% for other head and neck cancers [11.53, 11.54]. Two other retrospective studies used proton therapy alone at doses of 60–70 CGE and showed a two year local control rate of 50% for recurrent nasopharyngeal carcinoma and one

year local control of 77% for sinonasal cavity tumours [11.55, 11.56]. Other less common head and neck tumours, such as olfactory neuroblastoma and malignant melanoma, have also been treated successfully with proton therapy (local control 84–88% at one to three years post-treatment) [11.57, 11.58]. The treatment of head and neck cancers with proton therapy is evolving, particularly as new methods for modulating beam shape and size (such as intensity modulated proton therapy) become more readily available.

### 11.4.7. Paediatric malignancies

Paediatric malignancies are uncommon, but devastating to patients, families, clinicians and society at large when they occur. Aggressive treatments are intended to cure children, who have many decades of life ahead of them. However, late toxicity from the treatments can alter the patient's quality of life in the future [11.59, 11.60]. Nearly 50% of paediatric solid tumours are brain tumours and, unfortunately, radiotherapy has deleterious effects on the developing brain [11.61]. Adverse effects of radiotherapy are also reported in growth and development of soft tissues, bones and nerves. Maintaining the delicate balance required to achieve treatment efficacy while minimizing toxicity is a challenge, and proton therapy provides a unique opportunity to minimize long term treatment toxicity in children treated for cancer. As such, proton therapy has been used to treat medulloblastoma, ependymoma, craniopharyngioma, rhabdomyosarcoma, neuroblastoma and many other paediatric tumours in various sites all over the body.

There are numerous dosimetric studies which demonstrate the superiority of proton therapy in sparing normal tissue and decreasing total integral dose [11.62–11.66]. Clinical data have been published for orbital rhabdomyosarcomas demonstrating excellent local control of 85%. When compared with historical controls, sparing of the optic structures, optic chiasm and temporal lobes was found to be greater [11.67]. Similarly, retrospective data examining the use of protons for craniopharyngioma, a benign but locally destructive tumour, have shown excellent local control results of 94% with minimal toxicity, particularly in patients with subtotal resection [11.68–11.70]. Another retrospective study in children with ependymoma treated with proton therapy shows excellent disease control while sparing normal structures such as the cochlea, hypothalamus and temporal lobes [11.71]. The treatment of paediatric malignancies is one of the most important applications of proton therapy, particularly in cases where craniospinal irradiation is required. The potential reduction of severe late toxicity and decreased risk of secondary malignancies provide a compelling rationale to further investigate the use of proton therapy in paediatric malignancies. Emerging data on the efficacy and toxicity profile of proton therapy for a variety

of paediatric malignancies will be forthcoming as more children are referred to proton therapy centres for treatment.

## 11.5. FUTURE DIRECTIONS

Direct comparisons between proton therapy and photon therapy (IMRT, conventional conformal radiotherapy) cannot be made without randomized clinical trials. However, the existing data provide a strong case for the superiority of proton therapy for carefully selected patients, particularly those with ocular tumours, base of skull tumours or paediatric malignancies. Furthermore, randomization of patients to a less conformal radiation technique may not be ethical, and there is ongoing debate about whether true equipoise exists given the current data [11.72–11.75]. The need for and feasibility of prospective clinical trials comparing protons with photon beam therapy is the subject of heated debate among radiation oncologists today.

While newer radiation techniques such as IMRT have improved local control and decreased late toxicity as compared with conventional conformal treatment, the larger number of monitor units required and the use of multiple fields may increase the volume of normal tissue exposed to radiation, and therefore increase the risk of secondary malignancy [11.76, 11.77]. One of the major benefits of proton therapy is the reduction in integral dose, which may result eventually in a decreased risk of secondary malignancy as compared with photon therapy [11.78].

At present, studies examining the use of proton therapy in nearly every tumour site are ongoing at facilities around the world. At the University of Pennsylvania Medical Center (Fig. 11.4), proton therapy has been used to spare breast tissue in young women with mediastinal lymphoma, spare connective tissue in patients with sarcoma and minimize normal tissue toxicity in re-irradiation cases when a second course of radiotherapy is required after tumour recurrence. As the dosimetric parameters and delivery techniques of proton therapy continue to evolve, in particular the use of the pencil beam scanning technique to create highly conformal proton plans, the applications of proton therapy will continue to grow.

## 11.6. APPLICATIONS FOR DEVELOPING COUNTRIES

At present, the cost of proton therapy is higher than that of photon therapy because of the large initial investment required in equipment and infrastructure, as well as ongoing operational costs [11.79]. In the future, the cost of building

and maintaining a proton therapy facility will decrease owing to increased demand, competition among commercial companies and the development of compact accelerators [11.80]. While the cost effectiveness of proton therapy is an active area of research and debate [11.73, 11.79, 11.81, 11.82], the available data suggest that the treatment is cost effective in appropriately selected patients.

Current estimates are that 15% of patients radiated for cancer in Europe have an indication for proton radiation [11.83], and while the proportion may be lower in developing countries, there is still a need on the part of many patients. Currently, the most urgent priority in low and middle income countries (LMICs) is to establish access to basic cancer screening and treatment services. With the current shortage of radiotherapy centres and skilled personnel in developing countries, the establishment of proton therapy centres may not be feasible in the near future. However, one option to increase access to proton therapy is multinational investment in the development of regional 'centres of excellence', where proton therapy can be administered to patients referred from a large 'catchment area'. Specialized training and exchange learning can be developed between countries such that local care providers and oncologists will be able to identify those cases most likely to benefit from proton therapy — for example, children with curable malignancies — and make appropriate referrals to the regional proton centre.

## 11.7. CONCLUSION

In theory, any tumour can be controlled by radiotherapy if the appropriate dose of radiation is administered. In practice, the safe delivery of a very high dose of radiation is not feasible with standard radiation techniques owing to the limited tolerance of surrounding normal tissues. Proton therapy represents a major advance in the delivery of radiotherapy that offers the advantage of effective tumour control while minimizing acute and late morbidity. Clinical implementation of proton therapy has been based on the dosimetric advantages and promising early clinical results. At present, the establishment of a proton therapy centre requires considerable financial investment, as well as physics and clinical expertise. Validation of the existing technology and techniques can be achieved in a reasonable time frame if multicentre collaboration is implemented worldwide. It is hoped that as the clinical utility of proton therapy continues to be realized, the cost of this novel therapy will decrease and access for appropriately selected patients will increase worldwide, including in LMICs.

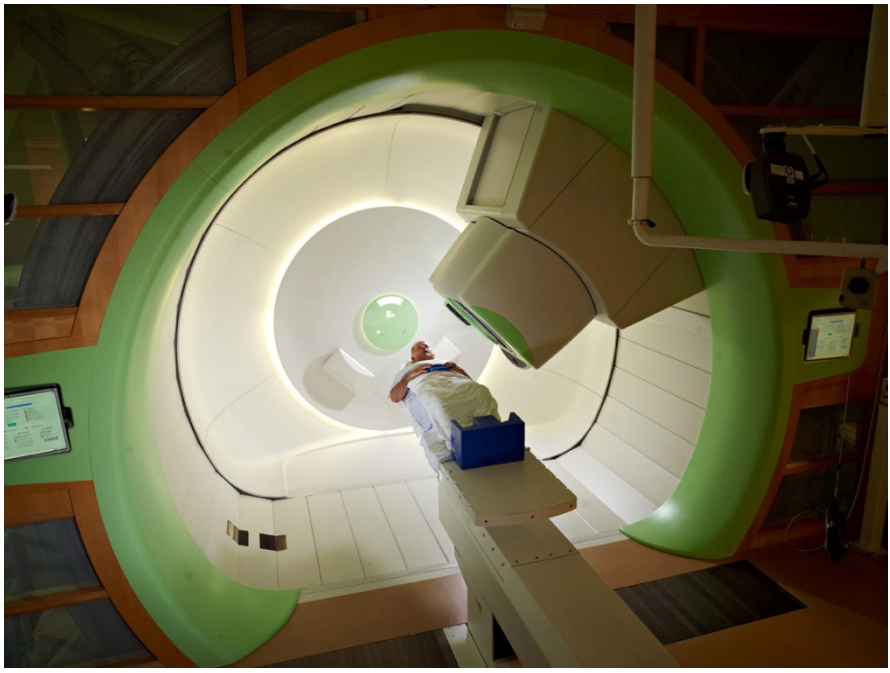

*FIG. 11.4. University of Pennsylvania Proton Facility, Philadelphia.*

## 11.8. KEY POINTS

— Protons deposit little energy on the surface of the body. Because of their high velocity, protons produce more dense ionizations near the end of their path in tissue. This release of energy (or dense ionization) is called the Bragg peak. In front of the Bragg peak the radiation dose is low, and beyond the Bragg peak the dose falls to zero over a very short distance.
— Protons and photons are generally regarded as having equal efficacy of tumour cell kill.
— Prospective randomized clinical evidence is limited. However, many prospective non-randomized and retrospective studies have been published, and the body of literature is growing rapidly as more proton centres are opened worldwide.
— Existing data provide a strong case for the superiority of proton therapy for carefully selected patients, particularly those with ocular tumours, base of skull tumours or paediatric malignancies.
— At present, the cost of proton therapy is higher than that of photon therapy because of the large initial investment required in equipment and infrastructure, as well as ongoing operational costs.

— In the future, the cost of building and maintaining a proton therapy facility will decrease owing to increased demand, competition among commercial companies and the development of compact proton accelerators.

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# Chapter 12

# CARBON ION RADIOTHERAPY IN PERSPECTIVE

**K. Karasawa, T. Kamada, T. Nakano**

## 12.1. INTRODUCTION

In cancer radiotherapy, ion beams such as proton and carbon ion beams have unique characteristics that improve dose distributions, enabling the delivery of sufficient doses to the target volume while minimizing the dose to the surrounding normal tissues [12.1]. In addition, carbon ions, being heavier than protons, provide a higher biological effectiveness while increasing the depth and reach of the maximum energy delivered at the end of the beam's range [12.2, 12.3]. Over the last decade, carbon ion radiotherapy has been applied to a number of tumours that are difficult to control with other modalities, and the number of facilities offering carbon ion radiotherapy has increased worldwide. At these facilities, including the National Institute of Radiological Sciences (NIRS) in Japan and the Gesellschaft für Schwerionenforschung (GSI) in Germany, clinical studies have focused on attempting to identify tumour sites suitable for carbon ion therapy and determining the optimal dose fractionation and irradiation methods [12.4–12.9] (Fig. 12.1).

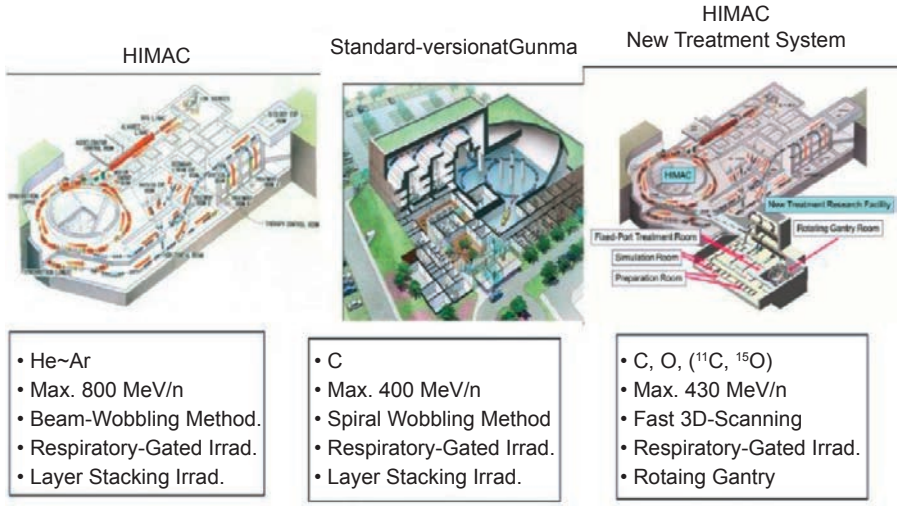


*FIG. 12.1. Development of heavy ion radiotherapy technologies.*

There are at present ten operational facilities treating patients with carbon ion beams. They are located in Chiba, Gunma, Hyogo, Tosu and Kanagawa, Japan; in Lanzhou and Shanghai, China; in Heidelberg and Marburg, Germany; and in Pavia, Italy. Three other new clinical facilities are in the final stages of development in Wiener Neustadt, Austria; Lanzhou, China; and Busan, Republic of Korea. Other facilities are under construction in Marburg, Germany, and Fudan, University of Shanghai, China.

## 12.2. CHARACTERISTICS OF CARBON ION BEAMS

### 12.2.1. Physical aspects

Unlike X rays, which deposit most of their energy just below skin surface, particle beams, such as proton and heavier ion beams, show an increase in energy deposition with increasing depth. The penetration dose of these beams achieves a sharp maximum at the end of their range to form the so-called Bragg peak. Beyond the Bragg peak, almost no dose is deposited in normal tissue [12.9]. In addition, ion dose localization in the tumour improves as the peak to plateau ratio increases. In this respect, carbon ion radiation is particularly outstanding because its peak to plateau ratio is larger than that of any other ion beam under certain conditions [12.10].

At NIRS, carbon ions are accelerated to 800 MeV/u (83% of the speed of light) by major synchrotrons, and the resulting beams can penetrate as deep as 30 cm in water. For modulation of the Bragg peak to conform to a target volume, the beam lines for treatment are equipped with a pair of wobbler magnets, beam scatterers, ridge filters, multileaf collimators and a compensation bolus. The ridge filter is designed to produce biologically equal effects throughout the spread-out Bragg peak (SOBP). The compensation bolus is fabricated for each patient so that the distal configuration of the SOBP is similar to any irregular shape of the target volume, with the collimator used to define the lateral outline. Favourable dose distributions will have a steep dose fall-off at the field borders. As a consequence, more precise dose localization can be achieved with carbon ion beams compared with photon beams [12.10].

### 12.2.2. Biological aspects

Carbon ions cause a different type of cellular damage than do protons and photons, and deliver a larger mean energy per unit length (linear energy transfer (LET)) of their trajectory in the body [12.11]. This unique property provides high local tumour control when used for radiotherapy. Carbon ions directly

cleave double stranded DNA at multiple sites, even at low oxygen content, which allows access to hypoxic parts of tumours that would be resistant to low LET radiotherapy. As a result, carbon ion beams are described as high LET radiation, and in this regard are similar to neutron beams. The LET of neutron beams remains uniform at any depth in the body. However, the LET of carbon ion beams increases steadily from the point of incidence in the body with increasing depth, reaching a maximum at the Bragg peak region. This property is extremely advantageous from a therapeutic point of view in terms of increased biological effect on the tumour. The reason is that carbon ion beams form a large peak in the body, as their physical dose and biological effectiveness increase while advancing to the more deep-lying parts of the body. This quality of carbon ion beams provides promising potential for their highly effective use in the treatment of intractable cancers that are resistant to photon beams [12.12].

In view of these unique properties of carbon ion beams, it is theoretically possible to perform hypofractionated radiotherapy using significantly smaller numbers of fractions than have been used in conventional radiotherapy. Experiments conducted with fast neutrons have demonstrated that increasing the dose per fraction tends to lower the relative biological effectiveness (RBE) in both tumour and normal tissues [12.13]. The RBE in the tumour, however, did not decrease as rapidly as the RBE in normal tissue [12.14, 12.15]. This experimental result substantiates the fact that the therapeutic ratio increases, rather than decreases, even though the fraction dose is increased. At NIRS, hypofractionated carbon ion radiotherapy has been investigated systematically for a variety of tumour entities. The use of these properties makes it possible to complete the therapy in a shorter time without increasing toxicity. At present, the average number of fractions and treatment time per patient at NIRS is 12.5 fractions and three weeks, respectively.

## 12.3. BENEFITS OF CARBON ION RADIOTHERAPY

Carbon ions are very useful in cancer therapy, for even when there are critical organs in the vicinity of the lesion it is possible to safely concentrate sufficient dose to the lesion. Furthermore, as the LET of carbon ions is higher than that of protons or photons, they have a high RBE in the Bragg peak, two or three times greater than that of photons in a given clinical situation.

The carbon ion beam has further advantageous biological features in that cancer tissue does not easily recover from the radiation damage it causes, the oxygen concentration in the tumour has little effect on radiosensitivity, and there are only small differences in radiosensitivity among different phases of the cell cycle. Furthermore, comparison of the ratio of the RBE in the peak portion to

the RBE in the plateau portion of the different ion beams shows that carbon ion beams have the highest value for this ratio among all particle beams [12.14, 12.16]. This means that carbon ion beams have the best balance of all particle beams in terms of both physical and biological dose distribution.

Such unique features of carbon ions allow the treatment period to be shortened significantly as compared with conventional treatment modalities. Indeed, clinical experience at NIRS has shown that the hypofractionated regimen is effective against a wide range of tumours [12.4–12.6]. For stage I lung cancer and liver cancer, for example, an ultrashort irradiation schedule, completed in only one or two sessions, has been achieved. Even for tumours like prostate cancer and head and neck cancers, the fractionation regimens are much shorter than those used in the most sophisticated photon intensity modulated radiation therapy and proton therapy. This means that the facility can be operated more efficiently, to offer treatment for a larger number of patients than using other modalities over the same period of time.

## 12.4. ION BEAM RADIOTHERAPY FACILITIES IN THE WORLD

The use of proton beams in radiotherapy began at the Lawrence Berkeley National Laboratory (LBNL) in 1954 [12.1]. Since then, the efficacy of heavier charged nuclei, such as helium, carbon, nitrogen, neon, silicon, and argon has also been assessed for clinical use at LBNL. The major pioneering work for heavy ions was carried out at LBNL between 1977 and 1992, in which most patients were treated with helium and neon ions. In 1994, a clinical study on carbon ion radiotherapy was started at NIRS with carbon ions generated by HIMAC (Heavy Ion Medical Accelerator in Chiba, Japan), the world's first accelerator complex dedicated to cancer therapy. As of January 2017, there were 61 operating proton facilities in the world, while carbon ion radiotherapy was performed at 10 facilities.

Following HIMAC/NIRS, GSI in Darmstadt, Germany, started carbon ion radiotherapy in 1997 and then terminated its clinical activity. It was succeeded by the Heidelberg Ion-Beam Therapy Center (HIT) in 2009. HIT is the world's first particle therapy facility for treatment with protons and carbon ions with a scanned beam delivery system. In fact, the Hyogo Ion Beam Medical Center (HIBMC) in Japan, established in 2001, is the first facility dedicated to proton and carbon treatment using a broad beam technique. At the Institute of Modern Physics (IMP) in Lanzhou, China, clinical trials have been performed since 2006, where carbon ion beams with energy up to 100 MeV/u have been supplied for the treatment of superficial tumours. Based on technological research and development performed at NIRS, Gunma University in Japan constructed a

compact carbon ion facility called the Gunma University Heavy Ion Medical Center, where clinical studies started in 2010.

At the CNAO Foundation, Italy, an accelerator complex was completed for proton/carbon treatment; clinical studies on proton therapy were started in October 2011 and carbon ion radiotherapy began about one year later. Under a licence agreement between GSI and Siemens AG, two facilities modelled on HIT are under construction in Marburg and Kiel in Germany, as well as one in Shanghai, China. There are three more institutions with carbon ion facilities currently under construction or commissioning: in Wiener Neustadt, Austria; Lanzhou, China; and Busan, Republic of Korea.

## 12.5. CLINICAL RESULTS OF CARBON ION RADIOTHERAPY

Clinical application of heavy ion beams was successfully performed by NIRS in 1994, and various types of tumours have been treated with carbon ions. Between 1994 and the end of 2011, more than 6000 patients were treated with carbon ions at NIRS, where the benefit of carbon ion radiotherapy over other modalities has been demonstrated in terms of high local control and survival rates. A significant reduction in overall treatment time with acceptable toxicities has been achieved in most cases. Similar results have been obtained at HIBMC. At GSI, the first patient was treated in 1997 using GSI's heavy ion synchrotron, which was used jointly for physics research and clinical application. Clinical study at GSI was terminated in 2008, by which time they had treated a total of 440 patients with carbon ions. Based on that experience, the new HIT facility was built in Heidelberg, Germany. At IMP in China, an accelerator that was also primarily built for physics research has been used for carbon ion radiotherapy. As compared with standard radiotherapy, they prescribed higher total doses in smaller fractions for superficial lesions, by which they successfully obtained high local control with a relatively low rate of radiation induced reactions.

Tumours of a relatively large size or irregular shape located in the vicinity of critical organs, such as the eye, spinal cord and digestive tract, are good indications for carbon ion radiotherapy. However, tumours that infiltrate or originate in the digestive tract are difficult to control with carbon ion radiotherapy alone. The experience to date at NIRS (Figs 12.2–12.4) indicates that carbon ion radiotherapy is advantageous for the types of tumours described in the following sections.

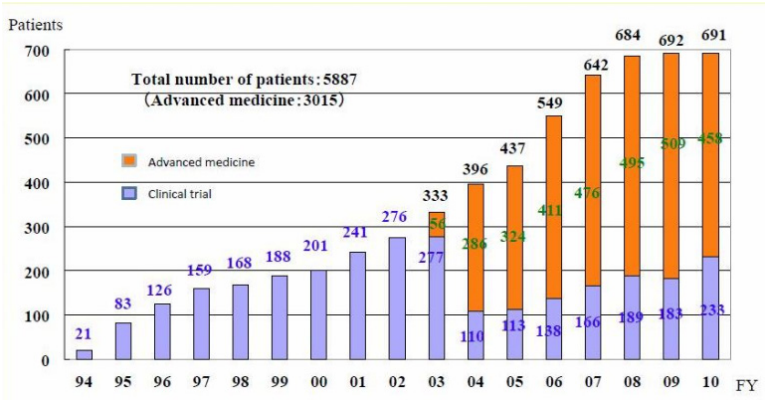


*FIG. 12.2. Number of patients undergoing carbon ion radiotherapy at NIRS (June 1994 to February 2011).*

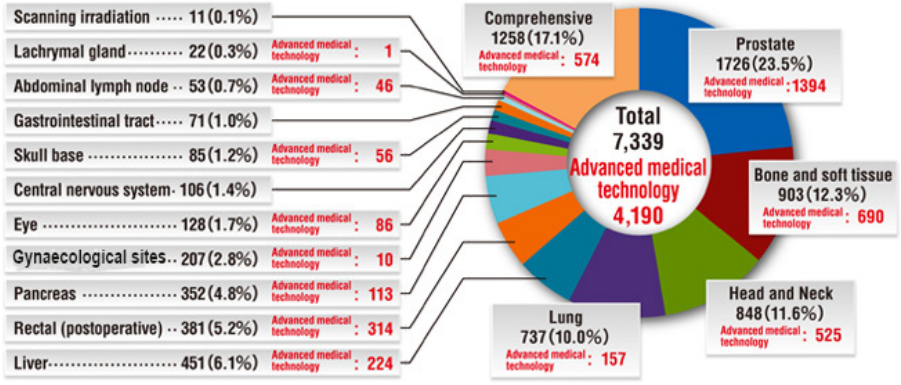


*FIG. 12.3. Number of patients receiving heavy ion radiotherapy at NIRS, June 1994 to March 2013 (graphic courtesy of NIRS).*

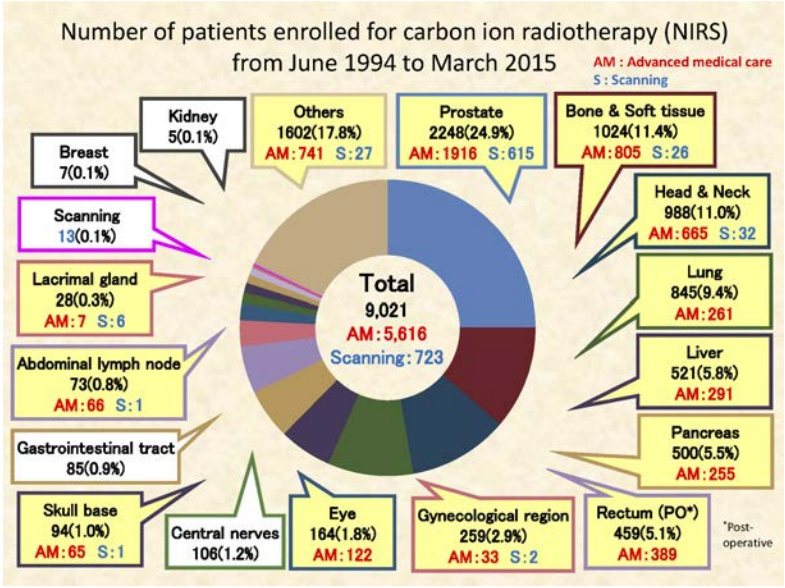


*FIG. 12.4. Number of patients treated at various tumour sites with a carbon ion beam at NIRS, Chiba, Japan, as of March 2015.*

### 12.5.1. Skull base and paracervical spine tumours

A phase I/II dose escalation study for skull base and paracervical tumours was initiated in 1997. The patients were treated with 16 fractions for four weeks with a total dose of 48.0–60.8 Gy equivalents (GyE). In 2004, a phase II study was initiated with an irradiation schedule of 60.8 GyE in 16 fractions over four weeks. There were 76 patients (chordoma 44, chondrosarcoma 12, olfactory neuroblastoma 9, malignant meningioma 7, and others) included in the analysis. At the time of median follow-up (46 months), there was no evidence of any serious acute (grade ≥4 in NCI-CTC-AE ver. 03) or late (grade ≥3 in LENT/SOMA) reactions. The five year local control and overall survival rates for all patients were 88% and 82%, respectively. The five year local control and overall survival rates for chordoma patients were 88% and 87%, respectively [12.17].

### 12.5.2. Advanced non-squamous cell carcinoma of the head and neck

Between April 1997 and February 2011, 407 cases with locally advanced, histologically proven, and primary or recurrent malignant tumours of the head and neck were treated with carbon ions. Most of them were adenocarcinoma, adenoid

cystic carcinoma, malignant melanoma, sarcoma and the other non-squamous cell carcinomas.

The planned treatment dose was 64.0 GyE in 16 fractions over four weeks. There were no acute reactions worse than grade 3 and no late toxicities worse than grade 2. The five year local control and overall survival rates in all cases were 73% and 53%, respectively. Based on the results of the analysis, this part of the study was divided into two additional protocols, one for bone and soft tissue sarcomas and another for mucosal malignant melanomas [12.8, 12.18].

### 12.5.3. Non-small cell lung cancer (T1–2N0M0)

Between April 1994 and February 2011, 642 cases with non-small cell lung cancer were treated with carbon ions. The tumours were divided into two groups according to location: peripheral type and central type. For peripheral type, a phase I/II clinical trial was conducted and the optimal dose and fractions were determined to be 72.0 GyE in nine fractions. Moreover, the fraction number and treatment time were reduced in gradual steps to 52.8 GyE for stage IA and 60.0 GyE for stage IB in four fractions/one week. In this study, the five year local control rate was 90%, with a cause specific survival rate of 68% and an overall survival rate of 45%. A dose escalation study with single fraction treatment was initiated in April 2003. The initial dose was 28.0 GyE, with the total irradiation dose being escalated to 50.0 GyE. In this trial, the five year local control rate for 131 patients was 81% [12.8, 12.19].

For the treatment of central type lung cancer, a larger number of fractions than for the peripheral type was used. A phase I/II study was initiated using 12 fractions over three weeks. To avoid serious toxic reactions for the hilum, including the main bronchus, the dose was set at 68.4 GyE. This trial is still ongoing, with early encouraging results in terms of local control and acceptable toxicities.

### 12.5.4. Bone and soft tissue tumours

As of February 2011, a total of 767 patients had been enrolled in clinical trials. Among them, sacral chordomas accounted for the largest proportion and osteosarcomas of the trunk for the next largest group. After a phase I/II dose escalation study from June 1996, a fixed dose phase II trial has been ongoing since April 2000 using a total dose of 70.4 or 73.6 GyE. As of February 2011, 500 patients were enrolled in this study and 514 lesions in 495 patients had been analysed for six months or longer after the treatment. As of August 2011, the two year and five year local control rates were 85% and 69%, respectively. The two year and five year overall survival rates were 79% and 59%, respectively.

Overall, the toxicity was acceptable, with 2% skin/soft tissue late G3/4 toxicity observed. Late skin toxicities, including grade 3 in six patients and grade 4 in one patient, were also observed [12.8, 12.20].

### 12.5.5. Hepatocellular cancer

A total of 403 patients with hepatocellular carcinoma were enrolled in this clinical trial. Based on the results of the phase I/II dose escalation study, a phase II study was initiated using a recommended dose of 52.8 GyE in four fractions over one week. In these patients, post-treatment impairment in hepatic function was minimal, and the five year local control and survival rates were recorded as 94% and 33%, respectively. The fourth clinical study was conducted from April 2003 to August 2005, with a more hypofractionated regimen of two fractions/two days, in which 36 patients were safely treated within a dose escalation ranging from 32.0 GyE to 38.8 GyE. The two fraction therapy protocol is continuing as a clinical practice. There have been no severe adverse events [12.8, 12.21] (Fig. 12.5).

### 12.5.6. Pancreatic cancer

A phase I/II clinical trial for pre-operative radiotherapy for resectable pancreatic cancer was started in 2000. Twenty-six patients were registered from April 2003 through February 2010, and dose escalation was performed from 30 to 36.8 GyE. Twenty-one out of 26 patients received curative resections (resection rate 81%), but the remaining five patients did not undergo surgery due to liver metastases or refusal. In the 21 surgical cases, the five year local control and overall survival rates were 100% and 53%, respectively.

A phase I/II clinical trial for patients with locally advanced pancreatic cancer combined with gemcitabine was also started. After a dose escalation study of gemcitabine, the radiation dose was increased by 5% from 43.2 GyE/eight fractions with 1000 mg/m$^2$ of gemcitabine. Sixty patients were registered from April 2007 through February 2011. The two year local control rate and two year overall survival rate were 26% and 32%, respectively [12.8, 12.22].

### 12.5.7. Post-operative pelvic recurrence of rectal cancer

A phase I/II study for recurrent rectal cancer was started in April 2001. After a dose escalation study, a phase II study was initiated in April 2004 in which the total radiation dose was fixed at 73.6 GyE. The three and five year local control rates were respectively 89% and 89% for patients treated with 70.4 GyE, and 95% and 95% for those treated with 73.6 GyE. The five year survival

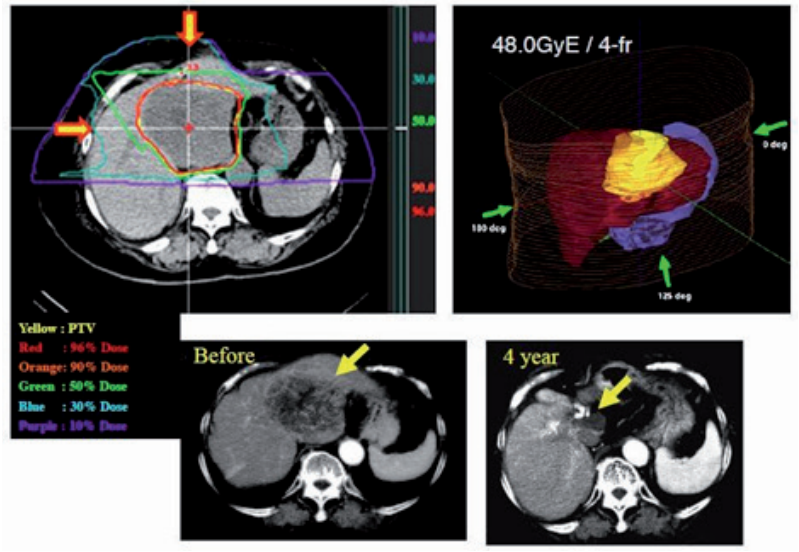


*FIG. 12.5. A case of hepatocellular carcinoma treated with carbon ion beam radiotherapy.*

rates were 24% with 67.2 GyE, 28% with 70.4 GyE, and 42% with 73.6 GyE. The survival rates showed an increasing trend with radiation doses. Most of the patients studied reported rapid pain relief [12.8, 12.23].

### 12.5.8. Prostate cancer

The therapeutic outcome of hypofractionated conformal carbon ion radiotherapy for localized prostate cancer was investigated. The study analysed the treatment results of 1084 cases observed for six months or more after carbon ion radiotherapy up to February 2011. The five year biochemical relapse-free rate of whole cases was 91%. The Gleason score, prostate-specific antigen value and clinical stage were the significant prognostic factors for the relapse-free survival rate. No difference was found in the relapse-free survival rate between the two fractionation methods (20 fractions versus 16 fractions). Out of 1005 cases followed up for at least one year, only one developed grade 3 lower urological impairment, incidences of grade 2 were 6% in the lower urinary tract and 2% in the rectum. Furthermore, the toxicity incidence was lower in the 16 fraction schedule than in the 20 fraction schedule [12.24].

### 12.5.9. Locally advanced uterine cervical cancer

As of February 2011, a total of 166 patients were enrolled in the clinical trials. A phase I/II study for cervical cancer was initiated in 1995, and the following clinical observations were made:

— Whole pelvic irradiation at 36–39 GyE in 12–13 fractions adequately suppressed microscopic lymph node metastasis.
— Local control rate increased with total dose, and doses of around 72 and 68–74.4 GyE were necessary for local control of squamous cell carcinoma and adenocarcinoma, respectively.

The five year local control and overall survival rates for stage III and IV cervical adenocarcinoma were 55% and 48%, respectively. Studies on chemoradiotherapy for stage III and IV-A cervical cancers reported five year local control rates of around 70% and five year overall survival rates of 56–59% [12.8].

### 12.5.10. Uveal melanoma and lacrimal gland tumour

As of February 2011, a total of 109 patients with uveal melanoma were enrolled in the clinical trials. The three year local control rate of 97% was satisfactory and comparable to that reported for proton therapy, and the three year overall survival rate was 88% [12.8].

Surgery for lacrimal gland cancer offers poor results because of the difficulty of total tumour eradication. So far, 22 patients have been treated, with a total dose of 48 GyE in 5 patients, and 52.8 GyE in 17. The five year local control rate was 74% and the five year overall survival rate was 65%.

## 12.6. SUMMARY

The promising aspect of carbon ion radiotherapy for the treatment of cancer lies in its superior biological dose distribution, which makes the carbon ion beam the best-balanced particle beam available. Thus, comparison of the ratio of the RBE in the peak region against the RBE in the plateau region shows that carbon ion beams have the most favourable value of all heavy ion beams.

So far, with the support of the many involved investigators, considerable evidence has been accumulated in terms of the safety and efficacy of carbon ion radiotherapy for various types of malignant tumours. Studies aimed at clarifying the greater usefulness of carbon ion radiotherapy and elucidating any advantages from hypofractionation should be considered. A multi-institutional prospective

non-randomized concurrent phase II clinical trial is one such new approach, and it will be proposed not only to Japan, but also to the international particle therapy and radiation oncology community.

## 12.7. KEY POINTS

— The penetration dose of the carbon ion beam achieves a sharp maximum at the end of its range to form the so-called Bragg peak. Beyond the Bragg peak, almost no dose is deposited in normal tissue.
— More precise dose localization can be achieved with carbon ion beams compared with photon beams.
— Carbon ions cause a different type of cellular damage than do protons and photons, and deliver a larger mean energy per unit length (linear energy transfer) of their trajectory in the body.
— In view of these unique properties of carbon ion beams, it is theoretically possible to perform hypofractionated radiotherapy using significantly smaller numbers of fractions than have been used in conventional radiotherapy.
— At the present time, there are five operational carbon ion facilities in the world (in China, Germany and Japan) and four more under construction (in Austria, China, Italy and Japan).
— Experience to date at the NIRS indicates that carbon ion radiotherapy is advantageous for the following types of tumours: skull base and paracervical spine, advanced non-squamous cell carcinoma of the head and neck, non-small cell lung cancer, bone and soft tissue tumours, hepatocellular carcinoma, pancreatic cancer, recurrent rectal cancer, prostate cancer, locally advanced cervical cancer, uveal melanoma and lacrimal gland cancer.

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# Chapter 13

# INTRAOPERATIVE RADIOTHERAPY FOR BREAST AND RECTAL CANCERS

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## 13.1. INTRODUCTION

Intraoperative radiotherapy (IORT) is an intensive radiation treatment that is administered during surgery. It is used to treat cancers which are difficult to remove during surgery, to address the concern that microscopic cancer cells may remain behind. IORT allows direct radiation to the target area while sparing normal surrounding tissues. It allows higher effective doses of radiation to be used compared with conventional radiotherapy. It is not always possible to use very high doses during conventional radiotherapy since sensitive organs are often nearby. IORT also allows doctors to temporarily move nearby organs or shield them from radiation exposure. Experimental studies of IORT from the National Cancer Institute and Colorado State University in the United States of America (USA) have established a foundation of knowledge of the short and long term tolerance (dose as well as volume) of normal tissues frequently irradiated with IORT [13.1, 13.2]. These data have been useful in guiding the safe administration of single large fractions (10–20 Gy) of irradiation during surgery to large numbers of patients with a wide variety of neoplasms. Two alternative but complementary IORT methods (electron beam techniques such as intraoperative electron radiotherapy (IOERT) and high dose rate brachytherapy) have evolved into technically sophisticated treatments with the similar philosophy of achieving higher effective doses of irradiation while dose limiting structures are surgically displaced or shielded at the time of exploration and resection. In the past three decades, there has been substantial progress in the experimental, technical and clinical application of IORT as a treatment modality, especially for breast and rectal neoplasms.

## 13.2. BREAST CANCER

The concept of IORT during breast conserving surgery consists of the delivery of a single radiation dose to the area at highest risk for subclinical tumour cell contamination with high precision made possible by direct visualization.

This method was originally introduced by the Medical College of Ohio in Toledo, Ohio, USA, and the Institut du Cancer de Montpellier, the Regional Cancer Centre in Montpellier, France, based on reports of 72 patients [13.3] treated with an electron boost, mainly with 10 Gy. In the late 1990s, a broad clinical IORT application started at the European Institute of Oncology in Milan, Italy [13.4], and the Paracelsus Medical University in Salzburg, Austria [13.5]. Since then, IORT to the tumour bed during breast conserving surgery has become a major field of interest for partial breast irradiation, either as an anticipated boost or as the sole treatment strategy in limited stage breast cancer.

Direct visualization of the tumour bed during surgery guarantees the most accurate dose delivery. All other methods of later localization of the tumour bed (e.g. by clips) remain indirect; nothing competes with direct visualization of the tissues at risk. Furthermore, a growing number of surgeons use primary reconstruction techniques after a lumpectomy to optimize cosmetic outcome, which inevitably hampers tumour bed localization except when IORT is used, as it is performed before breast tissue is mobilized for cosmetic reasons. As a consequence of direct tissue exposure without distension by haematoseroma, IORT allows for small treatment volumes and complete sparing of the skin. Both should have a positive effect in terms of late tissue tolerance.

This has given rise to the development of different technical approaches, with the term 'IORT' frequently used for the following different techniques: perioperative interstitial multicatheter brachytherapy, endocavitary brachytherapy (MammoSite®), an orthovoltage system (Intrabeam®), and IORT with electrons on mobile or standard linear accelerators (IOERT). The dosimetric properties of these four methods in terms of dose homogeneity, flexibility towards asymmetric tumour volume shapes and hence their ability to deliver a reliable dose to a given volume differ tremendously (Fig. 13.1). The outcome analyses of local control rates as well as cosmetic results after IORT must be strictly performed according to the technique used.

In contrast to the brachytherapy techniques, only IORT and orthovoltage low kV treatments are truly intraoperative radiotherapies, where the dose is delivered during the operative procedure.

### 13.2.1. IOERT methods

Linear accelerator (linac) based IOERT is possible with various electron energies (4–18 MeV). When breast conserving treatment is likely, the tumour is excised and the surgical clearance confirmed by intraoperative pathological examination, which is also used to guide contingent re-excision in the case of close or positive margins. Afterwards, the tissue surrounding the excision cavity is surgically mobilized and temporarily approximated by sutures in order to

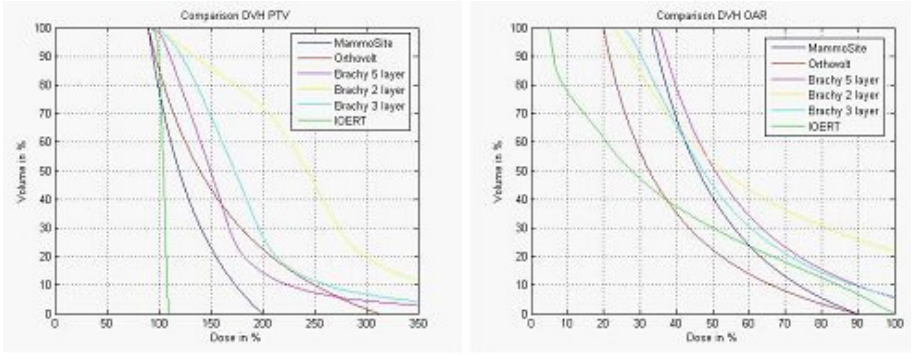


*FIG. 13.1. Dose volume histograms for the target volume (left) and the organ at risk (right) (from Nairz et al. [13.6]).*

bring adjacent walls into reach of the electron beam. The resulting tissue depth (i.e. distance to the anterior rib surface) is usually measured by intraoperative sonography or by scaled probes for depth dose prescription and choice of proper electron energies, respectively. Treatment is applied by circular applicators of different diameters; optionally, additional thoracic wall protection can be added using lead shielding. After IORT, the approximation sutures are removed and the breast tissue is reconstructed, including optional oncoplastic manoeuvres. When IORT is given as a boost, complete wound healing should be awaited before the onset of whole breast external beam radiotherapy (EBRT) — usually four to six weeks.

### 13.2.2. Target volume and design of breast IOERT

The work of Holland et al. [13.7] still builds the essential background for the boost design. Without detailed consideration of risk subgroups, microscopic disease can be expected in 40% of cases outside a distance of 2 cm away from the macroscopic edge of the tumour. The larger the distance, however, the lower the probability: a safety margin of 3 cm will match over 80% of residual tumour cells, and a distance of 4 cm accounts for about 90% of possible residual disease.

The amount of tissue irradiated by IOERT should therefore also be chosen with regard to the width of free margins in all directions. A major advantage of an immediate boost during surgery is the close proximity of the walls of the surgical cavity due to the fact that no fluid will artificially enlarge the volume at risk by spherical distension, resulting in larger treated volumes and hence increased risk of late effects. Analysis showed that the IOERT volumes treated by 85% of the maximum dose were comparable with those treated by brachytherapy of clipped

tumour beds (based on published sources), however, with more breast tissue at risk irradiated in the absence of post-operative seroma.

### 13.2.3. IOERT indications

#### *13.2.3.1. Boost*

IOERT addresses the question of whether this approach is an effective and/or superior alternative to conventional boost techniques. The advocates of an IOERT boost, also known as 'bio-boost', emphasize the use of lower single doses compared with a full dose concept, with dose ranges well understood in terms of tumour effects and late tissue reactions. Since IORT is normally followed by whole breast EBRT, the concept still addresses the (unknown) risk of occult tumour burden in distant quadrants. Therefore, it is less vulnerable to a possible underdosage in the periphery of the tumour bed and remains applicable in every risk scenario. Although subsequent whole breast EBRT remains mandatory, a shortening of its duration can be achieved by total dose reduction and/or hypofractionated radiotherapy schedules according to the patient's individual risk.

#### *13.2.3.2. Accelerated partial breast irradiation*

Accelerated partial breast irradiation (APBI) is an approach that treats only the lumpectomy bed and a 1–2 cm margin. The smaller volume of irradiation allows a higher dose to be delivered in a shorter period of time. Various APBI approaches have been tested in phase I–III clinical studies, including conformal external beam radiotherapy, balloon catheter brachytherapy, multicatheter interstitial brachytherapy and IOERT. Full dose IOERT is supported by the observation that tumour recurrences occur primarily close to the original tumour site [13.8].

Therefore, investigations are focused on the potential for APBI to replace conventional post-operative whole breast EBRT, especially in low risk patients. The main advantage lies in the substantial shortening of the duration of radiotherapy treatment. However, using only IOERT involves the risk of missing parts in the periphery of a relevant target volume; although the tumour burden is small, it is usually controlled by EBRT with doses of around 50 Gy. Omission of whole breast EBRT might lead to a higher frequency of local recurrences in sites where they have not been reported up to now after 'standard' treatment. Second, the $\alpha/\beta$ model does not give reliable information for dose levels in use during full dose IOERT. To date, long term outcome assessments accounting for both indications are still lacking and are the subject of ongoing clinical research.

*13.2.3.3. Clinical evidence*

As regards boost IOERT, the evidence to date derives from one randomized trial, six reports on non-randomized controlled studies and/or non-controlled cohorts [13.9–13.11], one pooled analysis [13.12] and one sequential intervention study [13.13]. Reported local tumour failure rates are remarkably low in all reports, in the range of 0–1.5% following IOERT boosts versus 1.7–4.3% following standard treatment. Interpretation of these studies' results has to account for partially overlapping patient cohorts. Despite its retrospective character, the best data evidence is derived from the ISIORT Europe pooled analysis on IOERT (see below). Cumulative evidence of the efficacy of boost IORT is high; however, at present there is only one randomized prospective trial with a long term follow-up expected. Starting in 2005, a collaborative pooled analysis of the outcome of a 10 Gy boost IOERT prior to a 50 Gy whole breast EBRT has been repeatedly performed among seven member institutions from Austria, France, Germany and Italy, all members of the European Group of the International Society of Intraoperative Radiotherapy (ISIORT Europe) [13.12]. The joint investigation evaluated the long term outcome of the IOERT strategy aimed at reducing local recurrences of breast cancer. Methods, sequencing and dosage in IORT and post-operative EBRT during breast conserving therapy were comparable. A total of 1110 patients were enrolled, of whom 60% (655 patients) presented with at least one adverse prognostic factor for local recurrence risk in terms of tumour size >2 cm, high grade, young age (<45 years) and/or positive lymph nodes. The most recent long term analysis from October 2005 to 2010 provided a total follow-up of all living patients with a median of 73.3 months, 120 of whom had a follow-up of >12 months. At this time point, 10% of patients had metastases, disease-free survival was 87.8%, disease-specific survival was 93.3%, and overall survival was 89.7%. A total of 16 in-breast recurrences occurred, half of which were true local recurrences, which yields a local tumour control rate of 99.2% at 73.3 months. These findings were superior to conventional boost treatment in all cases. In a multivariate analysis, a grade 3 tumour was found to be predictive for recurrence development ($p = 0.024$). Also, a significant univariate trend was found for young age (<40 years) and negative hormone receptor status.

Using IORT as APBI, there is a phase III, prospective randomized non-inferiority trial called TARGIT (targeted intraoperative radiotherapy) which began in March 2000. This trial compares single dose IORT targeted to the tumour bed to conventional whole breast EBRT in early breast cancer [13.14, 13.15]. Patients were enrolled from 28 centres in nine countries including Australia, Germany, Italy, the United Kingdom and the USA. Data accrual was closed in May 2010 and the results of this trial have been published by Vaidya et al. [13.16].

In this trial, 1113 patients were randomly assigned to the targeted IORT group and 1119 allocated to the whole breast EBRT group. Of the targeted IORT group, 854 patients received targeted IORT only, and 142 received targeted IORT and whole breast EBRT. In the external beam radiotherapy group, 1025 patients received the allocated treatment. At the four year follow-up, six local recurrences were observed in the targeted IORT group and five in the whole breast EBRT group. The Kaplan–Meier estimate of local recurrence in the conserved breast at four years was 1.20% (95% CI 0.53–2.71) in the targeted IORT group and 0.95% (0.39–2.31) in the whole breast EBRT group. The difference in recurrence rates between the two groups was not statistically significant. Similarly, the total rate of major toxicities was similar in the two groups [13.16]. This study presents the first level I evidence of the equivalence of APBI using IORT to whole breast EBRT and confirms that targeted IORT allows the entire dose of radiotherapy to be administered in a single fraction at the time of breast conserving surgery, thus avoiding the need for repeated radiotherapy treatments or placement of in-dwelling radiotherapy devices.

#### *13.2.3.4. Radiobiological value of higher single doses*

For breast tumours, a postulated low α/β ratio of around 4 was clinically corroborated by the British and Canadian hypofractionation trials [13.17–13.19]. Applied to a 10 Gy IOERT dose, this corresponds to an isoeffect of about 23 Gy with conventional fractionation. This could well be responsible for the remarkably low local recurrence rates, especially when administered under optimal conditions of visual clinical tumour volume control. In addition to dose estimations, it was hypothesized that immediate irradiation during surgery has implications for the tumour microenvironment, abrogating the proliferative cascade induced by surgical wound healing. Wound fluid has been described as stimulating tumour cell proliferation and invasion, and this process can be blocked by high dose IORT [13.20]. Another obvious aspect is the prevention of possible residual tumour cell repopulation between surgery and adjuvant radiotherapy. Furthermore, a good oxygenation status of the tumour bed during operation could also be a factor for enhanced biological effectiveness, though this has not been specifically investigated yet. These cellular and trans-cellular reactions in irradiated tissues are not completely clarified in detail and understood with regard to their particular value on clonogenic cell inactivation — and, hence, local control — and are the subject of ongoing research [13.21].

Besides biological considerations, age has unanimously been reported to have a strong influence on local control: the younger the patient, the higher the risk of recurrence. Patient groups with different risks for relapse have been proposed by several international societies, with slightly varying emphasis

on different adverse factors, but all of them with age as a highly relevant risk determining factor (ASTRO, GEC–ESTRO guidelines). Annual local recurrence rates are frequently used to benchmark the efficacy of different radiotherapy strategies, with steadily decreasing values over the past ten years. When reported along the usual age groups of ≤45, 45–50, 51–60 and >60 years, the lowest annual local recurrence rates for the respective groups yielded mean values of around 1.8%, 1.5%, 1% and 0.6%, respectively [13.22, 13.23].

Another aspect in every treatment modality is the consideration of the patient's comfort, and hence compliance with treatment. IOERT boost can shorten adjuvant radiotherapy by up to one and a half weeks when compared with external boost treatments. The Milano Group has tested the use of IOERT plus short term whole breast EBRT in a phase II study [13.9]. A prospective ISIORT multicentre trial (HIOB) is currently investigating a combination of IOERT boost with a three week accelerated whole breast EBRT regime. Superiority of the intervention is defined as falling below the recurrence rates of the best published non-IORT cohorts (i.e. local regional recurrence of 0.44%) [13.24].

#### *13.2.3.5. Toxicity/late reactions/cosmesis*

In all studies, IOERT manoeuvres turned out to be safe and feasible, showing no treatment related mortality or excess acute local morbidity in terms of delayed wound healing or infection rates compared with conventional treatment [13.13]. As for late reactions, cumulative incidences of fibrosis/sclerosis within the IORT volumes were slightly different according to the treatment concept: for the boost patients, tolerance was excellent, with incidences of 20–25% grade 1–2 and less than 2% grade 3 reactions [13.9, 13.10]. Following full dose IORT, reported rates amounted to up to 80% grade 1, 30% grade 2 and up to 6% grade 3 reactions [13.25].

The cosmetic outcome was analysed in a few reports: for bio-boost strategies, no difference was described in one prospective trial for the boost patients in comparison with conventional groups. Results were rated as 86/91% good or excellent for IORT boosts and 81/96% for the control groups, respectively [13.2]. The longest term experience is provided by Lemanski et al. [13.26], who reported on late reactions in 42 recurrence-free patients after a median follow-up of nine years. Six patients (14%) experienced grade 2 late subcutaneous fibrosis within the boost area. Overall, cosmesis was scored to be good to excellent. Reports on cosmesis following full dose IOERT describe cosmetic results ratings of 71% very good and 95% good [13.25]. In all these studies, the authors used different standardized cosmetic scoring systems based on qualitative estimations. However, in comparison with conventional techniques, no negative impacts on cosmesis have been reported so far following IOERT in any concept.

Toxicity results of IORT, as a single radiation treatment, were reported in a phase I–II study by the Nagoya University Graduate School of Medicine [13.27]. Early toxicity was evaluated with the Common Terminology Criteria for Adverse Events v3.0. Twenty-three patients received 21 Gy. After a median follow-up of 26 months, their toxicities within three months included grade 1 (23/26) and grade 2 (2/26) deep connective tissue fibrosis, grade 1 haematoma (9/26), grade 1 infection in the musculoskeletal soft tissue (4/26), and grade 2 soft tissue necrosis (3/26). There have been no local recurrences. Therefore, female patients treated with IORT showed very good tolerance. Ivanov et al. [13.28] reported the outcome of 11 patients utilizing electronic brachytherapy to deliver IORT for early stage breast cancer. At a mean follow-up of 12 months, overall cosmesis was excellent in 10 of 11 patients. No infection, fat necrosis, desquamation, rib fracture or cancer recurrence have been observed. There was no evidence of fibrosis at the last follow-up.

## 13.3. RECTAL CANCER

The local recurrence rate in locally advanced rectal cancer has been reported to be 16–29% [13.29]. In order to reduce the recurrence rate in the pelvic cavity, pre-operative or post-operative external radiotherapy (45–50 Gy) was administered. However, recent studies have reported that pre-operative radiochemotherapy has greater benefit on local control and side effects than does post-operative radiochemotherapy. As a result, pre-operative radiochemotherapy is being widely used [13.30].

It has been demonstrated by numerous non-randomized series in the literature that IORT has been able to reduce the local recurrence rate with an impact on survival [13.29]. Intraoperative radiotherapy allowing a higher dose to be delivered to the target volume without irradiating healthy tissues or a critical organ is a means to optimize the local effects of radiotherapy.

### 13.3.1. IOERT indications

IORT provides a consistent therapeutic edge for patients with locally advanced neoplasms where the likelihood of microscopic residual cancer after resection is high and the resultant local failure is a major factor in determining patient outcome. This clinical scenario is best illustrated by patients with primary unresectable or locally recurrent rectal cancer, where multiple single institution studies have reported reproducibly high rates of local control and improved survival for patients treated with pre-operative EBRT (and more recently radiochemotherapy), resection and IORT. The focus of these studies has been

on patients with rectal cancers that are adherent or fixed to adjoining structures such as the sacrum or pelvic sidewall, where resection is not feasible without leaving microscopic or macroscopic disease because of tumour adherence or invasion. Because these patients fare poorly with surgery alone, radiotherapy and chemotherapy have been added to improve outcomes. In an effort to further improve local control and outcome in this subset of patients, IORT (10–20 Gy) has been integrated into multimodality treatment strategies involving pre-operative EBRT, chemotherapy and surgery.

The other subset of patients with rectal cancer treated with IORT has been patients with locally recurrent tumours. Patients developing a local recurrence after curative resection of primary colon or rectal cancer are treated with palliative intent at most institutions. Local recurrence from rectosigmoid cancer often causes pelvic pain due to nerve involvement in the presacral space or pelvic sidewall. The likelihood of margin negative resection is low. For patients undergoing surgery alone for pelvic recurrence from rectal cancer, reported five year survival rates are 0% [13.31]. When IOERT is combined with EBRT with or without chemotherapy and surgical salvage, five year survival in the range of 20% has been achieved.

### 13.3.2. Clinical evidence

The Mayo Clinic in the USA uses a dose of 7.5–10 Gy when the resection margin is negative, 10–12.5 Gy when the resection margin is microscopically positive, 15 Gy when the residual tumour is less than or equal to 2 cm, 17.5–20 Gy when the residual tumour is greater than 2 cm, and 45–55 Gy as pre-operative or post-operative external radiotherapy [13.32]. There was a difference in the local relapse rate depending on the extent of the residual tumour: 5% for microscopically positive residual tumours and 25% for gross residual tumours. And there were no relapses within the IORT field, except in one patient for whom the tumour was not completely excised. On the other hand, patients who had incomplete removal and underwent only external radiotherapy had a high local relapse rate of 76% at the same institute [13.33].

In a report from the Massachusetts General Hospital in the USA [13.34], 101 patients with locally advanced primary rectal cancer underwent pre-operative irradiation (with or without fluorouracil) followed by resection and IOERT. Patients undergoing margin negative resection had a five year actuarial local control and disease specific survival of 89% and 63%, respectively. Patients with microscopically involved margins experienced five year local control and disease specific survivals of 68% and 40%, respectively, and patients with gross disease, 57% and 14%, respectively.

Lindel et al. [13.35] analysed 41 patients with locally recurrent rectosigmoid cancer undergoing IOERT; patients with gross residual disease experienced five year local control and disease free survival rates of 21% and 7%, respectively, versus 47% and 21%, respectively, with clear or microscopically positive margins. A Mayo Clinic analysis described 175 patients with locally recurrent colorectal cancer (123 no prior EBRT, 52 prior EBRT) undergoing IOERT [13.36]. The year five year survival in previously unirradiated patients was 20% versus 12% in previously irradiated patients. The three year local control for the same two groups was 75% versus 51%, respectively, and the three year distant metastases rates were 64% versus 71%, respectively.

Given the high rate of distant metastases developing in locally advanced and recurrent rectal cancer patients after local therapy, significant improvement in long term survival will likely be achieved through the integration of these systemic agents into current treatment strategies.

### 13.3.3. Toxicity

Common side effects that occur if IORT is executed inside the pelvic cavity are neuropathy and ureteral stricture. Neuropathy is mostly related to IORT dose and is rare at a dose of 12 Gy. The ureter has more resistance to radiation than the peripheral nerves, and in animal experiments, ureteral fibrosis or stricture occurred when a radiation dose greater than 30 Gy was delivered [13.1]. However, ureteral stricture can be treated with a stent, so the ureter near the tumour does not have to be displaced from the irradiation field. Accordingly, adding IORT of 12 Gy to external radiotherapy of 45–50 Gy is thought to be safe for normal tissue inside the pelvic cavity.

## 13.4. SUMMARY

The term IORT is currently used for various techniques, which show significant differences in dose delivery. It is very important that reports on clinical outcomes refer to the method used. So far, in most reports local recurrence rates are significantly low. Compared with other methods, an intraoperative treatment has evident advantages:

(a) *Precision:* Direct visualization of the tumour bed during surgery guarantees accurate dose delivery. All other methods of post-operative localization of the tumour bed (e.g. by clips) remain indirect; nothing competes with direct visualization of the tissue at risk.

(b) *Cosmesis.* As a consequence of direct tissue exposure without distension by haematoseroma, IOERT allows for small treatment volumes and complete skin sparing. Both should have a positive effect on late tissue tolerance.
(c) *Patient comfort.* IOERT marginally prolongs the surgical procedure, while shortening — or in selected cases maybe even replacing — post-operative radiotherapy.

## 13.5. KEY POINTS

— Intraoperative radiotherapy (IORT) is an intensive radiation treatment that is administered during surgery.
— IORT allows higher effective doses of radiation to be used compared with conventional radiotherapy. It is not always possible to use very high doses during conventional radiotherapy, since sensitive organs are often nearby. IORT allows doctors to temporarily move or shield nearby organs from radiation exposure.
— In breast cancer, all other methods of later localization of the tumour bed (e.g. by clips) remain indirect; nothing competes with direct visualization of the tissue at risk.
— Accelerated partial breast irradiation (APBI) is an approach that treats only the lumpectomy bed and a 1–2 cm margin. The smaller volume of irradiation allows a higher dose to be delivered in a shorter period of time.
— The TARGIT study presents the first level I evidence of the equivalence of APBI using IORT to whole breast radiotherapy and confirms that targeted IORT allows the entire dose of radiotherapy to be administered in a single fraction at the time of breast conserving surgery, thus avoiding the need for repeated radiation treatments or placement of in-dwelling radiotherapy devices.
— Reports on cosmesis following full dose IOERT describe cosmetic results ratings of 71% very good and 95% good.
— The focus of many studies has been on patients with rectal cancers that are adherent or fixed to adjoining structures such as the sacrum or pelvic sidewall, where resection is not feasible without leaving microscopic or macroscopic disease behind.
— Common side effects that occur if IORT is executed inside the pelvic cavity are neuropathy and ureteral stricture.
— The term ‘IORT’ is currently used for various techniques, which show significant differences in dose delivery. It is very important that reports on clinical outcomes refer to the method used.

— Compared with other radiotherapy modalities, intraoperative treatment has evident advantages: precision, cosmesis and patient convenience.

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# Chapter 14

# CONNECTIVITY ISSUES IN RADIATION ONCOLOGY: THE ROLE OF INTEGRATING THE HEALTHCARE ENTERPRISE — RADIATION ONCOLOGY (IHE-RO)

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## 14.1. INTRODUCTION

### 14.1.1. Data and work flow in modern radiation oncology

The delivery of radiation in the treatment of cancer represents a challenging technical and clinical undertaking. Technology is an integral part of radiation oncology, providing the advanced treatments that bring improved clinical outcomes, while also reducing the burden on the staff. The flow of patient treatment in a modern radiotherapy clinic is detailed in Fig. 14.1. It demonstrates the many exchanges of information between the different systems of radiotherapy. In each exchange of information between systems there exist opportunities for errors to be introduced. As new and future technologies are added to the treatment process (e.g. adaptive therapy, gating or active breath management, real time position monitoring), additional avenues for error open. Improvement in this area will further improve the safety and efficacy in the field of radiation oncology.

Understanding the work flow of treatment planning and delivery is fundamental to understanding the systems involved and the integration required. For a patient undergoing a simple radiation treatment, the work flow is as follows. The patient undergoes a computed tomography (CT) scan. A treatment isocentre is determined and marked on the patient externally with the aid of lasers connected to, but not part of, the CT scanner. The CT and isocentre are exported to the treatment planning system (TPS). The tumour and nearby organs at risk (OAR) are delineated by the physician, and then criteria for tumour and OAR radiation doses are set. A plan is developed to best meet these criteria. After the plan is accepted by the physician, a second calculation of the dose resulting from the planned radiation beams is performed to verify the accuracy of the TPS. This may involve the transfer of the beam parameters to a purpose built beam calculation programme. The plan is then sent to the treatment management system (TMS). Images for patient alignment may also be sent to the TMS. Additional details about the plan may be entered by hand in the TMS. The TMS stores the radiation treatment plan and is capable of communicating with the treatment

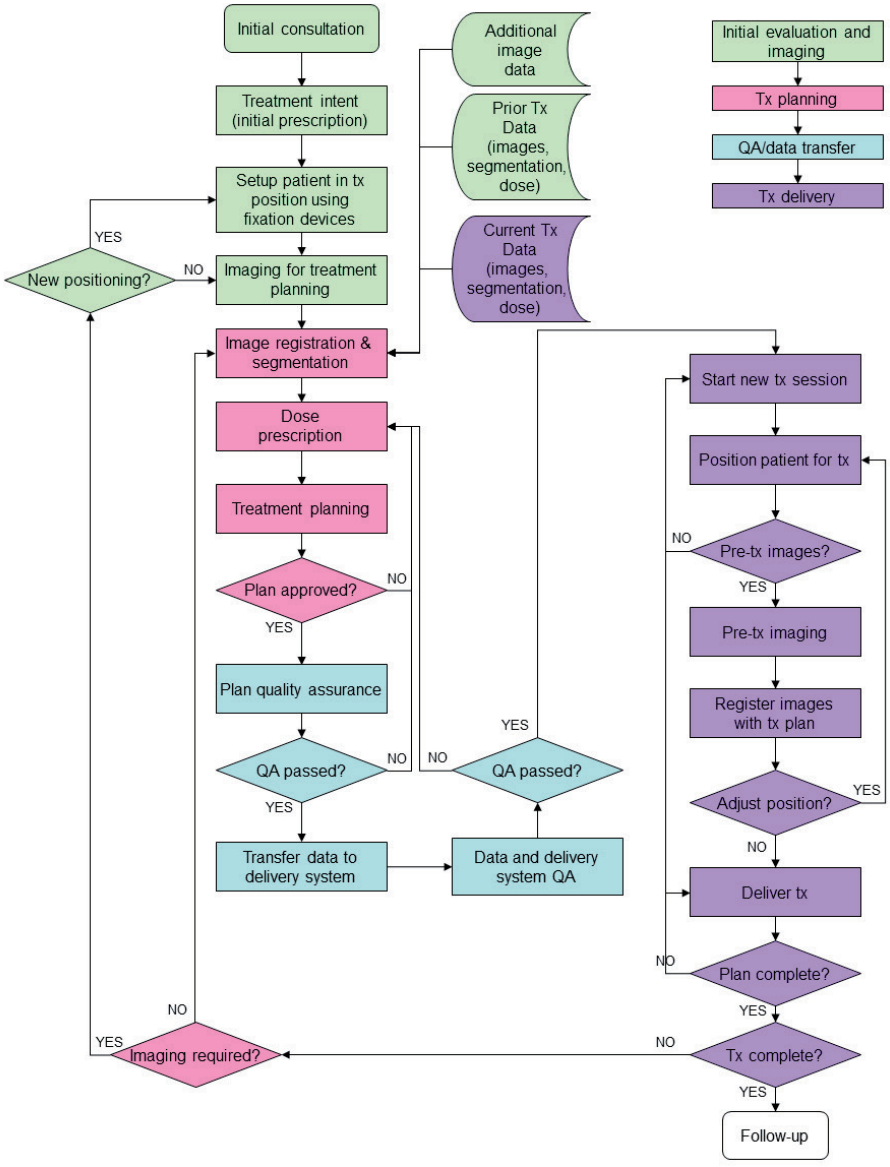


*FIG. 14.1. Work flow of a modern radiation oncology clinic (reproduced from IHE).*

delivery system (TDS), most often a linear accelerator (linac). The information in the TMS is verified to ensure fidelity with the TPS. Finally, once the treatment has been initiated, imaging and dosimetric data are collected for each fraction to record and confirm the accuracy of delivery and allow for modifications when necessary.

That is a simple treatment. There are many more systems (e.g. multileaf collimators, positron emission tomography (PET) and magnetic resonance imaging) that could be included. Additionally, patients often require re-treatment, or treatment to another site, necessitating the retrieval of the original treatment plan, which may be from many years prior, or from a decommissioned TPS. Storage of and access to data are therefore just as critical as data transfer in modern radiation oncology.

### 14.1.2. Defining the risks in radiation treatment delivery

Typically, the risks for medical procedures, including general medical treatment, surgical anaesthesia and prescription drugs, are of the order of $10^{-4}$ to $10^{-6}$ [14.1]. For comparison, the airline industry, often perceived as dangerous by the public, has a risk in the range of $10^{-6}$ to $10^{-8}$ per flight hour [14.2]. Given 40 patients treated daily by an accelerator, 250 treatment days annually and a 15 year lifetime, one critical overdose during that lifetime would give an error rate of the order of $10^{-5}$ [14.3]. A wide range of studies on the radiotherapy event rate have found rates ranging from 0.05% to 0.18% of fields treated [14.4–14.6]. The main types of errors arising in radiotherapy have been itemized [14.7]. Attention is usually focused on major, multipatient events, with correspondingly low probability, but the deleterious or hazardous effects of smaller events or errors that have a much higher probability of occurrence and frequently go unreported should also be considered. The increased complexity and rapid adoption of new technologies, coupled with increased patient throughput, creates an environment with more potential for accidents. Moreover, technologies intended to reduce the rate of treatment errors, if not used correctly, might act as a new source of error [14.8]. In addition, many issues and limitations of communication exist between various radiation oncology systems [14.9]. Errors can occur due to interconnectivity issues between different treatment planning, delivery and monitoring systems, resulting in unsafe treatment of patients [14.10]. Radiotherapy safety issues were considered one of the most important technology hazards for 2011 by the Emergency Care Research Institute (ECRI), an independent, non-profit organization that researches the best approaches to improving the safety, quality and cost effectiveness of patient care [14.11].

## 14.2. PITFALLS IN THE PROCESS AND THEIR SOLUTIONS

Human error and accelerator failures are common causes of mistreatments. These can include incorrect patient set-ups or the accelerator delivering an unsafe beam [14.5, 14.12, 14.13]. Accelerator failings have been catastrophic in the past [14.14]. From the beginnings of radiotherapy, safeguards have been in place to guard against errors. As a result, most mistreatments are the result of more than one failure [14.6]. Patient set-up errors are reduced with pretreatment imaging or table indexing, and accelerator interlocks have been improved to prevent delivery of erroneous radiation doses [14.15]. Accelerator and human errors are usually possible to detect.

Human error is best countered by education and by a system of quality assurance (QA) checks and cross-checks by vigilant and observant staff. Safety must be an integral part of the staff mindset, as errors resulting from systems failures should be detected by them [14.16]. Further, the process of QA must be monitored continuously to assess its effectiveness and improve it before it allows errors to slip through [14.17]. To reduce the scale of accelerator errors, there must be feedback between therapists, physicists and accelerator engineers [14.3]. This large user base ensures that unforeseen issues are discovered quickly and disseminated to other users while a solution is developed by the manufacturer [14.18].

A more insidious class of errors arises from the assumption that the systems are working together [14.9]. These systems require a great deal of effort to ensure that they function in unison. This is particularly the case when connecting systems from different manufacturers. As an example, we expect the TPS to correctly send the beam energy to the TMS, which in turn sends it to the TDS. Due to different formats or input/output expectations of the three devices, the beam energy may be misinterpreted and the wrong energy beam delivered by the TDS. These problems often do not cause interlocks or error messages, and are not noticed by therapists. Unless specifically checked, this fault, termed ‘connectivity error’, will cause patient mistreatment. Unfortunately, there is a great deal of information, repeatedly transferred, eventually producing too many exchanges to ratify manually [14.19]. This class of error must be mitigated in another fashion.

Because of its increasing quantity, information related to a radiation treatment plan must be stored electronically. It quickly becomes impossible for a human to check all of this information [14.17]. Instead, the TMS is largely responsible for this function. While the TMS reduces the number and scope of possible errors, it cannot prevent human errors and can create a false sense of security for the user [14.5]. Clearly, information must be entered correctly to be sent correctly [14.20]. Since the widespread introduction of TMSs, the overall

error rate has fallen by 40%. However, over-reliance on computer systems is responsible for a growing proportion of errors, with the percentage of events involving computer systems increasing from 17% in 2001 to 30% in 2006 to 2010 [14.6]. More system related errors are seen than any other type [14.8]. Users rely on computer systems as if they were mature and time tested technologies, which is often not the case. Further, once a mistranscription of a beam parameter occurs in a treatment plan, it will be repeated throughout the course of treatment unless caught by a human [14.13]. Lastly, electronic oversight is not always focused on areas with the highest probability for human error [14.17].

Poor integration of systems can lead to incomplete transfer of data, requiring manual entry of the remaining data. An example of this is sending the treatment plan to the TMS. Variables such as dose rate and bolus use often need to be entered by hand. Data transfer by humans is noticeably more error prone. In fact, human data entry is one of the most common causes of error, involved in 23% of events [14.21].

Even within a given system it is difficult to ensure proper functioning under all circumstances. Failures can result from errors in the software, or unexpected inputs from hardware or the user [14.3]. Software will require increasing regulation and oversight. Another specific class of connectivity issues arises from incorporation of varying image modalities for treatment planning. Consistency in image identification, particularly orientation, will be critical [14.22].

Computer networks are not flawless. Before system errors involving interpreting the transmitted data can occur, there is a possibility of data not even arriving. This can be due to incomplete set-up of the system connections, a change in the system connection, new product installation or a transient network state [14.23]. Considerable effort is expended in designing and fulfilling the information technology requirements of a radiotherapy clinic [14.24].

The most dramatic example of the difficulty and time consuming nature of connectivity issues occurs during a patient re-treatment. Often, the re-treatment is years or even decades after the original treatment. This original treatment, however, must be taken into account in the preparation of the new radiotherapy course. Resurrecting an old treatment plan, potentially from a TPS that has been decommissioned, and bringing it into a usable form is an arduous task. Even in the case of a recent treatment, the plan may have been created at another clinic or using a different TPS. If the plan cannot be directly loaded into the current TPS, the information in the plan will be significantly degraded in manually estimating prior radiation dose or treatment beams. This situation is less common than the daily transfer of data between the TPS, TMS and TDS; however when it does occur, the complications are much more significant [14.25].

Other errors can arise from integrating patient databases. Radiation oncology generally stores a large amount of data (on the order of a terabyte). The

standard electronic medical record is not designed to cope with such a quantity of data, and so separate databases are used in radiotherapy clinics, with just a subset of the data included in both databases. This information must be kept in synchrony, with data transferred between the two. However, the two systems, from separate worlds, are unlikely to have the same structure to allow easy interfaces.

As with user or accelerator errors, event reporting and user groups are the keys to understanding and overcoming connectivity issues. Rapid dissemination of information about connectivity issues is crucial to keep up with the evolving technologies of radiotherapy [14.12]. Once the collective data have been analysed, the connectivity issues between the TPS, TMS and TDS can be determined. Individual clinics often still have to find their own solutions to avoid these issues. This is because of the multitude of systems and equipment available, with compatibility not always having been a focus of their development. Furthermore, it is possible that a clinic is experiencing a unique issue, or is the first to experience such an issue. In this case, the solution will be unique. Solutions generally involve special cases (e.g. including the dose rate for sending a treatment plan to one accelerator but not the others), manually editing or renaming image and plan files, and 'knowing' when certain error messages can be ignored. These workarounds cause confusion and additional stress, and are clearly dangerous and best avoided. Transfer of therapists between machines also becomes unnecessarily difficult if there are differences in operating each accelerator just to allow it to deliver the correct beam, in addition to learning a distinct set of controls.

Connectivity is an integral part of radiation oncology, yet it has also been revealed how dangerous and unreliable it can be. Errors occurring in radiotherapy have been highlighted recently [14.26]. Like those discussed above, these errors are all avoidable. The need to protect the public interest has produced a strong reaction within the radiation oncology community, causing it to increase its efforts to overhaul the underlying framework that can produce these avoidable errors [14.26]. The effective solution to connectivity errors is standardization of the information flow. This is the approach championed by the Integrating the Healthcare Enterprise (IHE) initiative [14.27].

The goals of IHE are particularly crucial to radiation oncology, a field that has already adopted digital imaging, sophisticated computer modelling of radiation distributions in tissue, computer control of linac systems, computerized treatment management as well as digital patient records. As such, a subgroup of IHE specific to radiation oncology (IHE-RO) was formed to address the particular issues of connectivity between the systems of radiotherapy [14.28]. Further details about the structure and function of IHE-RO will be discussed later.

By developing protocols for the transfer of information that all equipment vendors can adhere to, connectivity issues can be drastically reduced. The effect of this is twofold: an immediate reduction in the number of connectivity related errors, and an increase in the time available to radiation oncology staff to check and prevent other errors from occurring.

In radiotherapy and medicine in general, there has been improvement with regard to the computerization of the process [14.29]. It now remains to fine-tune this computerization. With IHE-RO determining and rectifying the causes of connectivity issues, this fine-tuning can lead to a substantial improvement in both patient safety and clinical work flow.

## 14.3. THE IHE-RO PROCESS AND EXAMPLES OF HOW IT CAN HELP

IHE is an international collaborative effort that aims to improve compatibility across all segments of health care technologies. IHE-RO systematically addresses radiotherapy connectivity issues. The IHE-RO effort was initiated in 2004 through a multisociety, multinational, multispecialty task force, spearheaded by the American Society for Radiation Oncology (ASTRO). This effort was meant to address issues of interoperability and information sharing that impact the quality of care in radiation oncology.

IHE-RO includes members from the United States of America and international professional societies and academic institutions, as well as a large number of vendors and radiotherapy product manufacturers. This diverse group, in close collaboration with radiotherapy product manufacturers, develops appropriate solutions (integration profiles) for radiotherapy connectivity issues. Furthermore, the group has set up a testing process for seamless communication between the radiotherapy products.

IHE-RO performs functions through a planning committee (PC) and a technical committee (TC). The membership of these committees, along with schedules of activities, meeting agendas and minutes, and working documents, can be found on the IHE web site (http://www.ihe.net/).

### 14.3.1. The IHE-RO process

The IHE-RO process [14.30] begins with identification of a clinically relevant connectivity issue that needs a solution. This issue can be identified from feedback or submissions from the radiation oncology community, or from the IHE-RO PC members themselves. The issue is then described, analysed and developed using a standard template (use case) by the IHE-RO PC. The TC then develops a solution (integration profile) to the issue raised by the PC.

### 14.3.2. Connectivity solutions

Examples of completed integration profiles are basic radiotherapy planning, multimodality registration for radiation oncology and radiotherapy treatment work flow. The need for communication between systems is addressed by the 'Advanced RT Objects' profile. This profile was designed to facilitate the advanced objects integration protocol, which is crucial to providing a means of easily comparing plans from two TPSs [14.29].

### 14.3.3. Multimodality image registration

Multimodality images are increasingly used for delineation in TPSs; these include ultrasound, CT, PET, CT plus PET, different metabolic tracers and hypoxia markers, MRI with various spin echo sequences, and contrast [14.31]. The solution developed by IHE-RO also includes image guided radiation therapy acquired cone beam CT, with the patient in treatment position just prior to radiation delivery. In addition, image studies are taken for follow-up (tumour regression or metastatic disease imaging) after therapy has been completed.

The multimodality image registration solution clarifies the use of spatial registration objects; promotes compatibility; and specifies how the images, contours (Digital Imaging and Communications in Medicine (DICOM) radiotherapy structure sets) and doses and their associated special registration object, can be exchanged between systems, stored, retrieved, processed and displayed. This IHE-RO solution has resolved the issues with image registration information transfer between TPSs, applications in the TMS, and diagnostic radiology workstations.

### 14.3.4. Advanced radiotherapy objects

This IHE-RO solution defines the structure for exchanging DICOM radiotherapy plan data between TPSs and TMSs. By defining the structure, the integration profile addresses the ambiguity involved in the exchange between systems for the purposes of replanning a patient's treatment on a different vendor system. The profile defines the following radiotherapy beam techniques or processes for TPS and TMS: motorized, hard and virtual wedge beams, arc and conformal arc beams, step and shoot and sliding window beams, static electron beams, stereotactic beams, intensity modulated arc therapy/volumetric modulated arc therapy beams, bolus, block, compensator, and hard wedge beam modifiers. Implementation of the advanced radiotherapy object integration profile by a TPS will enable a patient treatment plan to be reproduced based on the output of another TPS for all of the techniques listed. Furthermore, the implementation

of this profile by TMSs will allow data to be transferred to treatment delivery systems produced by multiple vendors [14.32].

### 14.3.5. Implementation

Once the integration profile is finalized, vendors implement the connectivity solution on their products and test it through software tools (test tools) provided by IHE-RO. Finally, confirmation testing is performed at an annual live testing event ('Connectathon'), where vendors receive and submit the test data from and to at least three other vendors.

Finally, radiation oncologists, medical physicists, and administrators can use the resulting technical specifications in requests for proposals during the process of procurement of new software/equipment. A purchase specification template will become available.

IHE-RO can thus simplify the purchase process and lead to better connectivity and smoother integration of the new equipment with the existing equipment in the department. The process also helps enhance vendor efficiency by highlighting issues with connectivity early in the development phase of the product.

### 14.3.6. Limitations of IHE-RO

The IHE-RO solutions (integration profiles) are very specific to each function, rather than global to a product. This means that the user must identify and specify the particular functions critical to a particular clinic. The purchase specification template provided by IHE-RO gives the user the ability to target those clinical processes that impact their particular practice and to clearly communicate these requirements to the vendor.

Thus, the limitations of the IHE-RO process include the specificity of the solutions to a particular problem and the fact that connectivity is tested with a limited, specific set of vendors. It is important to understand that the solutions are not applicable to all the functions of a product, but rather to a specific set of predetermined functions. For example, the product may be compatible in importing a set of images and opening a plan, but not in other functions.

### 14.3.7. Future IHE-RO projects

QA testing prior to the delivery of radiotherapy is recommended in order to create a safe radiation oncology environment. It should cover all steps in the treatment delivery process [14.33]. An automated process is proposed by the IHE-RO safety connectivity solution [14.25]. IHE-RO addresses safety

connectivity issues with an automated QA system, where the desired treatment plan is verified to be correct by the TMS and then transferred to the TDS. The TDS in turn will have an internal check and verification of this plan and will stop delivery of the treatment if these parameters do not match. While this system is only in the developmental phase, the ultimate goal is 'automated quality assurance' of all these different connections. The role of IHE-RO is to verify the accuracy of connections between diverse TPSs and TDSs that are available on the market.

In addition, IHE-RO is developing a web based tool to aid the user concerned about a specific connectivity issue in determining if a connectivity solution has been developed. This tool can specify which vendors have successfully passed an IHE-RO Connectathon. This will help streamline and simplify the use and understanding of IHE-RO compatibility for the general radiation oncology community.

## 14.4. POSSIBLE IMPACT ON LOW AND MIDDLE INCOME COUNTRIES

The results of IHE-RO will benefit the global radiation oncology community, most notably when all systems in use are IHE compliant. Although comprehensive IHE-RO connectivity solutions will take time to develop, IHE-RO efforts have already resulted in some solutions. In low and middle income countries (LMICs), there may be old systems with less interconnectivity [14.8]. For these countries, which may also purchase refurbished equipment or older versions, greater freedom to choose from a wider range of equipment manufacturers avoids the financial pitfalls that result from a lack of competition in pricing. Thus, the benefits of compatibility may be greater and the effects more pronounced with unique financial advantages to these countries from IHE-RO.

Improved cost effectiveness and patient safety are the obvious impacts of IHE-RO, but another area of improvement is time management and patient throughput. Limited access to accelerators is a common situation in LMICs. This results in many patients being treated by a single accelerator, or extended waiting times for treatment. With a properly integrated system, connectivity errors have been removed. Thus, the amount of information therapists must verify during QA before initiating patient treatment, and at each subsequent fraction, is reduced, allowing more patients to be treated and relieving the pressure on the staff and the accelerator. This has a cascading, positive effect. Composed therapists are less likely to cause an error or to overlook one. Therapists can concentrate on their specific tasks of radiation delivery and patient care and not play technology watchdog.

The extra steps taken and workarounds used by dosimetrists and physicists in getting current systems to communicate would be alleviated by fully integrated systems. This would be complemented further by seamless data transfer between systems, resulting in faster generation of high quality treatment plans and, again, less time conducting QA of data transfer. These improvements would allow more patients to be treated, with fewer errors, and would have a positive impact on cancer radiotherapy in LMICs.

There is great potential for cost savings as well. Clinics would not be required to purchase all systems from one vendor to ensure compatibility. Moreover, backwards connectivity to current equipment may be provided by a new IHE-RO compliant system.

A clinic without IHE-RO compliant equipment could still benefit from the initiative today. Separate databases, utilizing IHE-RO integration protocols and test systems, could provide lists of known connectivity issues and potential fixes. These could prevent known issues from causing patient treatment errors before systems can be replaced with IHE-RO compliant versions. IHE-RO could also work with vendors to provide patches to previous non-IHE compliant software, to mitigate particularly hazardous issues.

Purchasing equipment without also investing in adequate training and QA is not advisable [14.34]. Staff training on new devices has been shown to be critical [14.12]. Purchasing equipment without understanding how it connects to other equipment is equally dangerous. IHE-RO can reduce the amount of training required if systems are similar in function and design. Expected components of treatment planning, management and delivery should all be present and should operate in a similar manner across different vendors. This will help clinics know exactly what will happen when they integrate their new system with their current systems.

## 14.5. CONCLUSION

Advances in radiation treatment design and delivery, as well as imaging, have resulted in new challenges for the radiotherapy team. The initial challenge is to ensure that imaging data from the CT simulator and other sources flow seamlessly to dosimetry for radiation treatment planning. After completion of the treatment planning process, data sets must flow to the linac for delivery to the patient. Furthermore, once treatment has been initiated, imaging and dosimetric data must be collected to confirm, record and verify accuracy of delivery, and allow for modifications when necessary.

As treatments become more sophisticated, transfer of data while maintaining their integrity becomes more challenging and solutions become more complex,

leading to potential detriments in patient safety and work efficiency. Solutions to the many challenges of connectivity can lead to a seamless integration and flow of data between the various planning and treatment components, leading in turn to safe and successful radiation treatment of the patient [14.32].

## 14.6. KEY POINTS

— Understanding the work flow of treatment planning and delivery is fundamental to understanding the systems involved and the integration required.
— Human data entry is one of the most common causes of error, involved in 23% of adverse events.
— Poor integration of systems can lead to incomplete transfer of data, requiring manual entry of remaining data. Other errors can arise from integrating patient databases.
— Connectivity is an integral part of radiation oncology, yet it has also been shown to be dangerous and unreliable. By developing protocols for the transfer of information, connectivity related errors can be drastically reduced.
— The Integrating the Healthcare Enterprise — Radiation Oncology (IHE-RO) initiative systematically addresses radiotherapy connectivity issues. The IHE-RO effort was initiated in 2004, and includes members from international professional societies and academic institutions as well as vendors and radiotherapy product manufacturers.

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# Part IV

# EDUCATION AND TRAINING

# Chapter 15

# EDUCATION OF RADIATION ONCOLOGISTS

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## 15.1. INTRODUCTION

The availability of trained staff in adequate numbers is one of the main obstacles to the development of modern radiotherapy in developing countries. While radiation oncologists practising in affluent environments may not be aware of this reality, limited number of positions, low wages, limited access to sources of evidence and 'brain drain' are common in countries with limited resources. Epidemiological predictions of an increase in the crude incidence of cancer that will affect predominantly developing countries represent an alarming situation in which the countries that will face the steepest increase are those most poorly prepared to cope with it.

Modern cancer radiotherapy is characterized by team work in which different professionals have different roles and responsibilities. The radiation oncologist is the physician who has been trained to participate in diagnosis, staging, prescription of the radiotherapy dose and patient follow-up. The radiation oncologist is ultimately responsible for the outcome of his or her patient, and although other professionals also have significant responsibility in the radiotherapy process, the International Basic Safety Standards [15.1] state the following:

> "**Requirement 35: Responsibilities of the regulatory body specific to medical exposure**
>
> "**The regulatory body shall require that health professionals with responsibilities for medical exposure are specialized in the appropriate area and that they fulfil the requirements for education, training and competence in the relevant specialty.**
>
> "3.150. The regulatory body shall ensure that the authorization for medical exposures to be performed at a particular medical radiation facility allows personnel (radiological medical practitioners, medical physicists, medical radiation technologists and any other health professionals with specific

duties in relation to the radiation protection of patients) to assume the responsibilities specified in these Standards only if they:

- Are specialized…in the appropriate area…;
- Meet the respective requirements for education, training and competence in radiation protection, in accordance with para. 2.32;
- Are named in a list maintained up to date by the registrant or licensee."

This means that adequate training and education of radiation medicine professionals, including radiation oncologists, is not only a medical and societal necessity, it is also a regulatory requirement in countries that have a regulatory infrastructure in place, including legal, normative and operational implementing mechanisms.

This chapter addresses the nature of radiation oncology work and discusses recent trends in radiation oncology education.

## 15.2. THE DISCIPLINE OF RADIATION ONCOLOGY

Radiotherapy is a clinical modality dealing with the use of ionizing radiation in the treatment of patients with malignant neoplasia, and occasionally non-malignant disease.

Radiation oncology is that discipline of human medicine concerned with the generation, conservation and dissemination of knowledge on the causes, prevention and treatment of cancer and other diseases, involving special expertise in the therapeutic application of ionizing radiation. The specialty can be practised as an independent oncological specialty or may be integrated into the broader medical practice of 'clinical oncology' with the use of chemotherapeutic agents and targeted molecules to enhance the effectiveness of radiation in a multimodality setting, thus providing comprehensive treatment to cancer patients [15.2].

Radiation oncology includes the responsibility for the diagnosis, treatment, follow-up and supportive care of the cancer patient. The radiation oncologist sets the overall treatment policy for the radiotherapy programme and should participate in the evaluation of the proposed department clinical load, the design of facilities and the procurement of equipment. For individual patients, the physician is responsible for participating in a joint evaluation and clinical assessment of optimal therapy for the patient, the patient's care and the patient's follow-up evaluation. The dual terminology of radiotherapy or radiation oncology is still used, because a number of countries adopt either of these nomenclatures to indicate this speciality. The term 'radiotherapist' is preferred by those who treat a large number of patients with non-malignant disorders. Following

successful completion of training, the specialist could be considered either a radiotherapist or a radiation oncologist, depending on the country of his or her training. However, due to its broader scope, as defined above, the term 'radiation oncologist' is preferred here.

## 15.3. TRAINING RESIDENTS

The current scope of practice of radiation oncology demands that residents be trained in areas such as systemic therapies, toxicity of combined modality therapy, treatment of non-malignant disease, new and emerging technologies, principles of quality assurance, palliative and supportive care, and multidisciplinary aspects. New radiotherapy techniques are currently being introduced and are rapidly becoming popular. These require additional training for clinicians. Notably, more conformal radiotherapy (CRT) will require more attention and skills (as well as time) devoted to the localization and delineation of tumours, target volumes and organs at risk using modern imaging techniques. Three dimensional conformal radiotherapy (3-D CRT) has become the standard approach for the planning and delivery of radiotherapy treatments. In recent years, intensity modulated radiation therapy (IMRT) and other advanced techniques (radiosurgery, stereotactic body radiotherapy, image guided radiation therapy, robotic radiotherapy) have also become more and more popular. These newer techniques demand that the radiation oncologist define target volumes to be treated by the radiation beams, as well as the organs at risk, whose exposure to radiation must be accurately calculated and kept below predetermined dose volume constraints. The delineation of volumes on a computerized treatment planning system demands knowledge of cross-sectional anatomy and a robust interpretation of structures as seen on computed tomography, magnetic resonance imaging or positron emission tomography–computed tomography scans. Therefore, reading of cross-sectional imaging must be included in all radiation oncology training programmes. Without this additional training, the inaccuracy of margins may result in inaccurately defined volumes and poor treatment outcomes. Standard training programmes include exposure to disciplines such as medical physics, radiobiology and pathology, and imaging (radiology and nuclear medicine) and should also include rotations through the internal medicine wards. Training of a radiation oncologist must be such that the graduate of such programme would be able to practise as a competent and independent specialist.

'Competent' means capable of performing the duties of one's profession in general, or of performing a particular professional task, with skill of an acceptable quality. The independent quality of radiation oncology practice has become particularly relevant today. In fact, the specialty of radiation oncology is at a

crossroads. Currently, various factors pose a potential threat to the independent character of the radiation oncology profession [15.3]. High reimbursement in certain countries makes radiotherapy an attractive and lucrative target for other specialists. The trend of urological and neurosurgical practices establishing their own radiotherapy centres, hiring a radiation oncologist and delivering gamma knife, IMRT or prostate brachytherapy will probably increase. In addition, the process of reimbursement in many countries assigns more value to the technology itself than to clinical skills. Clinical care is becoming subordinate to other specialties, and the radiation oncologist runs the risk of becoming the deliverer of a single form of physical therapy [15.2].

The amount of training in systemic modalities of therapy varies from limited exposure to a full comprehensive programme that combines both medical and radiation oncology. The former programmes should allow the radiation oncologist to be able to prescribe radiation sensitizing chemotherapy drugs and combined regimes that are standard practice today in the management of most tumour sites such as rectal cancer, cervical cancer or cancers of the head and neck region, to name just a few. The latter programmes may be appropriate for small countries where a limited number of practitioners must handle all oncology cases. In this situation, an inclusive knowledge of both disciplines (medical and radiation oncology) becomes extremely useful.

## 15.4. RADIATION ONCOLOGY AND CLINICAL ONCOLOGY

There are basically two models of oncology postgraduate education. In one model, the specialist name is ‘radiation oncologist’ or ‘radiotherapist’ depending on the country. This system focuses almost exclusively on teaching radiation oncology. Given the current and frequent use of chemotherapeutic agents, and now also targeted agents in concomitant chemoradiotherapy protocols, the case is made that even in this model trainees need to be exposed to the principles and practice of cancer chemotherapy. Canada and the United States of America (USA) are countries where this model is applied. In these countries, radiation oncology and medical oncology training are completely separate postgraduate courses.

The second model names the specialty ‘clinical oncology’ or simply ‘oncology’. The education in this model consists of a comprehensive programme that includes full training in both medical and radiation oncology. In the United Kingdom, specialist training in clinical oncology takes a minimum of five years (whole time equivalent) and comprises two phases: basic and higher training [15.4]. The purpose of specialist training is to obtain the knowledge and the clinical and non-clinical skills required for the certificate, and to prepare

trainees for a career as a consultant in clinical oncology. The mainstay of training is supervised provision of service, supported by formal teaching.

The basic training (years 1–3) addresses the basic oncological sciences of cancer biology, radiobiology, medical physics, medical statistics and clinical pharmacology. During this time, the trainee is guided to develop an understanding of the application of these sciences to clinical oncology. Trainees should aim to have passed all five of these subjects within 12–18 months of starting training. During years 1–2, clinical experience and formal coursework should provide a general grounding in the principles of clinical oncology, and in year 3 this should become comprehensive and expand to the standards required for the final Fellowship of the Royal College of Radiology examination in the UK system.

The higher level training (years 4–5) is a more selective phase, and is likely to include many of the following: non-surgical oncology; site specific experience in two areas and experience in multidisciplinary clinics; clinical research, including preparation of manuscripts for publication; experience at another centre, either in the United Kingdom or abroad; teaching of other residents; management training; and leadership roles in audit projects.

## 15.5. TEACHING CORE COMPETENCIES

In contemporary medical practice, graduate and postgraduate training are moving from an emphasis on knowledge only to a spectrum of core competencies upon which education is based. Competencies include knowledge, but also skills and attitudes. In the CanMEDS framework, for example, seven competencies are identified. The physician and medical specialist should be: a medical expert, communicator, collaborator, leader, health advocate, scholar and professional [15.5].

Recent trends in medical education demand the inclusion of disciplines and competencies that were not taught a few years ago. These include competencies such as principles of management, basics of medical research, interpersonal and communication skills, and professionalism. In addition, the training programme must include both basic sciences of oncology and organ or site oriented clinical applications. It must have dedicated hours for theoretical teaching (lectures, seminars, journal club) as well as clinical skills training through the supervised care of patients.

## 15.6. ASSESSMENT AND EVALUATION

Assessment constitutes an ongoing process of gathering and interpreting information about a learner's knowledge, skills and/or behaviour. It is the process of documenting, usually in measurable terms, the extent to which the learning outcomes have been achieved and can, in principle, cover knowledge, skills, attitudes and beliefs. Assessment is a process that leads to accreditation and subsequent certification of the trainee. Methods of evaluation and assessment of medical residents should be studied relative to their comparative validity and reliability.

Accreditation is a voluntary process of evaluation and review based on published standards and following a prescribed process, performed by a non-governmental agency of peers. Certification, on the other hand, is a process to provide assurance to the public that a medical specialist has successfully completed an approved educational programme and evaluation, including an examination process designed to assess the knowledge, experience and skills requisite to the provision of high quality care in a particular specialty. As such, certification is provided by a governmental agency or office.

Assessment plays a very important role in the education process and often dictates what a student will learn. To a large extent, it determines what is taught and how it is taught. It should not simply be about the allocation of grades, but should help to inform and support student progress and identify areas where additional input is required. Assessment should be seen as facilitating learning, and should focus on what is learned rather than what is taught, as well as on learning outcomes [15.6].

Assessment should be transparent and assist rather than intimidate students. In this context, assessment should reflect the learning outcomes [15.7] and measure to what extent they have been met; that is, an evaluation of the effectiveness of the teaching process. It can be used by the faculty to measure how effective the linkages are between the learning outcomes and the teaching methodology and indicate areas where further review is required.

Assessment is one of the most obvious ways to evaluate what students have understood, whether they can apply the knowledge and/or carry out the particular practical skill and whether they have developed the affective skills such as good communication. It is also a means of evaluation of the effectiveness of the programme as a whole as well as its individual components.

Assessment should be an integral component of course design, and the amount and level of assessment should be consistent with the defined learning outcomes. It is about finding out what the student has achieved and giving it a value.

Assessment can be classified in many different ways, some of the most usual of which are [15.8]:

— Cumulative or formative;
— Objective or subjective;
— Formal or informal.

Cumulative assessment occurs *at the end* of a course, and its purpose is generally to enable the awarding of a grade; formative assessment takes place *throughout a course* or project and is used to aid learning and give continuous feedback on performance to students. These two methods are routinely used in larger courses to complement each other. This evaluation must document the resident's performance during the final period of training and verify that the resident has demonstrated sufficient competence to enter practice without supervision.

In formative assessment, the faculty must evaluate resident performance in a timely manner during each rotation or similar educational assignment, and document this evaluation at assignment completion. The programme must therefore: provide objective assessment in all the above competencies, ideally using multiple evaluators (faculty, peers, patients and other professional staff); document the progressive performance improvement of residents appropriate to the educational level; and provide each resident with documented regular evaluation of performance with feedback. The evaluations must be accessible for review by the resident in accordance with institutional policy.

The simplest explanation of objective assessment is the use of a form of questioning where there is a single correct answer. This could be something like multiple choice questions (MCQs) or a mathematical calculation as in dose/fractionation calculations. Subjective assessment, on the other hand, may have more than one correct answer, or there may be more than one way of answering the questions. Essays can be used for this type of assessment; an example would be the treatment of a tumour site where more than one option could be considered correct.

Informal assessment does not usually require a written answer and can be very useful in guiding students during class or practical sessions. Informal assessment can include observation, peer and self-evaluation, discussion or use of checklists. Formal assessment, on the other hand, usually implies a written examination in some format and may be external.

Outlined below are some of the common methods used in student assessments. The individual lecturer or the faculty must decide on the most appropriate form of assessment for each subject based on the content, learning outcomes and available resources.

## 15.7. ASSESSMENT METHODS

Assessment can and should take many forms [15.9], thereby testing a wide range of knowledge, skills and attitudes consistent with the taxonomy defined by Bloom et al. [15.7, 15.10]. In all assessments that will be allocated a mark or grade, it must be made clear to the students how the marks are going to be allocated. This will also indicate to them the level of detail required on each aspect of the topic.

The assessment of radiation oncology residents has traditionally included three approaches: ward evaluations, written examinations, usually with the MCQ approach, and oral examinations. Newer evaluation methods include: the Objective Structured Clinical Examination (OSCE) [15.11], the Standardized Patient and the 360 degree feedback assessment.

## 15.8. THE EUROPEAN MODEL: DEVELOPMENT OF A CORE CURRICULUM

Over the past 20 years, the European Society for Radiotherapy and Oncology (ESTRO) has been working on designing core curricula for the training of radiation oncologists in Europe [15.12]. These core curricula were meant to serve as a template for the national curricula, which are the responsibility of national authorities.

The aim of creating core curricula has been to harmonize the radiation oncology training programmes across Europe. This is expected to facilitate the free movement of medical specialists throughout the region based on increasing confidence that their training is sufficiently good to make such an exchange possible.

The core curricula were based on a combination of knowledge and skills. In the first two versions (1991 and 2004), an attempt was made to define the areas in which the trainees had to demonstrate their ability to treat patients and the topics they should have knowledge of. Being aware of the differences in cancer epidemiology, and in the availability of resources across the various countries in Europe, the core curricula were drafted in such a way that national authorities could adapt them to their own circumstances and realities. The risk of this approach was, of course, that much freedom was allowed for interpretation and deviation from the general goal. But, on the other hand, being too stringent would result in the risk that implementation of core curricula guidelines would not be accepted by all national authorities.

With the two previous versions of the curriculum endorsed by the national authorities in the past, the drafters had struck the right balance. However, radiation oncology education is currently on the threshold of a new approach: a competency based curriculum. The change and challenge in establishing the radiation oncology curriculum today is to move from implicit understanding of professional behaviour to an explicit assessment of the professional performance of the trainees. Consequently, the latest core curriculum of ESTRO is based on the seven general competencies, or roles, described in the CanMEDS system [15.5]. These are:

(1) Medical expert;
(2) Communicator;
(3) Collaborator;
(4) Leader;
(5) Health advocate;
(6) Scholar;
(7) Professional.

Some of these are not that different from the competencies in existing radiation oncology programmes in Europe. However, some items, as indicated, are more explicitly mentioned in the programme and, consequently, should also be assessed more explicitly. Introducing the evaluation of competencies into European training programmes would mark a change from the traditional means of evaluating residents. The new ways of testing competencies are:

— Feedback at the workplace;
— Workplace assessment;
— Use of 360 degree feedback;
— Use of a portfolio, including a log book.

In the old training programmes, the performance of trainees in daily practice was not seen by the tutors. In the new training programmes, this is no longer the case. Feedback at the workplace and workplace assessment means that the resident is being observed carrying out actions in practice, such as history taking, physical examination, obtaining informed consent, delivering bad news and other tasks.

The 360 degree feedback is a structured evaluation of residents by members of the staff, secretaries, technologists and fellow residents, focusing mainly, but not only, on the competencies of communication and collaboration. It has been accepted by the national representatives in Europe as a useful tool for evaluating the performance of trainees.

ESTRO has created a web based portfolio that could serve as a 'European passport' for graduates in radiation oncology, demonstrating the skills and knowledge achieved during the training [15.13]. In the portfolio, the trainee is asked to record the training schedules, the supervisors' assessments, the 360 degree evaluations, and the results of examinations, publications, conferences attended and other academic achievements reflecting the trainee's performance over the years of training.

ESTRO encourages the use of this European portfolio/log book and hopes it will be used in all European countries, as it will help not only to harmonize training programmes but also to support trainees in demonstrating that their training has been conducted according to European standards.

The major change in the new European core curriculum is that what was implicit in the old curricula has been made explicit. Professional behaviour is now an item to be evaluated; therefore, professional behaviour is more explicitly described in the curriculum, with more emphasis on communication, health advocacy, management and professionalism.

Although not everybody supports these changes, they are being driven by changes in medical practice and society. Therefore, it is better to be prepared for these changes in the radiation oncology community and train residents for the demands they are going to face in the future. The new ESTRO core curricula for all three professions — radiation oncology, medical physics and radiotherapy technology [15.14] — and the consequences in training and evaluation represent an effort to keep up with these new developments.

The situation in Europe is different from that in the USA. In Europe, specialist training programmes are the responsibility of national authorities. European professional organizations such as ESTRO can only provide guidelines on which these national authorities can base their national programmes, taking into account their national regulations and resources. Consequently, a European standard or a European examination with formal statutory applicability cannot be expected. The best that can be achieved is an agreement on a core curriculum and a common system of evaluation of competencies.

The ESTRO Annual Meeting in Barcelona in 2010, where ESTRO agreed on a common ground for evaluating competencies, showed that European countries have more in common than previously believed. ESTRO is planning a series of workshops to support national authorities in implementing the present guidelines of the competency based curriculum.

The concepts and approach to training and assessment presented here have been incorporated in the IAEA Syllabus for the Education and Training of Radiation Oncologists [15.15]. This syllabus has been endorsed by ESTRO and the American Society for Radiation Oncology (ASTRO) for the establishment of radiation oncology training programmes in developing countries.

## 15.9. THE MODEL USED IN THE USA: A UNIFIED APPROACH ACROSS 50 STATES

Over the past decade in the USA, the primary organization overseeing physician residency education (Accreditation Council for Graduate Medical Education (ACGME)) and the primary organization overseeing physician specialty board certification (American Board of Medical Specialties (ABMS)) implemented what are currently referred to as the 'six core competencies' that physicians should achieve in their medical education and training and, ultimately, in their daily practice [15.16]. The six competencies are:

(1) Medical knowledge;
(2) Patient care;
(3) Professionalism;
(4) Communication;
(5) Practice based learning;
(6) Systems based practice.

Through their initial certification process and maintenance of certification process, the specialty boards certify that each of their graduates demonstrates achievement and maintenance of these competencies through a lifelong process of continuing medical education, self-assessment and improvement of practice. In this section, the focus is on evaluation and assessment of competence in residency training and education in radiation oncology as is implemented in the USA.

The ACGME has residency review committees for each specialty. The residency review committee, composed of specialists and administrative staff, periodically reviews every residency programme, at least every five years. The residency review committee in radiation oncology is composed of six radiation oncologists, a resident member, administrative staff and an ad hoc member from the American Board of Radiology to ensure that the training programme is reasonably aligned with the certification process. The rigorous review process includes: an on-line application outlining the programme structure and rotations; a description of facilities, the laboratory and equipment; the caseload by site; the credentials of faculty; didactic programmes; case log books of residents; and evaluation methods. A document outlining programme training requirements in radiation oncology and application forms for programmes is available at www.acgme.org. The intent of the application is to document that each training programme has the appropriate resources and systems in place to train, evaluate and assess the competence of their trainees in each of these six areas of competence.

Following completion of the application, an on-site review takes place where the details of the application are reviewed and confirmed by a trained site visitor, residents and other referring specialists are interviewed, and a detailed site reviewer report is generated to confirm that the information on the application is accurate and to outline any areas of concern or discrepancies. The site visitor pays particular attention to evaluation processes, not only for evaluation of residents by faculty, but also evaluation of the faculty by residents, evaluation of each component of the programme and processes for programmatic improvement. The site reviewer report and application are then evaluated by the review committee, and recommendations are made to either continue approval of the programme (with or without specific recommendations or citations), place the programme on probation, or close the programme. Each programme is approved for a specified length of time (up to a maximum of five years) and a specified number of trainees.

In radiation oncology, as with many of the other medical specialties, competencies are assessed based on individual evaluations of each trainee during each of their rotations. While programmes are allowed flexibility in how they structure their rotations, trainees will typically rotate on a given service with one or two faculty, for a period of two to four months. Detailed evaluations of the resident are generated after each rotation by the supervising physician or physicians. In addition, other personnel, such as therapists, physicists, dosimetrists and nurses, will often evaluate residents in what is referred to as a 360 degree global evaluation of residents. Currently, most programmes have structured their evaluation forms such that the trainee is evaluated in each of the six competencies. Evaluations from therapists and nursing and dosimetry staff are valuable in assessing the competence of residents in communication, professionalism and systems based practice. While the supervising physician also addresses these areas, medical knowledge, patient care and practice based learning are more thoroughly assessed by the supervising physician. The programme director is expected to sit with each trainee at least twice yearly over the four year residency programme, to go over his or her evaluations and identify areas which require improvement. Case log books are also reviewed during these sessions to ensure that each trainee has the appropriate level of experience expected during the rotations. Over the course of four years of training, current requirements indicate that the resident is expected to participate in at least 450 external beam radiotherapy cases, 12 paediatric cases, 15 intracavitary brachytherapy cases, 5 interstitial cases, 10 radiosurgery cases and 6 cases involving unsealed sources. These specific requirements may be modified from time to time as procedures in the specialty evolve. As residents progress in their training, they are expected to assume increasing levels of responsibility with increasing understanding and competence in the management of the patient undergoing radiation treatments.

In addition to these global evaluations of each trainee throughout his or her rotations, other assessment methods include a yearly 'in-service' examination, which is typically a multiple choice written examination covering clinical radiation oncology, physics and radiation biology. These examinations are scored nationally such that each trainee receives a score of how he or she performed in relation to peers in equivalent training around the country. Programme directors receive scores for each resident as well as aggregate scores for their programme compared with others, so they are able to identify strengths and weaknesses in their training.

In general, competencies in medical knowledge, patient care, professionalism and communication are assessed through the routine evaluation process outlined above. Practice based learning and systems based practice are not as familiar to physicians in the evaluation process and have been somewhat more difficult to assess. However, trainee involvement in quality assurance programmes, including chart rounds and other quality assurance and quality improvement initiatives; participation in multidisciplinary clinics and tumour boards; and chart reviews and clinical research projects help to fulfil these competencies. Resident involvement in research as well as quality assurance and quality improvement programmes is expected for all trainees in radiation oncology, and residents are routinely assessed and evaluated in these areas.

At the completion of the four years of training, provided the trainee has fulfilled his or her requirements, including participation in the established minimum numbers of cases of external beam radiation, brachytherapy, stereotactic radiosurgery and unsealed sources, and has had satisfactory evaluations, the programme director is expected to verify that the resident has demonstrated sufficient competence to enter practice without direct supervision.

While the current system of evaluation and assessment is considered to be a marked improvement and has helped to establish more uniform standards expected of any practising physician, ACGME is moving toward the creation of milestones of resident competence. These milestones will define the essential behavioural attributes to be demonstrated in each competency before a resident moves on to the next level or graduates. Development of milestones in diagnostic radiology training and some of the other medical specialties is already well under way. Radiation oncology has not yet fully developed its milestones, but this process is moving forward and will likely unfold in the next few years.

## 15.10. THE IAEA SYLLABUS

In 2009, the IAEA published the IAEA Syllabus for the Education and Training of Radiation Oncologists [15.15]. This publication includes a description

of the various elements and components to be considered when planning and initiating a radiation oncology training programme. While it can be applied and followed in any country, the publication was tailored to the needs of developing countries.

The IAEA advises that a national authority be created which acts as the ultimate responsible body for the organization and monitoring of the training programme, including the implementation of an audit system for the periodic evaluation of accredited training institutions and programmes. The national authority should also be responsible for the eligibility of the trainees and their subsequent certification. It is advised that the national authority create a suitable mechanism to keep those already certified as radiation oncologists updated regarding recent developments in the field through a system of lifelong learning to maintain competence within the evolving practice environment (continuing medical education).

The overall length of a training programme in radiation oncology should be the shortest possible to ensure the initiation of the graduate's work in his or her country, without compromising the quality of the training. It must be recognized that in low and middle income countries, the lack of trained professionals in radiation oncology is an acute problem. Therefore, when resources are available from local or external sources to establish or upgrade radiotherapy services, there is usually a pressing need to have the staff trained in the shortest time possible. The minimum training period in radiation oncology should be three years full-time following medical school graduation or, if part-time, an equivalent period spent in the specialty. This period of three years should be regarded as the minimal period of time to cover the suggested curriculum. A period of four years is the more accepted time frame internationally. Over this full-time equivalent of four years, the candidate will be expected to gain a sound knowledge of radiation oncology as part of the comprehensive management of cancer as well as other diseases. During this period the candidate will work as a resident in radiation oncology and participate in seminars, conferences, teaching assignments and interdepartmental clinics, and both external beam and brachytherapy procedures [15.16].

The IAEA Syllabus recognizes that different levels of skills may be needed depending on the differences in infrastructure and equipment present in different institutions. Levels 1 and 2 (mandatory), as described in the syllabus, are required for all radiation oncologists, and this training should be provided in all training programmes. The elements presented as level 3 are considered desirable but not mandatory. However, all trainees should familiarize themselves with them, through didactic training and/or clinical experience.

## 15.11. CONCLUSIONS

A national authority should be responsible for establishing the mechanism of resident evaluation. Trainee evaluation records should be permanently maintained by the training institute. Assessment mechanisms may include some or all of the following: evaluations by the faculty (supervisors); periodic interviews with the programme director; evaluation of the portfolio; and in-service, written and oral examinations.

The trainee's record should include a final programme director's certification of satisfactory fulfilment of the programme's requirements. The trainee will then be certified as per the mechanism established by the national authority to practice independently as a radiation oncology specialist.

Curriculum changes need to be made to accommodate topics such as cross-sectional anatomy, deeper knowledge of computerized treatment planning and contouring, and definition of volumes in those programmes that do not currently include these skills.

Training programmes need to expose trainees to the new radiotherapy technologies such as IMRT, image guided radiation therapy, stereotactic radiotherapy, intraoperative radiotherapy and, if possible (level 3 — desirable), also to particle therapy modalities. If these modalities are not available in the main venue of the training programme, such exposure has to be guaranteed through partnerships with other centres and a system of rotations.

Modern programmes have to include elements of systemic therapy, including cancer chemotherapy, and hormone and targeted therapy.

Radiation oncology training and evaluation in developed countries have moved from the traditional knowledge based focus to training and assessment based on new competencies, such as clinical skills, attitudes, management and professionalism. The 'core competencies' discussed above should be considered part of the radiation oncology education, either in its original structure or in some adapted or simplified way. A system of assessment of these competencies has to be incorporated in the training programme.

## 15.12. KEY POINTS

— Radiation oncology is a discipline of medicine concerned with the generation, conservation and dissemination of knowledge on the causes, prevention and treatment of cancer and other diseases, involving special expertise in the therapeutic application of ionizing radiation.
— A period of four years is the most accepted time frame internationally for radiation oncology training.

— Radiation oncology training and evaluation in developed countries has moved from the traditional knowledge based focus to training and assessment based on new competencies, such as clinical skills, attitudes, management and professionalism.
— The core competencies should be considered part of radiation oncology education, either in its original structure or in some adapted or simplified way.
— Accreditation is a voluntary process of evaluation and review based on published standards and following a prescribed process performed by a non-governmental agency of peers.
— Certification, on the other hand, is a process to provide assurance to the public that a medical specialist has successfully completed an approved educational programme and evaluation, including an examination process designed to assess the knowledge, experience and skills requisite to the provision of high quality care in a particular specialty. As such, certification is provided by a governmental agency or office.
— In 2009, the IAEA published the IAEA Syllabus for the Education and Training of Radiation Oncologists, which includes a description of the various elements and components to be considered when planning and initiating a radiation oncology training programme.
— While it can be applied and followed in any country, the IAEA Syllabus has been tailored to the needs of developing countries.

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# Chapter 16

# EDUCATION IN MEDICAL PHYSICS

**A. Meghzifene, D. Van Der Merwe**

## 16.1. INTRODUCTION

Medical physics is a specialty which applies physics principles to medicine. It covers a wide range of subspecialties, including ionizing and non-ionizing radiation. Medical physicists work in clinical settings, academic and research institutes and the commercial sector. They fulfil an essential role in modern medicine, most commonly in the fields of diagnosis and treatment of cancer. Those working in the field of radiation oncology are generally called 'clinically qualified medical physicists (CQMPs) in radiotherapy', or 'radiation oncology medical physicists', depending on the country in which they work. They are part of an interdisciplinary team in a radiation oncology department dedicated to providing safe and effective treatment of cancer. Other members of the team include radiation oncologists, radiographers, dosimetrists, maintenance engineers and nurses.

In radiation oncology, CQMPs contribute to the safe and effective treatment of patients. Their knowledge of radiation physics and how radiation interacts with human tissue and of the complex technology involved in modern treatment of cancer are essential to the successful application of radiotherapy. The primary responsibility of the CQMP within this team is to optimize the use of radiation to ensure the quality and safety of a diagnostic or therapeutic procedure. This is achieved predominantly through the use of physical and technical aspects of appropriate quality assurance (QA) programmes and control of dosimetry and calibration of beams. CQMPs working in radiation oncology are expected to have a core competency in medical physics, acquired through a postgraduate academic education programme. In addition, clinical competence, acquired through a structured clinical training programme or residency within a clinical department, is also required. It has been well documented that accidents can occur in the practice of radiation oncology when proper QA is not performed [16.1, 16.2]. Appropriate QA can only be implemented and practised by adequately trained staff.

At the international level, the International Organization for Medical Physics (IOMP) has published policy statements to stress the important role and responsibilities of medical physicists and requirements for their education and

clinical training [16.3]. The IAEA has published education and training material in radiation oncology [16.4, 16.5] and has supported the organization of training courses in this field. Through its technical cooperation project on strengthening medical physics in radiation medicine, the IAEA, jointly with professional societies and international organizations, has prepared a publication which aims at defining the roles and responsibilities of a CQMP in radiation medicine specialties [16.6]. In addition, the publication provides information on minimum requirements for the academic education and clinical training of CQMPs, including recommendations for their accreditation, certification and registration.

This chapter will start with a review of the roles and responsibilities of medical physicists working in radiation oncology. The international recommendations for academic education and clinical training requirements, as well as on accreditation, certification and continuing professional development (CPD) requirements, will then be summarized. The contents of this chapter draw heavily on the recommendations included in Ref. [16.6].

## 16.2. ROLES AND RESPONSIBILITIES OF MEDICAL PHYSICISTS IN RADIATION ONCOLOGY

When working in radiation oncology, the CQMP is a member of a multidisciplinary, professional health care team in charge of imaging and treating patients with radiation. The primary responsibility of a CQMP is to optimize the use of radiation to ensure the quality and safety of an imaging or therapeutic procedure. As a scientist and clinically trained professional, the CQMP is responsible for the physical and technical aspects of the QA programme, both in diagnostic and in therapeutic procedures. In addition to clinical duties, the CQMP plays a major role in the preparation of equipment specifications, and in conducting acceptance testing and commissioning. In many hospitals, the CQMP is also responsible for radiation protection aspects and for ensuring compliance with national regulations. The CQMP often takes part in hospital teaching of clinicians, medical physicists, dosimetrists, technicians, radiographers, nurses, and other hospital staff. Research and development is also carried out by the CQMP in radiation dosimetry, treatment planning, treatment verification and other areas. A detailed description of the roles and responsibilities of CQMPs is given in a number of recent IAEA publications [16.1, 16.5, 16.6]. A brief extract of recommendations from Ref. [16.6] is given below.

### 16.2.1. Facility design and shielding

The CQMP contributes to the design of new facilities. Specifically, the CQMP is responsible for determining the shielding requirements of new or refurbished radiotherapy rooms, ensuring that all radiation safety requirements are met.

### 16.2.2. Radiation safety and protection of the patient, the staff and the general public

The CQMP is responsible for the development and implementation of a clinical radiation safety programme for the radiation protection of the patient in radiotherapy. In many hospitals, the responsibilities also include safety of the staff and the public as it pertains to the radiotherapy service and infrastructure. The CQMP also participates in the investigation of incidents and near accidents involving radiation and provides appropriate reports and documentation.

### 16.2.3. Patient dosimetry

The CQMP is responsible for establishing procedures for the calculation and verification of the radiation dose to the patient. The duties include measurements for reference dosimetry and relative determination of absorbed dose from external radiotherapy beams and brachytherapy sources, development of methods to analyse the results of dose measurements, and checking of the accuracy of dose distributions delivered to patients. The CQMP is also responsible for patient specific dose verification measurements, including implementation of relevant in vivo dosimetry procedures.

### 16.2.4. Optimization of the physical and technical aspects of the therapeutic procedures

The CQMP participates in selection of the appropriate positioning and immobilization aids for optimization of the patient treatment plans; carrying out acceptance testing with the manufacturer and supervising maintenance of equipment; quality control and verification of beam shaping devices; and contributing to the development of methodologies used in the determination of set-up margins.

### 16.2.5. Quality management of the physical and technical aspects of radiotherapy

The CQMP participates in establishing a quality management programme and has the primary responsibility for implementation of its physical and technical aspects. The role of the CQMP includes the development of protocols and procedures for the optimal use of radiation, including dosimetry and equipment commissioning.

## 16.3. EDUCATION AND CLINICAL TRAINING REQUIREMENTS

The ideal education for an entry level medical physicist is agreed to consist of appropriate academic qualifications at the postgraduate level, coupled with structured and supervised clinical training in at least one area of specialization: radiation oncology, nuclear medicine or diagnostic and interventional radiology [16.3, 16.5, 16.6]. Ideally, a formal certification process is also needed for all clinical medical physics trainees before entering into clinical practice. In addition, an accreditation process, ideally through a professional organization, is needed to ensure that the curriculum meets minimum standards. Continuing professional development of the CQMP through attendance at courses, seminars and conferences should then follow.

The issue of clinical education is often neglected, with the assumption that an easy transition can be made from university education to clinical practice. Professional societies and international organizations such as the IAEA [16.5] have, however, highlighted the inadequacy of this approach and have focused attention on the need for specific clinical skills, which are an essential part of medical physics education. While short courses at the clinical level can be of help, properly structured and supervised clinical training requires a longer time frame to achieve the standards necessary for a competent clinical medical physicist. The IAEA decided to address the problems of clinical training in medical physics through the development of clinical training material. The first material to be developed was for the specialty of radiation oncology medical physics [16.5]; the training was later extended to include diagnostic radiology [16.7] and nuclear medicine [16.8].

The IAEA guidance [16.6] on education and clinical training of medical physicists states that a CQMP in radiotherapy must have:

(a) A basic university degree in physics, engineering or the equivalent (i.e. a three to four year degree, including advanced mathematics and physics), followed by:

(i) A postgraduate degree in medical physics. This should be an MSc or equivalent degree of one to three years, including courses covering all the specialties of medical physics. Examples of course syllabi for medical physics have been published by the IAEA in the form of handbooks on radiation oncology physics [16.4], on diagnostic radiology physics [16.9] and on nuclear medicine physics [16.10].
(ii) Clinical training for a period of not less than two years in one of the specialties of medical physics in the form of a structured residency programme supervised by a senior CQMP. Examples of medical physics clinical training programmes can be found in Ref. [16.5].

The following conditions should be observed for a clinical residency programme in radiation oncology:

(a) The training should be carried out in a hospital.
(b) The training should consist of full time equivalent years. If the clinical training programme includes academic courses or thesis research work, the total allocated time for the clinical training must be extended accordingly.
(c) The medical physicist trainees entering the programme and any academic courses included in it should be formally evaluated to assess their knowledge and competencies. Even when continuous assessment is conducted, it should be complemented by oral and/or written examinations.
(d) The centres where clinical training is conducted should offer a wide range of relevant clinical procedures and be equipped with a complete range of dosimetry and quality control equipment so that the resident will be appropriately trained in a wide spectrum of techniques.
(e) The number of trainees per supervisor should not exceed two or three at any given time to ensure quality training, depending on the clinical duties of the supervisor.

Candidates who already have a postgraduate degree (MSc or PhD) in physics, engineering or equivalent, should be given the opportunity to enter the education and training process. In this case, candidates should take appropriate academic courses covering all the relevant specialties of medical physics [16.11, 16.12].

Steps (a)–(c) above form the minimum qualification requirements for the CQMP. Both academic and clinical training should be competency based. Overall, the tertiary academic education and clinical training should extend over a minimum period of typically seven years.

While there are an increasing number of Master's level courses in medical physics offered by universities in many countries, the clinical in-service training

component of the total process has, in many cases, been missing. This has resulted in incomplete preparation of the medical physicist to practice independently, as important aspects of training cannot be completed in the university setting. It should be emphasized that practical sessions in a hospital on specific topics in radiation oncology physics, such as radiation dosimetry or treatment planning, are not considered an acceptable substitute for clinical training. The practical sessions are often conducted in groups, making the assessment of individual skills impossible. A structured in-service clinical training programme is a must, as it provides better preparation for medical physicists to ensure that they are capable of independent, safe and effective practice. Such a programme should reduce the total time needed for medical physicists to reach clinical competence and also prepare them to undertake the more advanced methodologies which are being rapidly introduced in radiotherapy. Relatively few countries have developed national standards of clinical training, which is an essential part of ensuring high quality and consistent training throughout a country.

Following the IAEA's recommendation [16.5, 16.7, 16.8], the persons undergoing training in this programme are referred to as 'residents' (also known as 'interns' or 'medical physics trainees'). A resident medical physicist is expected to be an employee of a hospital or clinical centre working in a radiation oncology department and contributing to the routine duties of medical physicists within that department under the supervision of a senior CQMP specializing in radiation oncology. This contribution is initially limited to that of an assistant, but should become more and more important as the resident's level of knowledge, competence and skills progress. During the final months of training, the resident should be able make an independent contribution to many of the duties of the medical physicist and require only limited supervision. Hence, the investment of time and efforts in training residents pays off as the residents become more experienced, thereby increasing their contribution to the routine medical physics work in radiation oncology.

## 16.4. ACCREDITATION AND CERTIFICATION OF CLINICAL MEDICAL PHYSICISTS

The formal process by which an independent recognized body (professional and/or governmental) evaluates a programme or a clinical site and recognizes that it meets predetermined requirements or criteria is called accreditation. It is highly desirable that both the postgraduate academic programme and the clinical residency be formally accredited by a national body. The process of accreditation of academic education and clinical training programmes usually requires that the programme administrator submit a self-assessment which gives information on

the programme and evidence of compliance with requirements. After review of the report, an on-site visit is conducted to ensure that requirements are met. If the mission is successful, accreditation is granted for a period normally up to five years. A renewal process usually calls for an updated self-assessment report. Additional information on the requirements and process of accreditation of medical physics education programmes can be obtained through the Commission on Accreditation of Medical Physics Education Programs [16.13], or the Institute of Physics and Engineering in Medicine [16.14].

Certification is the formal process by which an authorized body (such as a professional society or a health related committee) evaluates and recognizes the knowledge, skills and competence of an individual, which must satisfy predetermined requirements or criteria. It is a fact that in many countries no mechanism exists to certify the qualifications of a clinical medical physicist. However, all countries with a critical mass of clinical medical physicists should establish a certification process, as this is the best way to assess the knowledge, skills and core competence of candidates in a systematic way. It helps in achieving a recognized professional standard, which ensures quality and safety of patient treatment. For countries that have a low number of clinical medical physicists, certification in another country or by a regional professional society should be sought. The need for international certification of medical physicists has also been identified by the IOMP [16.15], and a process has been initiated for the establishment of an international certification board [16.16].

As with accreditation, certification does not provide a permanent standing, and a recertification process should be implemented to demonstrate that the CQMP maintains current knowledge, especially for new technologies, methods and practice standards. This is usually achieved through a CPD programme. Examples of well established certification bodies for medical physicists include the American Board of Radiology [16.17] and the Canadian College of Physicists in Medicine [16.18].

CPD is essential for maintaining professional competency, particularly for certified CQMPs. Its goal is to keep knowledge and professional skills up to date. Most CPD schemes include participation in educational and scientific activities such as conferences, symposia, courses and workshops, as well as education and training duties for medical physicists and other clinical professionals. Research and development oriented activities also pertain to CPD, including individual contributions to journals or books and other publications, and refereeing. Formally standardized CPD programmes should include an evaluation mechanism, for example, a credit based system, where medical physicists are awarded a number of points for each activity in which they participate. These should form part of the criteria for recertification. Some CPD programmes

also include an ethics component. A CPD scheme is recommended by most professional societies [16.3, 16.19].

## 16.5. CONCLUSION

Medical physicists who work in a radiation oncology department should have the knowledge, skills and competence needed to contribute to the safe and effective treatment of patients. International recommendations for education and training of medical physicists include a postgraduate degree in medical physics, followed by a structured and supervised clinical training programme of at least two years' duration in radiation oncology medical physics. In addition, clinical medical physicists working in radiation oncology should be subject to a certification process endorsed by professional societies or health related committees. This process of postgraduate academic education followed by structured clinical training will yield the required quality of medical physicists needed in radiation oncology. It is also hoped that this process will help establish a professional status for CQMPs in countries where such recognition is missing [16.20].

## 16.6. KEY POINTS

— Medical physicists fulfil an essential role in modern medicine, most commonly in the fields of diagnosis and treatment of cancer.
— The primary responsibility of a clinically qualified medical physicist (CQMP) in radiotherapy is to optimize the use of radiation to ensure the quality and safety of an imaging or therapeutic procedure.
— The CQMP is responsible for establishing procedures for the calculation and verification of the radiation dose to the patient.
— In addition to clinical duties, the CQMP plays a major role in the preparation of equipment specifications, and in conducting acceptance testing and commissioning.
— CQMPs working in radiation oncology are expected to have a core competency in medical physics, acquired through a postgraduate academic education programme.
— In addition, clinical competence, acquired through a structured clinical training programme or residency within a clinical department, is also required.

— The CQMP participates in establishing a quality management programme and has the primary responsibility for implementation of its physical and technical aspects.
— The ideal education for an entry level medical physicist consists of appropriate academic qualifications at the postgraduate level, coupled with structured and supervised clinical training in at least one of the following areas of specialization: radiation oncology, nuclear medicine or diagnostic and interventional radiology.
— The issue of clinical education is often neglected, with the assumption that an easy transition can be made from university education to clinical practice. Professional societies and international organizations such as the IAEA have, however, highlighted the inadequacy of this approach and have focused attention on the need for specific clinical skills, which are an essential part of medical physics education.
— A CQMP must have a basic university degree in physics, engineering or the equivalent, a postgraduate degree in medical physics, and clinical training for a period of not less than two years in one of the specialties.
— It is highly desirable that both the postgraduate academic programme and the clinical residency be formally accredited by a national body.
— A structured in-service clinical training programme is a must, as it provides better preparation for medical physicists to ensure that they are capable of independent, safe and effective practice.
— Clinical medical physicists working in radiation oncology should be subject to a certification process endorsed by professional societies or health related committees.
— Continuing professional development is essential for maintaining professional competency, particularly for certified CQMPs.

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# Chapter 17

# EDUCATION AND TRAINING OF RADIOTHERAPISTS

**M. Coffey**

## 17.1. INTRODUCTION

The radiotherapist (RTT) is a member of the multidisciplinary team responsible for the preparation and delivery of a course of radiotherapy to cancer patients. The roles and responsibilities of the RTT vary significantly among countries and, in some instances, within countries. They are a reflection of both the local or broader national factors and the available resources, but must always incorporate accurate and safe practice. Irrespective of the scope of practice, roles and responsibilities, any educational programme developed for this professional group must not only prepare the RTTs for current practice, but enable them to adapt to future developments and challenges. Quality and equality of care for all patients receiving radiotherapy are the ultimate goals. To achieve these goals, educational programmes must include the subjects underpinning accurate and safe practice and must integrate academic and clinical components.

Health care is undergoing reform in many countries, with a much stronger emphasis on patient centred care. However, reform of the delivery and quality of health care cannot be achieved without the parallel reform in health professional education. This need for reform is emphasized in the report on health professions education issued by the Institute of Medicine of the National Academies, wherein it is stated that "all health professionals should be educated to deliver patient-centered care as members of an interdisciplinary team, emphasizing evidence-based practice, quality improvement approaches, and informatics" [17.1]. This chapter deals with health care education in the United States of America, but the sentiment is equally applicable to the delivery of high quality health care for cancer patients throughout the world.

### 17.1.1. The global challenge

In striving to achieve the aims of equality of care for all cancer patients, it must first be acknowledged that wide variation exists in both radiotherapy resources globally and in the educational programmes for RTTs. In any environment the technology will dictate the level of complexity, but regardless

of the resource environment, accuracy and safety are integral elements of radiotherapy practice. In low and middle income countries (LMICs), where simpler techniques may be more commonly used, the correct application can achieve the desired goal. RTTs must be competent to carry out all treatments, simple or complex, accurately and in an environment characterized by safety awareness.

The cost of cancer care is increasing rapidly across the world. This issue is addressed comprehensively by the members of the Lancet Oncology Commission, who comment that the "ability to deliver affordable cancer care is at a crossroads" in high income countries [17.2]. The facts presented in this publication are no less applicable in LMICs, and careful consideration must be given to raising awareness of how efficiency and cost effectiveness can be increased. Educational programmes should reflect the importance of providing the best care in a cost effective environment. Baker et al. [17.3], discussing the improvement in health profession education, stated that health professionals "must be able to use fewer resources more effectively and be more innovative". Therefore, the leaders of RTT education should consider the inclusion of basic financial management and value for money approaches to health care delivery in educational programmes. A greater understanding of the breakdown of costs in the delivery of radiotherapy should raise awareness and encourage the more effective use of resources. This is particularly applicable in LMICs, where funding dedicated to radiotherapy may be limited.

#### *17.1.1.1. Cost factors in radiotherapy*

The cost of radiotherapy is increasing globally and can have an impact on the quality of treatment and treatment outcomes, particularly where resources are limited. All health professionals have an obligation to ensure they provide value for money in service delivery. Educational programmes for RTTs should address areas where cost implications can have a significant impact and explore how this impact can be kept to a minimum.

#### *17.1.1.2. Equipment*

While the major advances in radiotherapy equipment in recent decades have resulted in increasing precision, the cost has also risen proportionately. For high level precision, accessory equipment is required. If this equipment is not included in the initial tender, it can add significant and ongoing expense and may have an impact on the quality of care. One example that may result in suboptimal treatment is the lack of index linked accessory boards or overuse of immobilization masks. RTTs must understand the importance of accurate,

reproducible positioning and immobilization, and how it can be achieved in such situations. Educational programmes should introduce the RTT to departmental planning concepts and the factors that need to be considered as part of equipment purchase.

#### *17.1.1.3. Staffing*

As technology and its applications become more complex, additional staff members of all disciplines are required to ensure optimum use of available resources with accurate and safe treatment delivery. In their publication on organization theory, Burns et al. refer to the contrast between health care and industry with respect to technological innovation, stating that "In contrast to other industries, health care technology is often a complement rather than a substitute for labor — e.g., requiring many technicians to utilize the new equipment" [17.4]. In many countries, but more so in LMICs, and for many and complex reasons, staff shortages are a reality and RTTs may be required to fulfil roles not generally considered to be within their remit. Educational programmes must provide the basic knowledge and understanding on which to build the additional skills required to carry out non-traditional roles safely and effectively.

#### *17.1.1.4. Quality of life*

With improved techniques and increased knowledge and understanding of the scientific principles, more patients are cured or live longer with their cancer. The quality of life of cancer survivors is of serious concern and countries can suffer a significant economic loss due to cancer induced morbidity. Morbidity can cause great personal suffering and may necessitate long term care. Accurate treatment preparation and delivery can help to improve cure rates and reduce the incidence of avoidable morbidity. The direct costs associated with medical care are high and the patient's family and social network may also be impacted due to loss of earnings or increased need for their care and support. In addition, in LMICs, there is a higher rate of acute infections and chronic diseases, requiring an increased understanding of their impact on the planning and delivery of radiotherapy. Educational programmes for RTTs must address the importance of accuracy in minimizing morbidity.

### 17.1.2. Local, national and international factors

Like technology, education is also subject to external influences. Where education for RTTs is limited locally and/or nationally, with no academic staff available, there may be no mechanism for directly influencing the educational

institutions to establish or upgrade programmes. The role of the RTT may not be fully developed within the country, and therefore the scope may not be widely appreciated. International factors may also militate against higher level dedicated educational programmes for RTTs.

#### *17.1.2.1. Local*

The local radiotherapy department's focus is, and must be, the delivery of optimum service to the patient. A department may take a quantum leap forward in a technological sense but may fail to maximize its potential without the accompanying change at the managerial level, change in the approach of educational institutions to curriculum content and design, and motivational change at an individual level. It is the synergy between the three that will bring ultimate success.

The major changes occurring at the departmental level relate to technological developments, changing workforce profile and diminishing resources. In this context, RTTs must clearly define their role and contribution, and be enabled to fulfil this role through their undergraduate and postgraduate educational programmes. How the RTT is perceived in this context is very much dependent on the management structure and attitude. It is possible to deliver optimum service in a framework of innovation and professional development, and the appropriately educated RTT can be an integral component.

#### *17.1.2.2. National*

RTTs do not, however, exist only in the microcosm of the department. National policy dictates the structure and resources of both the clinical departments and the educational institutions. National policy may not be consistent with the aims and professional aspirations of the RTT, and financial constraints can impede progress and make change slow and tortuous. A policy change may be required at the national level if RTT graduates are to be educated, not only for current practice, but also to be aware of the new developments or changes planned for the future and to be in a position to meet new demand.

#### *17.1.2.3. International*

International factors can also impact, both positively and negatively, on RTT education. There is no defined title or role for RTTs at the international level, with a huge variation in the level of responsibility and scope of practice. Internationally, there are many examples of educational programmes for RTTs that fail to provide even the most basic elements essential to safe and accurate

practice, thus reducing the potential of the RTTs to embrace technological developments and changing practice in the future. In many academic environments, radiotherapy is a relatively new discipline with limited academic expertise. This restricts the development of the discipline and requires an element of flexibility to enable the discipline to become embedded in the academic environment.

The current educational level for RTTs in some LMICs is high, and these countries are sometimes targeted by countries with staff shortages that can offer higher salaries and better career prospects. This can create great difficulties for departments, and there is a danger in these situations that educational standards may be compromised in an effort to maintain the service. Efforts must be made by the educational institutions to maintain standards, even in very difficult situations, and to try to work with clinical departments to consider innovative approaches towards graduate retention in the national workforce.

### 17.1.3. The radiotherapy team

RTTs are members of a multidisciplinary team comprising the radiation oncologist and medical physicist, together with other health professionals, as appropriate. Functioning as an effective team member is an essential skill that must be addressed in RTT educational programmes.

"Effective and efficient performance of complex, interdependent tasks requires that providers be not only highly competent in their technical skills, but also proficient team members" [17.5]. This is very applicable in radiotherapy, where a team approach is essential to good practice. In low and middle income resource settings, it is crucial that tasks, roles and responsibilities are shared, and high quality education for all professionals is the key to achieving this [17.6]. This sentiment is also expressed by Headrick et al. [17.7], who recommend interprofessional education to increase understanding and appreciation of the roles of the other involved professionals. They state that "almost everyone who seeks medical care interacts with more than one health professional [and] the number of professionals involved and the importance of their ability to work collaboratively increases with the complexity of the patient's needs". Although this quotation relates to medical students and clinicians, it is equally applicable to RTT education and practice, where an understanding of the roles of other health professionals in the management of the cancer patient is crucial to optimum care.

### 17.1.4. The influence of education

The factors outlined above must be considered from an educational perspective as greater understanding can lead to improved quality of care and

greater efficiency and cost effectiveness. Accurate treatment by RTTs is based on knowledge and understanding of the scientific principles and the ability to apply these in the clinical setting. Correct image acquisition during treatment preparation, for instance, can reduce the need for repeat scans. Routine chart checks can detect and/or prevent incidents; clear and detailed set-up instructions can save unnecessary delays at first treatment, and careful management or documentation of acute toxicities, with early referral/intervention, may prevent treatment interruptions and reduce discomfort for the patients in both the acute and late settings.

Financial constraints at the departmental level may be reflected in high level technological developments with diminishing resources and a possible changing workforce profile. Education must prepare the RTT to adapt to changing technology, clinical developments, psychosocial factors, a greater emphasis on quality and risk management, legal and ethical issues and the importance of effective research. Where staff resources are limited, or shortages of other professionals exist, flexibility can be achieved if the initial educational programme for RTTs contains the necessary academic and clinical components to allow RTTs to be 'up-skilled', to carry out treatment planning/dosimetry or basic nursing care where these are not already a part of their responsibility. This could free other professionals to take responsibility for more complex elements of treatment preparation and patient care.

## 17.2. EDUCATION

The word 'educate' comes from the Latin 'e-ducere', to lead out. Two great educators of the past, Socrates and Galileo, saw education in this context. Socrates described education as drawing out what was already within the student [17.8], and Galileo said that "You cannot teach a man anything, you can only help him find it within himself" [17.9]. Education is a collaborative enabling process between the lecturer and the student to stimulate a continuously enquiring mind. This should be the aim of all educational programmes for RTTs.

Effective education in radiotherapy is an equalizer bringing professional freedom and impacting on professional practice, multidisciplinary relationships and ultimately the preparation and delivery of optimum treatment to cancer patients. There are many and varied influences currently affecting the education of RTTs, some of which have been referred to previously, but not the least of which is the lack of dedicated programmes and appropriately qualified lecturers. Irrespective of the external influences, the aspiration must be high quality care for all cancer patients, and the education of all health professionals involved in the preparation and delivery of radiotherapy underpins and supports this aspiration.

Health care students of the future, including RTTs, must be skilled and professional in their own field. They must learn to reflect on their practice and strive for improvement. Schön, a professor at the Massachusetts Institute of Technology, wrote extensively on reflective practice and the concept of knowledge in action [17.10]. Practitioners draw from their knowledge and past experiences to solve problems that arise in daily practice. This approach is consistent with the thinking of Socrates and Galileo, focusing again on encouraging the student to solve problems, and is an essential skill for RTTs working with a complex range of technologies coupled with individual patient issues. Reflective practice can be encouraged through the use of non-didactic teaching methods and problem solving approaches.

An effective RTT is a reflective RTT.

### 17.2.1. Educating the RTT of the future

Education should enable the students to ultimately know, be able to do and achieve more than their predecessors, and to engage with lifelong learning. Well educated RTTs will enhance the service offered to patients receiving radiotherapy. Weaver et al. emphasized the importance of lifelong learning, stating, "given the rate of technological and process advancement in health care today, the provision of safe and effective care demands a lifelong dedication to continuous learning and development" [17.5]. An educational programme for RTTs should inculcate within the graduate a desire for ongoing learning. In this context, educational institutions should provide or support both undergraduate and postgraduate programmes.

Education should provide the necessary knowledge, skills and attitudes for RTTs to readily adapt to change and development, and to consistently review their practice and research ways in which it can be improved. This aim was encapsulated by a report by the World Health Organization (WHO) on preparing a health care workforce for the twenty-first century:

> "The health care workforce not only needs to be capable of accepting change and managing it, but also to be prepared to embrace change and capitalize upon it. The success of health care systems depends on a flexible, innovative and adaptive workforce. All members of the workforce must have these competencies, or risk losing autonomy and influence."

This report focused on the challenge of chronic conditions, into which category many cancers now fall [17.11].

As technology changes so too does practice, with the current emphasis much more firmly on team work and partnership. As part of an adaptive workforce, the

RTT must be able to work in a collaborative framework with the other disciplines central to effective radiotherapy delivery. It is questionable whether single discipline education can create the correct environment for interprofessional practice. Wood et al. reflect sentiments similar to those of WHO when they refer to a "health care environment faced with patient safety issues, human resource shortages, and populations with increasingly complex health care needs", and discuss the importance of an interprofessional education approach stressing the benefits to the patients and service of this approach [17.12]. This approach to interdisciplinary education could also be very practical where resources and staff within the educational institutions are limited and would be most appropriately used for teaching the core competencies common to all health professionals.

#### *17.2.1.1. Education and professional practice*

Education underpins clinical practice, but should encompass more than the acquisition of clinical skills. The RTT is a professional who has a broader remit. Professionalism is about commitment to responding to the needs and concerns of others, which is an essential skill for the RTT. Professional practice is defined by the ability to distinguish between good and bad practice and to always accept only best practice. It is about mastering knowledge and skills in order to be of service, and this is where the educational programmes must enable RTTs by providing the appropriate content at the appropriate level in their programmes. Professional practice underpins best practice and implies at least a minimum level of autonomy and accountability.

Education should underpin professional practice and as such education and professional practice are inextricably linked. RTT educational programmes should enable RTTs to meet new challenges, to adapt to changes in the environment, to engage in research into their practice and to ensure evidence based best practice going forward. In the context of RTTs, it encompasses academic knowledge, technical competence, reflective practice and an ability to communicate. "Professional education is, on the surface at least, a particularly complex form of higher education having to satisfy a large number of educational objectives" [17.13].

Technological developments will continue and the new developments of today will become part of routine practice in the coming decades (see Chapter 30). Countries where technology and resources are currently limited will be implementing dose escalation, intensity modulated radiation therapy, and targeted molecular agents, amongst others, and the RTTs must be in a position to work with the other team members in this changing environment. The challenge for educational institutions is in preparing RTTs to fulfil both current and future practice requirements. One approach to meet this challenge is to define

the curriculum in terms of competencies. Competency based education can be considered "one response to demands for more effective, more accountable preparation for practice" [17.14].

*17.2.1.2. Competency based education for RTTs*

The Canadian CanMEDS approach is one example of competency based medical education and has been adapted by the European Society for Radiotherapy and Oncology (ESTRO) in the third revision of the core curriculum for RTTs [17.15] and by the IAEA in its recently revised curriculum for RTTs [17.16].

A competency based approach allows the educators to define the knowledge, skills and attitudes that underpin each competency and to match the teaching and assessment methodology best suited to achieving the desired learning outcomes. Competency based education also gives flexibility within the curriculum to add or remove competencies as practice changes. Greiner and Knebel refer to competency based education resulting in better quality and ultimately better patient care: "A competency-based approach to education could result in better quality because educators would begin to have information on outcomes, which could ultimately lead to better patient care" [17.1].

ESTRO's third revision of the core curriculum for RTTs has defined ten clinical competencies based on Bloom's taxonomy, thus incorporating knowledge, understanding, application, synthesis and evaluation described through a hierarchical scale and in terms of learning outcomes. These competencies cover the spectrum of roles and responsibilities carried out by RTTs in over 28 countries and can be modified to meet any national requirements in any country. The competencies described are: professionalism, positioning and immobilization, image acquisition and virtual simulation, treatment planning, treatment verification, external beam treatment delivery, quality assurance, brachytherapy, research and education [17.15].

The IAEA curriculum describes the competencies as understanding and interpreting the treatment prescription, patient positioning and immobilization, treatment delivery, treatment verification, information management, professional responsibility, radiation protection and health and safety, and the ability to critically evaluate practice [17.16]. Professionalism, research and education could be considered as core competencies, as they are shared with many other health professionals and could be taught as such. Other core competencies include communication and patient care and support, which have been incorporated in the external beam competency to avoid repetition.

There are other views on competency based education, with Rethans et al. comparing competency and performance from an assessment perspective and suggesting that performance is a more reflective measure of actual

practice [17.17]. Performance can be measured as part of a competency based educational programme by using a range of different methodologies, in both academic and clinical settings. One approach in the clinical setting can be to assess the student RTT over a period of time rather than during one single set-up procedure. This reflects more normal working conditions and enables the clinical staff to observe the student participating in treatment procedures, communicating with staff and patients, and completing any associated checks and documentation.

#### *17.2.1.3. Clinical practice — Theory in action*

Educational programmes must bridge the two components, academic and clinical, ensuring that they meet the academic requirements of the educational institution and the clinical practice competencies of the professional body. The clinical component of any degree programme must be significant, but must transcend skills training in the basic sense. Graduates need to be able to think and understand what they are doing while they are doing it. They need to be able to apply their knowledge in the clinical setting, implement or suggest change where appropriate and both participate in and initiate research into their practice. In this way, they become autonomous reflective practitioners. It is in the clinical setting that the RTT students learn to apply their knowledge and begin to evaluate practice.

A well structured clinical programme is an essential component of any educational programme for RTTs. It is through clinical placements that the basic skills necessary for safe and accurate practice are acquired. The acquisition of these skills depends largely on the knowledge and attitude of the clinical staff and is less dependent on the available technology; however, students should spend significant time during their clinical placement gaining experience on the most advanced technology available within the region.

Strong links must be established between the educational institutions and the clinical departments. Regular meetings should be facilitated and staff from the educational institutions should visit students on placement at frequent intervals. It is important to standardize the student experience as far as possible within the available resources and good liaison between the clinical and academic staff is essential to achieve this. Where resources are limited, countries could liaise to share facilities, thus maximizing the experience for students.

#### *17.2.1.4. Collaborative practice*

As stated previously, health care is more and more focused on team skills and a patient centred approach. A balance must be drawn by the educators as RTTs must become skilled and competent in their own field, secure in the

knowledge and understanding of their own practice. They must also understand and appreciate the skills and competencies of their professional colleagues and learn how good team work has a synergistic effect.

Health care students are expected to become skilful and professional in their own field. Interprofessional competence may be defined as the ability to collaborate with other professions, to know and understand the importance, functions and roles of others in other professions [17.18].

Greiner and Knebel describe an interdisciplinary team as "composed of members from different professions and occupations with varied and specialized knowledge, skills and methods" [17.1]. The members of the team each bring their own areas of expertise and in so doing "coordinate, collaborate and communicate with one another in order to optimize care for a patient or group of patients".

#### *17.2.1.5. Quality and safety*

Accurate and safe practice is the core of high quality radiotherapy and a key responsibility of the RTT. Radiotherapy can be considered a high risk area and RTTs must work with safety awareness at all times. A 2011 publication by WHO addressed patient safety in health care curricula. WHO stresses the importance of "building students' patient safety knowledge…throughout the entire education and training… Patient safety skills and behaviours should begin as soon as a student enters a hospital" [17.19].

The past decade has seen a major focus on safety and risk management. All educational programmes for RTTs must include modules on quality assurance and risk management. It is essential that RTTs have a strong understanding of the risks involved in the radiotherapy process and be able to evaluate clinical practice in this context.

## 17.3. CONCLUSION

Accuracy and safety are the essential components of RTT practice. Accuracy is achieved by an in-depth understanding of the scientific principles, coupled with skills training in a clinical setting, putting theory into practice. Safety is achieved through an understanding of the associated hazards and by instilling in the RTT the importance of constant awareness of and alertness to the risks associated with radiotherapy preparation and delivery.

Education for RTTs should provide them with the knowledge and understanding of the scientific principles underpinning best practice at all times. They should be competent to work efficiently and effectively on graduation and as they progress through their career become actively involved in education,

research and development. They should be confident in their own area of expertise and willing to participate in the multidisciplinary team providing high quality care to their patients.

The IAEA core curriculum for RTTs provides detail of curriculum content and teaching and assessment methodologies [17.16].

## 17.4. KEY POINTS

— The radiotherapist (RTT) is a member of the multidisciplinary team responsible for the preparation and delivery of a course of radiotherapy to cancer patients.
— RTTs must be competent to carry out all treatments, simple or complex, accurately and in an environment characterized by safety awareness.
— In many countries, but more so in low and middle income countries, staff shortages are a reality and RTTs may be required to fulfil roles not generally considered to be within their remit. Educational programmes must provide the basic knowledge and understanding on which to build the additional skills required to carry out non-traditional roles safely and effectively.
— There is no defined title or role for RTTs at the international level, with a huge variation in the level of responsibility and scope of practice.
— Efforts must be made by educational institutions to maintain standards, even in very difficult situations, and to try to work with clinical departments to consider innovative approaches towards retention of graduates in the national workforce.
— Effective and efficient performance of complex, interdependent tasks requires that providers be not only highly competent in their technical skills, but also proficient team members.
— Accurate treatment by RTTs is based on knowledge and understanding of the scientific principles and the ability to apply these in the clinical setting.
— A competency based approach allows educators to define the knowledge, skills and attitudes that underpin each competency, and to match the teaching and assessment methodology best suited to achieving the desired learning outcomes.
— Educational programmes must bridge the two components, academic and clinical, ensuring that they meet the academic requirements of the educational institution and the clinical practice competencies of the professional body.
— Graduates need to be able to think and understand what they are doing while they are doing it. They need to be able to apply their knowledge in the clinical setting, implement or suggest change where appropriate and

both participate in and initiate research into their practice. In this way they become autonomous reflective practitioners.

— A well structured clinical programme is an essential component of any educational programme for RTTs.
— Accurate and safe practice is the core of high quality radiotherapy and a key responsibility of the RTT.

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# Part V

# COSTS AND QUALITY

# Chapter 18

# COSTING IN RADIOTHERAPY

**E. Zubizarreta, Y. Lievens, V.C. Levin, D. Van Der Merwe**

## 18.1. INTRODUCTION

The available literature on the cost of radiotherapy yields a large variation in data related to the specifics of the methodology used (the viewpoint of the analysis, time frame, health care system, etc.) and to the cost components and radiotherapy activities included. To overcome this difficulty, the reimbursement paid by medical insurance is commonly used as a proxy for the actual radiotherapy costs. Costs, however, generally bear little or no resemblance to charges, as the latter also include allowances for non-capacity use and profit margins. Accurate resource cost data are therefore more valid and should ideally be used in the context of economic evaluations and public health provisions.

In addition to the theoretical problems related to obtaining accurate costs, it is difficult to interpret cost data across country borders because of differences in economics. If this is already the case for high income countries, using these cost data for low and middle income countries (LMICs) is even more problematic. Thus, there clearly is a need for calculations performed from the viewpoint of LMICs to prevent misapprehensions based on conclusions derived from data from their high income counterparts.

The IAEA endeavours to assist Member States in accumulating appropriate and sufficient cost data for the initiation or expansion of radiation oncology services. Although relatively simple and easy to understand, the IAEA has found that in many countries where it has been involved in the establishment of new radiotherapy departments, the basic principles of cost calculation for radiotherapy facilities were not followed by the local planners. Radiotherapy needs careful planning, organization and a strong quality assurance (QA) programme in order to deliver safe treatments, due to the complexity of the planning and treatment process and the possibility of systematic errors. Administrators should be aware that the cost of building a radiotherapy facility and buying machines represents only part of the total cost involved in running the department over a period of ten years. Training of personnel, salaries, maintenance and amortization can represent three times the initial investment in that period. But even when including all these costs, radiotherapy is a relatively inexpensive treatment modality, which can, as discussed later, be extremely cost effective.

## 18.2. ACTIVITY BASED COSTING

Various models have been proposed to calculate costing, such as an adaptation for radiotherapy of the activity based costing (ABC) model of the University Hospitals Leuven, Belgium [18.1, 18.2]. Considering different teletherapy alternatives, the ABC model was designed to calculate total departmental as well as individual patient costs, and to analyse equipment and personnel utilization for departments intended to deliver basic teletherapy services.

ABC is an advanced full costing technique focusing on activities instead of products [18.2, 18.3]. The assignment of costs through ABC generally occurs in two stages: resource costs are first allocated to the activities 'consumed' within the production process (e.g. for radiotherapy, medical wage costs are allocated to activities such as intake, treatment preparation, etc.); in the second step, the activities are allocated to the products based on the amount (time) of activity consumed. The cost of a product is thus equal to the sum of the costs of all the activities consumed to deliver the product.

The practical scheme that underlies this stepwise allocation procedure is unique for each specific situation. The definition of the components composing the model, mandatory in the design of each ABC system, should be driven by the required specificity and the ensuing complexity needed in the organization. The level of detail chosen is extremely important, as a very detailed approach, yielding the most accurate costs, results in a high workload and associated cost of development and daily use. Conversely, if the model is too simplistic, the lack of detail will result in major distortions in the costs.

## 18.3. DEVELOPMENT OF AN ABC MODEL FOR TELETHERAPY IN THE IAEA FRAMEWORK

Since it was the aim to develop a model that is easily applicable in different departments and countries, the model has been made as simple as possible, utilizing a limited number of files and straightforward entry data. Besides, it should be acknowledged that some estimates are difficult to derive for countries where radiotherapy hardly exists. For example, how is it possible to estimate the cost of bunker construction, or the likely mix of short, intermediate and long fractionation protocols in a country with no radiotherapy services? The former example requires the input of a local civil engineer, the latter that of a radiation oncologist thoroughly familiar with the cancer presentation patterns in the country being modelled.

For practical purposes, a limited number of parameters have fixed values. Figure 18.1 shows the components constituting the model and allocation of resource costs to radiotherapy activities before being further allocated to the treatments.

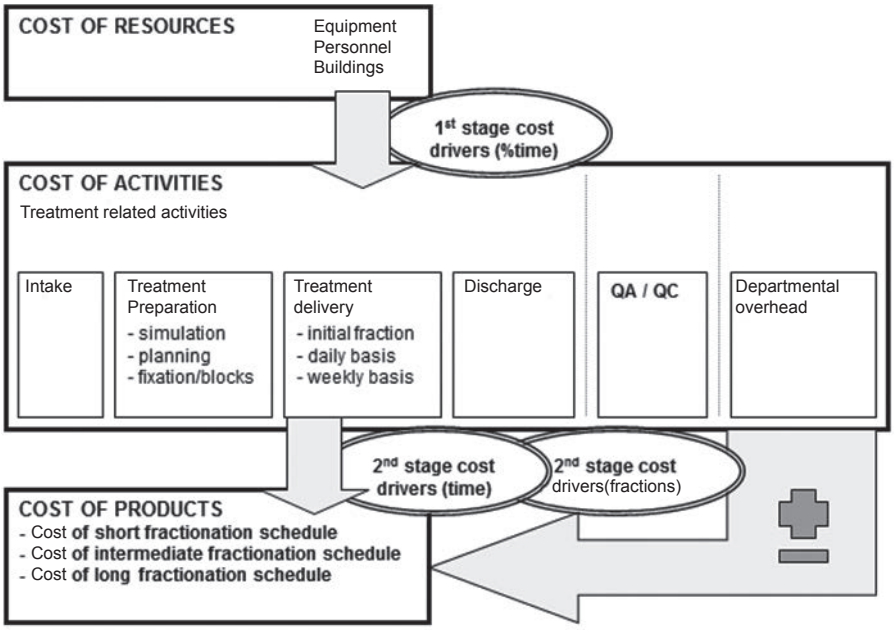


*FIG. 18.1. Overview of the allocation steps of the programme.*

The ABC model used in the IAEA Radiotherapy Cost Estimator (RTE) [18.4, 18.5] is presented here, and the calculation of costs will be explained through examples in hypothetical scenarios. RTE calculates teletherapy and brachytherapy capital, operational and product costs separately, and does not include the price of the land, training, or administration of chemotherapy in the analysis. A newer version is being prepared to include advanced technologies.

Costs can be basically divided into capital costs and operational or running costs. Capital costs are fixed, one time expenses incurred on the purchase of land, buildings, construction, and equipment used in the production of goods or in the rendering of services [18.5]. Operational costs include all expenses related to running a radiotherapy department (ready to operate), and include salaries, consumables, maintenance, amortization and overhead expenses such as electricity and cleaning. The cost per patient treated is obtained by dividing the sum of capital and operating costs through a lifetime period by the number of

patients treated during the same period. In the case of patients, the figures can change from department to department according to the treatment schedules used and the particular case mix scenarios. RTE delivers results per patient, and some adjustment of the protocols and case mix can be done.

Many components of the costs of radiotherapy are dynamic and interrelated. Staffing needs are strongly determined by the way work is organized and the case mix of the patients. Variations in the case mix will determine variations in staffing and workload on the machines, which will affect the final product cost. This is a dynamic process, and any variation in one of its components determines changes in the others. In low income countries, extension of the teletherapy work day is a low cost strategy to achieve the treatment of a large number of patients; in contrast, in industrialized countries, such economies are eroded by increased overtime wage costs. However, understaffing is seen frequently and usually affects the implementation of an optimal QA programme. According to the recommendations of the IAEA's Quality Assurance Team for Radiation Oncology (QUATRO) audits, 60% and 65% of the radiotherapy departments audited in Central and Eastern Europe and Latin America, respectively, were understaffed.

The costs of a small radiotherapy department in a middle income country can be analysed using the RTE as an example. In order to simplify the analysis, facilities, personnel and treatments for brachytherapy will not be included. Results are reported in euros. The analysis does not pretend to be exhaustive and is only presented as an example to help readers better understand the process of cost calculation.

## 18.4. DATA ENTRY

### 18.4.1. Resource costs

#### *18.4.1.1. Buildings*

The model comprises a core building cost for a patient service area (1200 m²), based on the unit cost per square metre, a yearly percentage for maintenance costs (2%) and the lifetime of the building (30 years). Appropriate additional buildings, all with a lifetime of 30 years and 2% yearly maintenance costs, are added to accommodate each separate teletherapy item or teletherapy related facility. These may comprise bunkers for linear accelerators (linacs) (150 m² each), simulators (75 m² each), a mould room (50 m²) and a treatment planning room (50 m²). For the initial example presented, there are no treatment rooms for cobalt, brachytherapy or orthovoltage machines.

The local construction costs per square metre, complying with international requirements for radiation shielding, will vary between countries because of differences in construction and material costs. This needs to be estimated for each country studied.

As stated earlier, the land is not included, but should be added to the initial costs, if applicable. In many low income countries, when the first radiotherapy facility is built, the government often owns the land adjacent to the general hospital, where the new department will be constructed.

Table 18.1 shows the area and building costs used in this model.

TABLE 18.1. AREA AND BUILDING COSTS

| Location | Area ($m^2$) | Cost (€) |
|---|---|---|
| Patient service area | 1 200 | 960 000 |
| 2 linear accelerator (linac) bunkers | 300 | 840 000 |
| 2 simulation rooms | 150 | 235 200 |
| Planning room | 50 | 68 000 |
| Mould room workshop | 50 | 68 000 |
| Total | 1 750 | 2 171 200 |

*18.4.1.2. Equipment*

The number and types of equipment are defined and comprise combinations of treatment machines (cobalt and orthovoltage and/or linac), simulator, treatment planning systems and mould room.

The model distinguishes between the costs of:

(a) Each item of equipment, based on the unit cost, the cost of any additional equipment, the yearly maintenance and/or upgrade costs, and the lifetime of the respective item;
(b) Quality assurance and quality control (QA/QC), based on the annual QA/QC hours and the wage cost of the medical physicist and senior radiation technologist performing the checks.

The model further identifies the number of working hours, based on the number of hours per work week minus the days of non-activity (public holidays, other days, repair downtime) and the number of hours devoted to QA/QC.

The selection of equipment depends on many factors, such as the stability of the power supply, the budget available, treatment techniques, clinical preferences, previously installed equipment and maintenance efficiency in the country/region. Teletherapy technology ranges from basic cobalt machines, mono- or multimodality linacs with or without multileaf collimators (MLCs) and electronic portal imaging devices (EPIDs), to sophisticated high end machines. For remote controlled afterloading brachytherapy, the options are cobalt or iridium based high dose rate machines.

Table 18.2 shows the capital cost used in the model for each piece of equipment.

TABLE 18.2. EQUIPMENT AND COSTS

| Equipment | Cost (€) |
|---|---|
| 2 × 6 megavoltage linacs (without multileaf collimators and electronic portal imaging devices) | 1 600 000 |
| 1 conventional simulator | 350 000 |
| 1 computed tomography simulator | 350 000 |
| 1 3-D treatment planning system | 100 000 |
| Mould room accessories | 30 000 |
| Dosimetry film developer | 100 000 |
| Total main equipment cost | 2 530 000 |

### *18.4.1.3. Personnel*

For each professional group (radiation oncologists, radiotherapy medical physicists, senior and junior radiotherapists (RTTs), nurses and administrative personnel), the local monthly wage costs are recorded or estimated from existing hospital personnel salary scales. The working hours are calculated on the basis of the numbers of hours per work week minus the days of leave (holidays, public holidays, sick leave and training). The number of full time equivalents (FTEs) of

personnel required in each professional class is an output of the RTE model. The salaries of the different categories are listed in Table 18.3.

TABLE 18.3. SALARIES

| Category | Monthly salary (€) |
|---|---|
| Radiation oncologist | 2400 |
| Medical physicist | 2400 |
| Radiotherapist | 1840 |
| Nurse | 1600 |
| Administrative personnel | 1320 |

### 18.4.2. Activities

Calculation of staffing needs is based on the activities involved. Staffing levels are dependent on the amount and complexity of equipment, the number of patients, the types of procedures and activities, and the number of students or trainees. A quantitative algorithm that proposes staffing levels based on all of these factors requires an analysis of the typical clinical workflow and then designation of professional roles to each of the activities that could be encountered. Non-clinical factors such as academic activities also need to be considered. This algorithm represents an activity based approach and attempts to capture all activities over the entire radiotherapy workflow:

(a) Intake: First contact with the patient and evaluation of the radiotherapy indication.
(b) Treatment preparation:
    (i) Simulation: Definition of the radiation fields.
    (ii) Planning: Calculation of the dosimetry of the treatment.
    (iii) Immobilization and blocks: Customizing immobilization material (e.g. masks) and shielding blocks.
(c) Treatment delivery:
    (i) Initial fraction: Extra QA/QC performed during the first treatment session.

(ii) Daily basis: Daily irradiation of the patient. Distinction is made between irradiation on cobalt or orthovoltage machines (four patients per hour) and on linacs (five patients per hour), based on a multinational assessment by the IAEA [18.6], but for the scenario presented here the same set-up was used.
(iii) Weekly basis: Considers the time needed for the weekly checks during irradiation (QA/QC, clinical follow-up).

(d) Discharge: Activities performed at the end of treatment (discharge letter, billing, etc.).

For each activity, the time taken by the different personnel categories is defined, making a distinction between the different fractionation schedules described in the product data. The time estimates are based on the assumption that two junior RTTs operate each treatment machine. The percentile proportion of time spent on external beam radiotherapy (patient related time) and departmental overhead (such as department management, follow-up consultations, teaching and general cancer control) is defined in Table 18.4.

TABLE 18.4. PERSONNEL TIME

| | Radiation oncologist | Medical physicist | Senior RTT | Junior RTT | Nurse | Administrative personnel |
|---|---|---|---|---|---|---|
| Patient related EBRT time | 60% | 70% | 85% | 100% | 75% | 60% |
| Total overhead | 40% | 30% | 15% | 0% | 25% | 40% |

**Note:** RTT — radiotherapist; EBRT — external beam radiotherapy.

### 18.4.3. Products

As the model calculates not only the departmental cost but also the treatment cost for each predefined fractionation schedule, the proportion of patients treated with each one and the use of blocks and immobilization devices should be defined. For the example presented, 800 patients are treated annually. Three fractionation schedules can be described as follows:

(a) Short (fewer than 11 fractions, mean of 5);
(b) Intermediate (between 11 and 25 fractions, mean of 15);
(c) Long (more than 25 fractions, mean of 30).

The relative proportion of each of these fractionation schedules and its complexity (blocks–immobilization) can be altered in the RTE, and for each fractionation schedule the additional complexity (number of treatments with blocks and immobilization) is defined in Table 18.5.

TABLE 18.5. RADIATION TREATMENTS

| Fractionation (fr) schedules (FSs) | Long | Intermediate | Short |
|---|---|---|---|
| | (>25 fr) average 30 fr | (11–25 fr) average 15 fr | (<11 fr) average 5 fr |
| Distribution of FSs | 50% | 30% | 20% |
| Use of blocks | 50% | 30% | 10% |
| Immobilization | 40% | 30% | 5% |

Buildings and equipment need to be maintained. In this model, the maintenance of buildings represents 2% of the building costs per year, and the maintenance of equipment has been calculated annually as 10% of the cost of equipment. The upgrade of certain equipment is important, especially accelerators and all software and computer hardware, and should be included in the calculation. Conditions for maintenance and upgrade contracts should be discussed and decided at the time of writing the specifications for equipment, and should be part of the documentation for tenders.

Amortization is another important component that should not be forgotten. In the context of radiotherapy costing, amortization is usually used as a synonym for depreciation, meaning the proportion of the cost of equipment or buildings that needs to be saved in order to replace them after their life cycle is completed. The usual values used for the life cycle of equipment and buildings can vary between 5 years for computers (depending on how upgrades were calculated and included in the maintenance contracts), 10–15 years for treatment machines (10 years will be used here) and 30 years for buildings.

## 18.5. RESULTS AND DISCUSSION

The analysis was divided into productivity, capital costs, operating costs and product costs. All the results are in euros.

### 18.5.1. Productivity

Productivity of a radiotherapy department can be divided into personnel and equipment utilization. Table 18.6 and Fig. 18.2 show how the working time of each profession is distributed between EBRT and other activities.

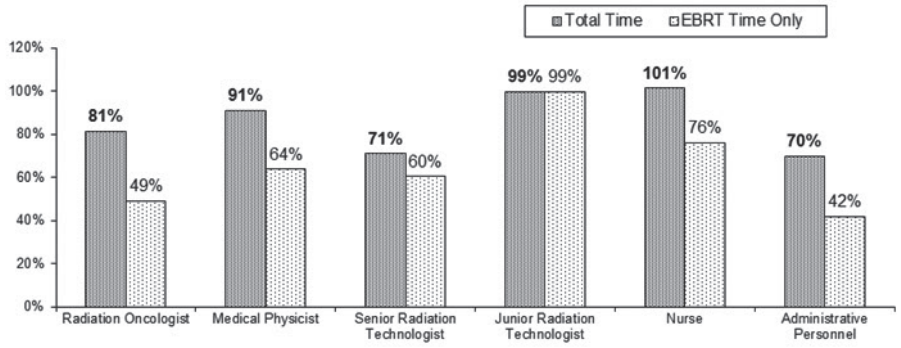


*FIG. 18.2. Personnel utilization.*

It can be seen that personnel utilization varies between 70 and 101%, depending on the specialty. The number of FTE staff is 15, including four radiation oncologists, two medical physicists, six RTTs, one nurse, and two administrative personnel. This calculation is done by RTE, and values can vary depending on the proportion of time assigned to different activities for each profession and on the case mix.

Table 18.7 shows equipment utilization. For the number of machines anticipated, the linacs are overutilized. A second shift of less than three hours per day will be necessary to cover needs. All other equipment is used less than 100%.

TABLE 18.6. PERSONNEL UTILIZATION

| | Calculated time (h) | | | Inclusive overhead | | Utilization |
|---|---|---|---|---|---|---|
| | Total time | EBRT time | FTE required | Utilization | Overused[a] | EBRT time |
| Radiation oncologist | 5928 | 3557 | 4 | 81% | | 49% |
| Medical physicist | 3315 | 2321 | 2 | 91% | | 64% |
| Senior RTT | 1292 | 1099 | 1 | 71% | | 60% |
| Junior RTT | 9065 | 9065 | 5 | 99% | | 99% |
| Nurse | 1845 | 1384 | 1 | 101% | | 76% |
| Administrative personnel | 2547 | 1528 | 2 | 70% | | 42% |
| Total FTE personnel | | | 15 | | | |

**Note:** EBRT — external beam radiotherapy; FTE — full-time equivalent; RTT — radiotherapist.
[a] Accepting a maximum of 20% overwork.

TABLE 18.7. EQUIPMENT UTILIZATION

| | Calculated time (h) | Number of units | Utilization |
|---|---|---|---|
| Linac | 4472 | 2 | 130% |
| Simulator | 592 | 1 | 30% |
| CT simulator | 592 | 1 | 30% |
| TPS | 1533 | 1 | 78% |
| Mould room | 257 | 1 | 13% |

**Note:** CT — computed tomography; TPS — treatment planning system.

### 18.5.2. Capital costs

As stated above, the land is not included in the present calculation. Capital costs are divided into building and equipment costs (see Tables 18.1 and 18.2). Capital investments per type of equipment, including building costs, can be seen in Fig. 18.3.

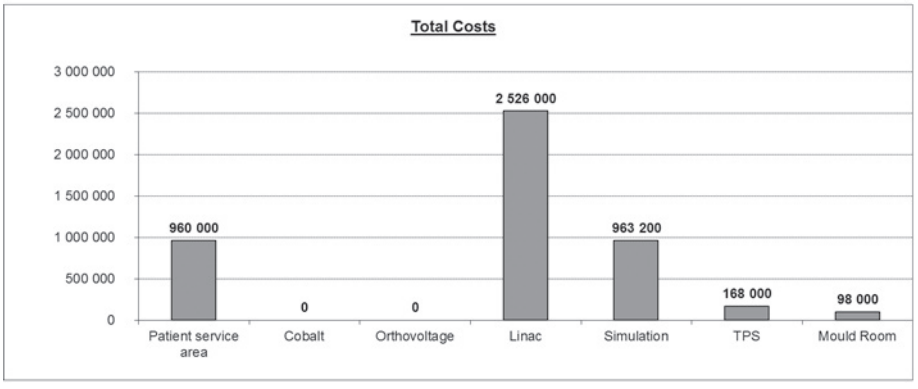


*FIG. 18.3. Capital investments per type of equipment, including building costs.*

The total capital cost of the department is €4 715 200. Equipment represents 54% and building 46% of the capital cost, i.e. €2 544 000 and €2 171 200, respectively.

### 18.5.3. Operational costs

The three main categories of operational costs in the example are maintenance costs at €338 924 per year, salaries at €356 160 per year and amortization at €323 798 per year, which gives a total of €1 018 882 per year.

Table 18.8 shows a detailed analysis of the operational costs.

TABLE 18.8. OPERATIONAL COSTS PER YEAR

| Category | Cost (€) |
|---|---|
| Main equipment maintenance[a] | 293 000 |
| Additional equipment maintenance[a] | 2 500 |
| Building maintenance | 43 424 |
| Salaries | 356 160 |
| Main equipment amortization | 238 300 |
| Additional equipment amortization | 13 125 |
| Building amortization | 72 373 |
| Total operational costs | 1 018 882 |

[a] Including upgrades.

Figure 18.4 shows the proportion between salaries, maintenance and amortization. The provision of adequate funding for maintenance and amortization is usually very difficult to manage in low income countries, where budgetary constraints and frequent changes of health and finance ministries and management discourage medium to long term policies. After the big initial investment effort, machines should be kept running every day for 10–15 years until being replaced. The cost of maintaining the building (€43 424/year) can be diluted in the maintenance budget of the hospital. Machines have at least a one year warranty, and the analysis of different maintenance options is frequently misunderstood or neglected. For the example presented, nearly €300 000 per year is spent on equipment maintenance. The reality of the breakdown of a poorly maintained machine comes sooner or later. Urgent disbursement to buy parts and repair the machine will be needed, and the amount is usually not budgeted. Downtime will affect efficiency and harm patient outcome. Amortization (€324 000/year) is even more difficult to address. When the available budget is

not enough to cover basic population needs such as potable water, immunizations and prevention and treatment of communicable diseases, amortization is usually forgotten. Maintenance then turns into ad hoc repairs, and running costs are represented by salaries only, jeopardizing adequate provision of radiotherapy and its future sustainability and development.

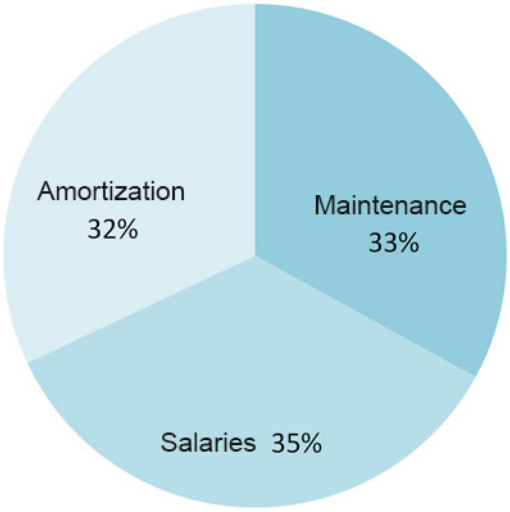


*FIG. 18.4. Relative weight of operational costs (salaries–maintenance–amortization).*

### 18.5.4. Product costs

IAEA Human Health Series No. 14, Planning National Radiotherapy Services: A Practical Tool, proposes the cost per radiotherapy fraction to measure the product cost [18.7]. This approach simplifies the calculation of the product cost, and as the number of fractions or slots per machine per time unit is often the bottleneck in radiotherapy productivity or utilization, it can help provide a clear overall picture. The RTE instead uses the cost per patient as its unit, which is obtained by dividing the total annual cost of the department by the number of patients treated annually. Treatments are divided into short, intermediate or long, and the average number of fractions for each type is predefined, as is the proportion of patients to be treated with each approach. An average cost for each category is obtained, and the total mean cost per patient is calculated depending on the relative weight of each type of treatment. All these variables are interdependent, and any change in the proportion of treatments under each

category will modify the staffing needs and the productivity of the machines, thereby changing the operational cost [18.8].

Table 18.9 and Fig. 18.5 show the different components of the cost per treatment type. Short treatments are cheaper than longer ones, as they include fewer fractions and use less equipment and professional time.

TABLE 18.9. COST PER TREATMENT TYPE

| Treatment type | Short (5 fractions) | Intermediate (15 fractions) | Long (30 fractions) |
|---|---|---|---|
| Building cost | 123 | 141 | 187 |
| Equipment cost | 656 | 788 | 1193 |
| Personnel cost | 204 | 364 | 590 |
| Total cost per patient | €983 | €1293 | €1970 |

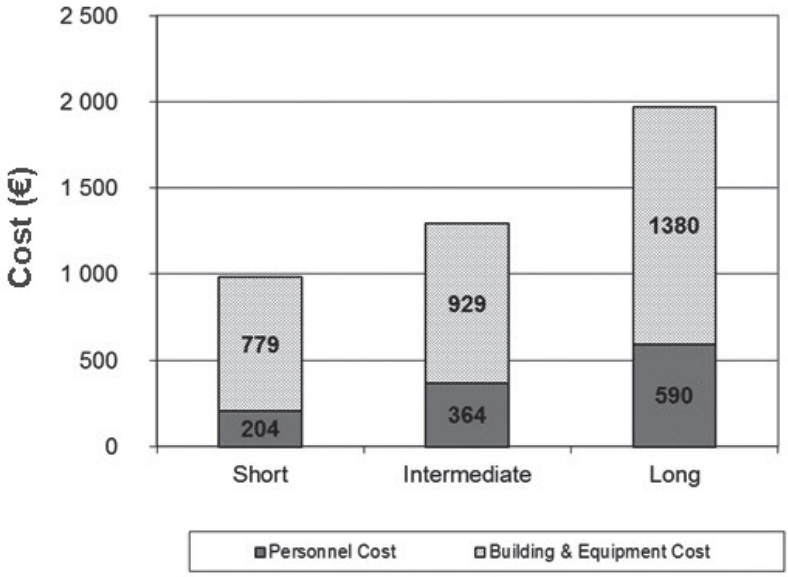


*FIG. 18.5. Personnel, building and equipment costs per patient per treatment type (includes departmental overhead).*

When putting together all components, personnel costs represent 32% of the total annual cost, building costs are 11%, and equipment related costs are 57%. For the scenario presented, the average cost per patient is €1274, which results from dividing the total annual departmental cost of €1 018 882 by 800 patients treated in one year.

It should be emphasized again that this is a dynamic process, and changes in the case mix (or the clinical protocols) can modify productivity, staffing needs, operational costs and product costs, meaning that different scenarios should be tested to have a range of values. This exercise can also be used to test different equipment configurations.

Many countries planning to establish their first national radiotherapy facility want to begin with a multimodality (MM) linac (two photon energies plus electrons) with MLC and EPID. The following analysis compares three different megavoltage treatment unit configurations:

(a) Two cobalt machines;
(b) Two single photon energy (SE) linacs (no MLC or EPID);
(c) One MM linac (two photon energies plus electrons) with MLC and EPID.

The three departments work 13 hours per day. Table 18.10 summarizes the analysis.

TABLE 18.10. COST AND CAPACITY ANALYSIS OF THREE DIFFERENT CONFIGURATIONS OF MEGAVOLTAGE TREATMENT UNITS

| | 2 cobalt machines | 2 SE linacs | 1 MM linac |
|---|---|---|---|
| Capital cost (€) | 3 993 700 | 4 715 200 | 4 709 700 |
| Departmental cost (€)/year | 952 156 | 1 160 465 | 907 196 |
| Total cost per patient (€) | 953 | 1 161 | 1 815 |
| No. of staff (RO–MP–RTT) | 4–2–8 | 4–2–8 | 2–1–4 |
| Patients treated/year | 1 000 | 1 000 | 500 |

**Note:** SE — single photon energy; MM — multimodality; RO — radiation oncologist; MP — medical physicist; RTT — radiotherapist.

The capital investment of the department with two cobalt machines is 85% of that of the departments which opted to install linacs. Departmental costs per year for the two cobalt machines are 102% of the departmental costs of the MM linac and 92% of those of the two SE linacs. Staffing is double for the two machine configurations. On the other hand, departments with such configurations can treat twice the number of patients per year. The cost per patient for the department with two basic linacs is 121% of the cost of the department with two cobalt machines, and the figure is 190% for the MM linac case. Some of these comparisons can be seen in Fig. 18.6.

The analysis shows that the approach of beginning a radiotherapy programme with sophisticated machines in a country where demand is not yet satisfied is not a cost effective solution and affects access to radiotherapy. Two simpler machines can be installed at more or less the same budget needed for an MM linac, and twice the number of patients can be treated at a much lower cost per patient. Another advantage of having twin machines is the possibility to continue treating patients in the case of a breakdown.

## 18.6. CONCLUSIONS

The challenge met in devising this model is that it is easy to use and only requires data on or estimates of the most essential cost and activity drivers, which are reasonably available in most developing countries. For this reason, for example, disposable material cost was excluded, as other computations showed that this cost does not exceed 5% of the total external beam radiotherapy costs [18.2].

During teletherapy, patients may receive any number of radiotherapy fractions, from 1 (typically used in the management of bone metastases) to 35 or more fractions in curative settings. In the model, three fractionation intervals (i.e. three radiotherapy products) have been defined, with a fairly equal distribution of the patients among these for the baseline approach. In countries with increased cancer awareness and screening, and hence earlier diagnosis, it may be more appropriate to use predominantly long fractionation treatments. In countries with limited resources and lower cancer awareness, on the contrary, the product mix might shift towards a more palliative approach, with overall shorter treatments. A closer fit of the fractionation schemes and the activity data with the actual practice might be achieved by linking them to a cancer management decision tree or by performing in-depth on-site interviews or measurements, but this is unattainable for most target beneficiaries of this model. Examples of more detailed approaches have been described in Belgian and Canadian studies [18.2–18.8].

The ABC model gives quantitative support for the intuitive conclusions on economic considerations involved in operating and maintaining a radiotherapy department in developing countries. Some are especially valuable in developing a strategy for radiotherapy services in a low resource environment.

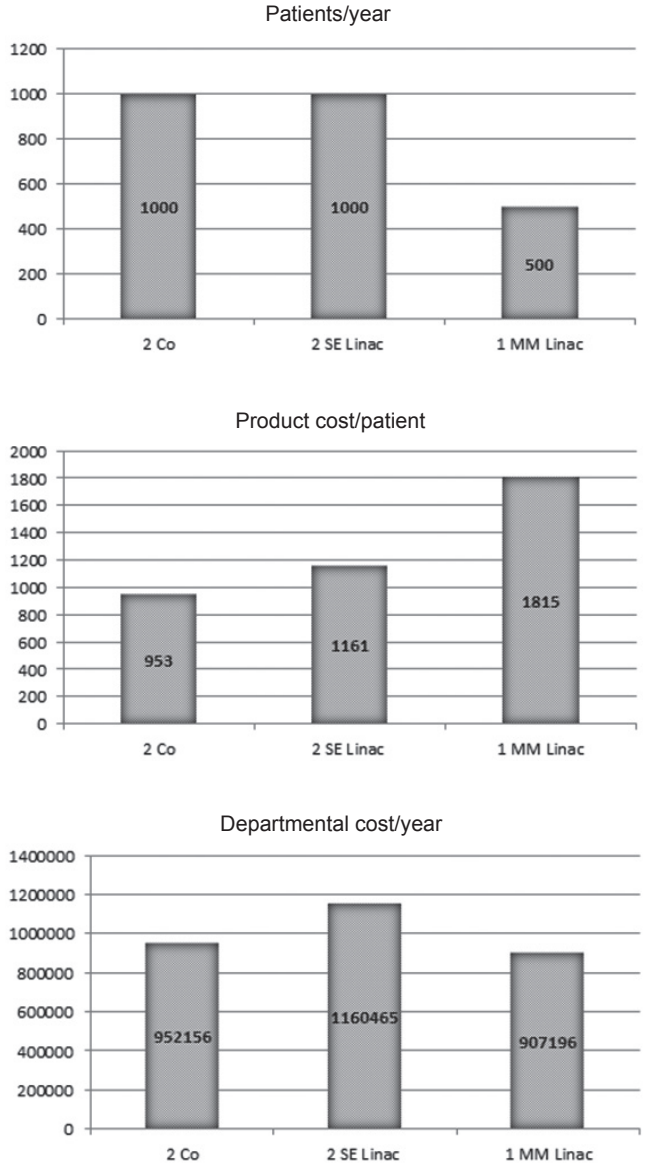


*FIG. 18.6. Cost and capacity analysis for three configurations of megavoltage machines: (left) two cobalt machines; (centre) two single photon energy linacs; (right) one multimodality linac.*

## 18.7. KEY POINTS

— In low income countries, extension of the teletherapy workday is a low cost strategy to achieve the treatment of a large number of patients; in contrast, in industrialized countries, such economies are eroded by increased overtime wage costs.
— Departments treating larger numbers of patients with multiple teletherapy machines have lower costs per patient treated, attributable in part to enhanced utilization of the treatment preparation tools. Conversely, small loads, especially those below 500 patients per year where all items are underutilized, will be associated with vastly increased costs.
— If cost recovery from patients in developing countries is set at a level that reduces patient access to services, and thus reduces the total number of patients treated, it will significantly drive up the cost of individual patient treatment.
— The introduction of national screening programmes (with increased numbers of patients presenting with earlier stage disease, shifting the product mix towards longer fractionation regimes) is not expected to translate into a dramatic rise in radiotherapy costs in developing countries, as the higher workload can be accommodated mainly by an increase in relatively inexpensive personnel.
— The strategy of beginning a radiotherapy programme at the national level with expensive and sophisticated machines will limit access to radiotherapy services, which should be the priority in those cases. The average cost per treatment will be increased using this approach.
— Low income countries with low budgets for health care and a long list of relevant and urgent needs should be particularly careful when designing a plan for radiotherapy development. Such a master plan should include a realistic calculation to address the needs, equipment selection, timelines to establish the first department and to expand the provision of radiotherapy, including training of new professionals, and adequate allocation of a budget to enable efficient radiotherapy delivery and future expansion, as needed.

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# Chapter 19

# QUALITY MANAGEMENT IN RADIOTHERAPY

**P. Scalliet**

## 19.1. INTRODUCTION

Soon after the discovery of X rays and natural radioactivity, the therapeutic use of ionizing radiation grew into what has today become an important oncological specialty, with unmatched cost–benefit features. Radiotherapy is an inexpensive solution to many cancers; it is a reproducible technique with fundamentals that rely both on a large set of evidence based medical data and on high technology equipment that has benefited from the digital revolution in the second half of the twentieth century.

One characteristic of radiotherapy is its narrow therapeutic window, with cure being never very far from injury. Therefore, radiotherapy administration requires great accuracy in target volume definition and dose control. Modest underdosage leads to the recurrence of cancer, while overdosage leads to unacceptable toxicity. While more sophisticated treatment techniques have emerged recently (intensity modulation, image guidance, hadrons), equally sophisticated means to control the actual delivery of radiotherapy have been developed.

Better control of dose delivery allows for better delineation between target tissue exposed to high doses and normal tissue shielded to the maximum, with steep dose gradients sometimes over a few millimetres. This, in turn, requires better volume definition and better control of patient positioning.

A fundamental question in radiotherapy is what exactly needs to be irradiated, and at which dose. It is by sustained efforts, through a better knowledge of anatomy and oncological surgical techniques, that the current approach has emerged. A continuous dialogue with other specialists, anatomists, surgeons, radiologists and nuclear medicine specialists has enlarged the radiation oncologist's understanding of anatomical and functional imaging. Atlases for delineation of gross tumour volume (GTV), relying on multimodality imaging (CT (computed tomography) scan, MRI (magnetic resonance imaging), and PET (positron emission tomography) scan), have been produced for a variety of tumours. Atlases of the natural routes of cancer spread, through lymphatic channels and anatomical planes, are now available for all parts of the human body. This in turn facilitates the definition of the 'clinical target volume' (CTV) [19.1, 19.2].

Four dimensional imaging has introduced the dimension of time, with the ability to see target and organ movements during free breathing irradiation.

A picture emerges where all steps between the diagnosis of cancer until cure of the patient can be merged into a single elaborate system whose objective is the safe and appropriate delivery of radiotherapy. This system is called 'quality assurance' (QA).

## 19.2. QUALITY ASSURANCE

The concept of 'total quality' has been borrowed from industry, particularly from the standardized approach to quality taken by the International Organization for Standardization (ISO) [19.3, 19.4]. It is a set of control points that ensures that each element of a process or a series of processes conforms to a pre-established standard. The idea behind it is that if a process conforms to its standards, then the result will actually meet expectations. In radiotherapy, the expectations are control of a cancer with a minimal and predictable impact on the quality of life.

Quality can be assessed by three different approaches [19.5]:

(a) *By the results.* The ultimate goal of radiotherapy, as mentioned earlier, is disease control. Five year survival, years of survival adjusted for quality of life (QUALY), local control and other clinical end points are all measurements of the appropriateness of radiotherapy interventions. It is indeed a requirement that radiotherapy departments question their outcome levels and benchmark them against published peer reviewed data. This is a difficult undertaking because radiotherapy is rarely the decisive intervention in cancer control. More often, it is part of a multimodal approach where the surgical or medical oncology elements escape the quality system of radiotherapy departments, while they are equally decisive in the ultimate treatment success. In addition, for survival data to be a relevant indicator, time is needed before a significant figure can be calculated. If results do not match expectations, little can be known about the underlying reasons, and what elements need to be improved for a correction of this underperformance. Last but not least, five year results actually assess the situation prevailing five years earlier. In the meantime, many elements might have changed in terms of staff, equipment or procedures. Therefore, long term survival data only give information on the past.

(b) *By the infrastructure.* The rationale here is that quality can only be produced within an appropriate infrastructure (buildings, staffing, competencies and equipment). In most developed countries, the local health authorities accredit radiotherapy departments on the basis of the infrastructure in

place. Indeed, several examples have been published demonstrating that the absence of a minimal level of infrastructure is responsible for suboptimal cancer control. However, this approach lacks specificity, as it does not provide information on precisely what element of the infrastructure is responsible for the suboptimal performance. Clearly, norms are desirable on infrastructure details, but they say nothing about the actual utilization of competencies and equipment. Infrastructure is therefore a necessary but not sufficient condition to guarantee a service of quality.

(c) *By the control of processes.* This approach focuses on process control. It is based on the observation that if a process conforms to a standard, then the quality of its result is predictable. This is the standard industrial approach to quality: no risk that a product will not match its quality specification can be taken (for obvious commercial reasons). Therefore, all steps of its manufacture are tightly controlled. Similarly, but for ethical rather than commercial reasons, all steps of the radiotherapy process need close monitoring of their conformity, to ensure the expected outcome: cancer cure. This approach is complementary to the two previous ones. Also, because the radiotherapy process can be deconstructed into a large number of elementary procedures, it is easier to spot and correct specific deficiencies within a programme that is otherwise appropriate.

Process control, adequate infrastructure and permanent audit of outcomes are the three pillars of a comprehensive quality system. Such a system will be organized following a detailed structure of its constitutive elements (see Ref. [19.6]). The QUATRO (Quality Assurance Team for Radiation Oncology) approach of the IAEA is based on this concept [19.7].

## 19.3. DETAILS OF A QUALITY SYSTEM

The first element of a quality system relates to the aim of the organization; that is, the mission statement of the department or the hospital, its position in the national or regional health care organization (primary, secondary or tertiary care), and mention of specific missions like teaching or training of professionals. The question to be answered is simple: Who are we, and what is our mission?

The second element is the organigram, or organizational chart; that is, clear management and reporting lines, job descriptions, qualifications for specific jobs, and anything else that helps a co-worker understand his or her mission and position in the often complex organization of a radiotherapy department. Of particular importance is the explicit allocation of responsibilities for every single

process and provision for absences, holidays or any irregularity in the planning of the department.

The third element is 'obtaining and maintaining the means and materials for radiotherapy treatment', an elaborate way of describing all processes regarding equipment. Historically, this is the part of the QA programme that has been developed first. It relies largely on the competencies of the medical physics and engineering team. The purpose of this element is to address the following items:

(a) Calibration of the equipment with traceable regular dosimetry checks;
(b) Systematic verification of mechanical parameters of the equipment (isocentre, collimator movements and alignment);
(c) Verification of the data transfer between simulation, planning and treatment;
(d) Verification of the imaging equipment for simulation (CT scan, MRI, PET scan);
(e) Verification of the transfer of data between simulation and planning;
(f) Quality control of the treatment planning system (at commissioning and at every single software update);
(g) Commissioning of new linear accelerators (linacs) and decommissioning of obsolete equipment;
(h) Management of radioactive sources (purchase, stock, decommissioning);
(i) Conditions for treatment interruption (who has authority);
(j) Procedures for repair;
(k) Tests before return to clinical operations.

This list is not exhaustive.

The fourth element, 'process control', is the largest one. The general philosophy is to indicate what should be regulated, rather than how things should be regulated. In this, each department must make its own decision on the matter of where to draw the line between written instructions and professional judgement and expertise. All activities, from the moment a patient enters the department until he or she leaves it, should be clearly stated, described and recorded. It starts with unambiguous patient identification on a daily basis until discharge, and includes follow-up procedures for specific cancers, and volume definitions and contour specifications (International Commission on Radiation Units and Measurements volume definitions, anatomical atlases and disease specific contouring guidelines). Comprehensive procedures should cover the following elements: patient data (identification, diagnosis, staging), treatment protocols (disease specific), treatment prescription and planning (including contours, radiotherapy techniques), treatment delivery, treatment verification (in vivo dosimetry, portal imaging), treatment summary and follow-up, and information

flow through the process (including communication between professionals, communication with the patient).

As far as treatment protocols are concerned, a multidisciplinary approach to cancer care should be fostered in all circumstances. As mentioned earlier, radiotherapy is often part of a more elaborate treatment. Not infrequently, radiation oncologists might want to extend this part of the quality system to other disciplines (medical oncology, surgery). It is indeed a challenge for the future to reconsider quality management at the entire oncological level. Radiation oncology, with its systematic approach to quality, is in a perfect position to take the lead in this field.

To emphasize their importance, knowledge and skills are a separate part of the quality system. It is of the utmost importance that a process as elaborate as radiotherapy be carried out by well trained professionals whose competencies are permanently updated. Formal procedures should be in place regarding access to continuous professional education and adequate training whenever new techniques are implemented. Particular attention should be paid to bridging the gap between radiation oncologists, medical physicists and radiotherapists, who often progress at a different pace.

The last element addresses the control of the quality system. Indeed, far from being a set of written procedures carefully aligned on a shelf, the elements of the quality system need to be permanently updated as experience is gathered throughout the daily operations. A quality system is, in itself, a dynamic process.

Various elements fit in the 'control' category:

(a) Internal audit ensures that working procedures are followed appropriately, and that quality indicators meet their pre-established performance levels. Long term registration of cancer control levels and of side effects and complications is part of the internal audit.

(b) Procedures frequently need updating as radiotherapy practice evolves and/or equipment is upgraded. It is appropriate to develop separate procedures that specify the rate of renewal of working instructions, and that ensure that adequate procedures are prospectively developed whenever new techniques are implemented. Updating of cancer treatment protocols also belongs here, to keep the practice aligned with evidence based medicine.

(c) A powerful tool for permanent quality improvement is external audit. The IAEA has been a pioneer since the end of the 1990s in developing QUATRO, its comprehensive methodology of external audit. QUATRO contains checklists that can be a helpful tool for auditors, depending on the local situation. The objective is to provide a general audit methodology that can be applied in a range of economic settings. The audit includes the assessment of the ability of an institution to maintain the radiotherapy

technology at the level corresponding to the best clinical practice in the specific economic setting (related to the ability of a country to sustain the technology). A comprehensive audit of a radiotherapy programme reviews and evaluates the quality of all elements involved in radiotherapy, including staff, equipment and procedures, patient protection and safety, and overall performance of the radiotherapy department, as well as its interaction with external service providers. Gaps in technology, human resources and procedures are identified so that the institution can document areas for improvement.

## 19.4. QUALITY INDICATORS

A measurement of the quality 'levels' achieved is desirable in many instances. Health authorities usually wish to verify the homogeneity of cancer care across a region or a country, to ensure proper utilization of government funds and look for areas where similar quality levels can be achieved at a lower cost, or where quality levels can be improved at a socially acceptable cost. Wide differences exist across the countries and continents, depending on the revenues (usually per capita gross domestic product), but the common goal is to monitor cancer care performance.

Developing indicators in radiotherapy is a serious challenge. An indicator should be reliable so that it has a low intra- and inter-observer variability. It should be accurate, allowing data collection without systematic errors, and it should be sensitive to changes and specific in terms of quality [19.8]. There are different classifications of the quality domains that are monitored through indicators, the classic one being the Donabedian classification [19.9]. This classification separates indicators into three quality domains: infrastructure (equipment and staffing); process (system design, existence of quality management programmes, attention to equity, continuity of service); and outcome. Few countries have developed an extensive set of indicators specific to radiotherapy, but two deserve to be mentioned:

(a) The Higher Institute of Health (ISS) in Rome, Italy, has developed an extensive set of indicators of wide applicability, through a collaboration with the Italian Association of Radiation Oncology (AIRO). Details can be found in the original publication [19.10]. The main indicators concern the waiting times, the use of three dimensional conformal radiotherapy, the use of CT based planning, the use of beam shaping devices and the number of fields per plan. In addition, staffing and qualification plus a measurement of workload are registered.

(b) Australasian indicators have been developed by the Australian Council on Healthcare Standards (ACHS) and the Royal Australian and New Zealand College of Radiology (RANZCR); they concentrate mostly on access to radiotherapy and waiting times [19.11].

In addition to indicators specific to radiotherapy, a number of indicators exist that are organ or disease oriented; they apply more to cancer centres as a whole than solely to radiotherapy departments.

## 19.5. SAFETY MANAGEMENT

Even in the best of departments, operations can deviate from their goal and threaten treatment results (fail to cure, induce complications, harm staff and others). The roots of such deviations are often multimodal. Reason's model for systemic failure explains that unsafe acts or violations cannot provoke treatment failures on their own, unless other managerial deficiencies are in place [19.12]. Accidents in radiotherapy are systemic in nature, as they indicate the failure of the quality system to put appropriate defences in place, rather than revealing human weaknesses. Indeed, humans are fallible, and radiotherapy processes should include this important fact in their design. Therefore, these processes should be redundant in nature to increase the probability that a mistake will be detected before it reaches the patient level. A classic example is double, independent calculation of monitor units. Another example is in vivo dosimetry. A correct approach to safety should be both proactive and reactive.

Developing radiotherapy processes should include a preventive analysis of possible failures (failure mode and effect analysis (FMEA)) and an adaptation of the process accordingly. This is especially true with new, less transparent techniques, such as intensity modulated radiation therapy and all its variants, where classical monitor unit verification and in vivo dosimetry no longer qualify as adequate verification tools. FMEA is an intellectual collective exercise during which all possible reasons for a process to fail are identified. Of course, it is not possible to develop an exhaustive picture of all possible failure modes (the human mind has an infinite creativity in making mistakes). Therefore, FMEA is able to drastically reduce the risk of nonconformities, but it is not able to eliminate all of them. FMEA was originally developed by the United States Department of Defense (MIL-P-1629 in 1949, updated in 1980), and was later applied to a wealth of activities, ranging from aerospace activities to the health care industry.

In spite of preventive efforts, mistakes of all sorts and severity happen. Most errors have no consequence for the patient; they can be benign or serious in nature but are detected (often by chance) before the treatment is actually

misapplied. The frequency of all these 'nonconformities' is unknown, but some departments have attempted to register them exhaustively. In Maastricht, for example, in the MAASTRO Clinic radiotherapy institute, over 1800 nonconformities were registered in 2009. A recent inquiry in the 25 radiotherapy centres of Belgium revealed that between 1 and 20 nonconformities are registered monthly. Amazingly, the number of events per month was not related to the size of the centre. It was merely a reflection of the local reporting culture. In France, the French Nuclear Safety Authority (ASN) publishes a trimestrial review of significant events (e.g. level 1); 39 events were registered during the last three months of 2011. Of particular importance is the fact that, in France, significant events have to be reported to the regulatory agency in the most transparent way [19.13].

Reporting is the key word here. Nonconformities can be retrospectively reported in a local database, together with an analysis of the root causes and a proposal of preventive actions to avoid repetition. Systematic registration and analysis of nonconformities is a powerful tool for continuous quality improvement as it offers genuine feedback on the actual workability of radiotherapy processes. It is often said that every incident is a 'free lesson' on the actual health of the quality system.

## 19.6. TAXONOMY FOR NONCONFORMITIES

One issue that still needs clarification is the exact meaning of words with regard to incidents and accidents. The word 'nonconformities' has been used here, as it does not bear any meaning regarding the consequence of an unexpected event. It is beyond the scope of this chapter to resolve the issue, but some proposals can be made.

The Joint Commission, a private, not-for-profit organization that accredits and certifies health care organizations and programmes in the United States of America, has coined the term 'sentinel event' with the following definition: "a sentinel event is an unexpected occurrence involving death or serious physical or psychological injury, or the risk thereof". The important part of the definition is that it is not necessary that a process variation actually results in harm or death for it to be a sentinel event. It is sufficient that such a variation could have resulted in severe harm for it to be classified as a sentinel event. This is also often called a 'near miss'. Such events are called sentinel because they signal the need for investigation and response [19.14].

It would obviously be an exaggeration to classify all sentinel events in a single category. Some are clearly benign, while others are potentially harmful. A simple, two level classification has been used by ROSIS (Radiation Oncology

Safety Information System) with ‘recoverable’ and ‘non-recoverable’ events, referring to the amplitude of the deviation during a radiotherapy treatment and its consequences on the patient’s health (http://www.rosis.info) [19.15].

Other, more elaborate, scales have been used, like the adaptation of the International Nuclear and Radiological Event Scale (INES) by the French ASN and Société Française de Radiothérapie Oncologique (SFRO). It consists of a 7 level scale, with level 0 corresponding to recoverable events (no harm) and levels 5 to 7 corresponding to one or more deaths from radiotherapy misadministration (http://www.asn.fr). The scale is summarized in Table 19.1.

TABLE 19.1. ASN–SFRO SCALE OF SENTINEL EVENTS

| | Event | Cause | Consequence |
|---|---|---|---|
| Level 5–7[a] accident | Fatal outcome | Very severe overdosing | Death |
| Level 4 accident | Event that has or could have resulted in a fatal outcome | Severe overdosing | Complications of grade 4 common toxicity criteria (CTC) |
| Level 3 incident | Event that has or could have resulted in a severe functional alteration | Irradiation at doses over the normal tolerance dose | Complications of grade 3 CTC |
| Level 2 incident | Event that has or could have resulted in a moderate functional alteration | Irradiation with moderate overdosing | Complications of grade 2 CTC with little impact on quality of life |
| Level 1 event | Event with a dosimetric consequence but no harm to the patient | Non-recoverable overdosing with no expected complication | No expected complication |
| Level 0 event | Event of no consequence to the patient | Recoverable dose error | No clinical effect |

[a] Level 5 for one victim, level 6 for two to ten victims and level 7 for over ten victims.

The merit of this classification is in its precision regarding the outcome of a mistake. It is based on an a priori analysis of the potential harm caused by the misadministration. It also makes the distinction between events (levels 0 and 1), incidents (levels 2 and 3) and accidents (levels 4 and above). One important

category is missing here, as the scale only focuses on overdosage and makes no mention of underdosage. This is not appropriate because underdosage can also be the cause of patient death because of the failure to control the disease.

Joint efforts should be fostered at the international level to try and create a common scale for sentinel events and an appropriate taxonomy or classification to separate them in meaningful categories. This is needed to allow for grouping of events of a similar nature, and to help in the identification of common cause and of common areas for improvement.

## 19.7. FAILURE OF THE QUALITY SYSTEM: ACCIDENTS IN RADIOTHERAPY

Accidents in radiotherapy are infrequent, but they often draw the attention of the media, fuelling the population's distaste, rightly or wrongly, for all that relates to ionizing radiation. It is an additional difficulty to the radiotherapy sector that any accident resulting in patient harm gets wide negative publicity, while other mishaps in the hospital rarely make it to the front pages.

Severe accidents (levels 5 to 7 on the ASN–SFRO scale) are rare events. They often result from a widespread systemic failure of the quality system and, as such, will paradoxically offer little information that can be useful in the daily management of quality. The IAEA has an extensive database of such accidents, and through its audits has gained major insights into the root causes of systemic failures. At the centre of all accidents lies a lack of expertise and understanding of the radiotherapy process due to deficiencies in training and continuous education.

Another common feature is the absence of any provision for possible errors that could prevent radiotherapy incidents and accidents, and a complete lack of sensitivity to safety issues. Responsibilities are managerial in the first place, at the level of the radiotherapy department as well as at the hospital and regional levels. Very often understaffing is present, reflecting the absence of understanding on the part of upper management of the necessity to care for quality and to invest sufficiently in safety. It is difficult to convince administrators of the need to expand staff for defensive reasons. This is not productive, because the outcome of such investment is the absence of accidents. Therefore, it is often deemed to be superfluous, or at least not a priority.

If education is the key to the safe management of radiotherapy, it should start with the health authorities and then cascade down to the hospital and the department levels. It is otherwise difficult to motivate radiotherapy operators if their environment does not take into account their needs.

One recent example are the measures taken in France after the severe accident at a hospital in Epinal, France, in 2006. An extensive reorganization of

the ASN, a clear definition of its missions and a thorough assessment of the local needs have resulted in very effective measures. The radiotherapy department of the hospital in Epinal had a severe shortage of medical physicists. This shortage was actually not peculiar to Epinal, but was prevalent in virtually all French radiotherapy departments.

As lessons learned from this event, specific needs have been identified and quantified, and 20 young medical physicists have been admitted to training programmes. Second, the ASN has developed its own methodology to audit the quality system of radiotherapy departments (178 centres in 2009 and 128 centres in 2010). Re-auditing is carried out systematically when necessary. Particular attention is paid to departments with a low volume of activity; they are often encouraged to merge with larger departments to gain some critical mass in workforce and expertise.

Again, accidents are rare. Conversely, events and incidents are frequent. In 1931, Herbert Heinrich, a pioneer in industrial safety, published a book entitled Industrial Accident Prevention: A Scientific Approach. One empirical finding from his book, which became known as Heinrich's Law, is that in a workplace, for every accident that causes a major injury there are 29 accidents that cause minor injuries and 300 accidents that cause no injuries. Because many accidents share common root causes, addressing more commonplace accidents that cause no injuries can prevent accidents that cause injuries.

As stated earlier, every incident is a 'free lesson' on the health of the quality system. Because incidents tend to be frequent, there is a lot to be learned by reporting, recording and analysing them, having as the ultimate goal the design of corrective measures, protocol alterations or equipment improvement. Quality is not a goal; it is a way to manage with a permanent concern for optimal results. It is an ongoing learning process. It is a working culture to be spread to the entire radiotherapy field of activity.

## 19.8. KEY POINTS

— Quality is not a goal; it is a way to manage with a permanent concern for optimal results.
— Quality can be assessed by three different approaches:
  • By the results.
  • By the infrastructure.
  • By the control of processes.
— Details of a quality system:
  • The first element relates to the aim of the organization.
  • The second element is the organigram.

- The third element describes all processes regarding equipment.
- The fourth element, process control, indicates what should be regulated rather than how things should be regulated.
- The fifth element refers to knowledge and skills.
- The last element addresses the 'control of the quality system', and includes:
  - Internal audit.
  - Updates and development.
  - External audit.

— One issue that still needs clarification is the exact meaning of words dealing with incidents and accidents. The word 'nonconformities' has been used here, as it does not bear any meaning regarding the consequence of an unexpected event.
— The adapted International Nuclear and Radiological Event Scale (INES) can be used to score the severity of 'sentinel events'.
— Reporting errors and incidents is key.
— Every incident is a 'free lesson' on the actual health of the quality system.
— Because incidents tend to be frequent, there is a lot to be learned by reporting, recording and analysing them, with the ultimate goal being the design of corrective measures, protocol alterations and/or equipment improvement.

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# Chapter 20

# QUALITY AUDITS IN RADIOTHERAPY

**J. Izewska**

## 20.1. WHAT IS A QUALITY AUDIT IN RADIOTHERAPY?

It is widely recognized that quality audits constitute a vital component of quality management in radiotherapy [20.1–20.3]. The main reason why quality audits are considered an important activity is that they help to review the quality of radiotherapy services and improve them. Quality audits check whether radiotherapy practices are adequate, i.e. that what should be done is being done; and in case it is not, audits provide recommendations to encourage improvements to be made. Without some form of auditing, it would be difficult to determine whether radiotherapy services are safe and effective for cancer treatment. In other words, a quality audit in radiotherapy is a method of reviewing whether the quality of activities in a radiotherapy department adheres to the standards of good practices to ensure that the treatment to the cancer patient is optimal. Overall, audits lead to improvements of professional practices and the general quality of services delivered.

There are many recommendations regarding quality in radiotherapy practice, both national and international. Practices vary depending on the economic level of States, including specific procedures, equipment and facilities, as well as available resources. Good practices evolve with research developments, including new clinical trial results, progress in evidence based medicine and developments in radiotherapy technology.

Quality audits involve the process of fact finding and comparing the findings against criteria for good practices in radiotherapy. Various issues and gaps may be identified by the auditors in the audit process, for example insufficiencies in structure, inadequacies in technology or deviations in procedures. This way the weak points or areas of concern are documented and recommendations for the audited centre are formulated that address these areas with the purpose of improving quality.

It should be clarified here that quality audits differ fundamentally from regulatory inspections, i.e. they are not used as an enforcement tool, but they serve as an independent source of advice on quality improvement [20.4]. Therefore, it is up to the audited centre to decide on the implementation of the audit recommendations. Careful analysis and acceptance of the audit recommendations

may help the centre to establish and implement a programme for improvement. A feedback system should normally be incorporated into the audit scheme in order to monitor the improvements as they are being introduced. Where appropriate, a re-audit should be foreseen in due time. With this scheme, the auditing system stimulates and promotes continual improvement for the benefit of the patient, as audits in radiotherapy typically use a patient centred approach, and they are focused on the quality of services provided to patients. Overall, the role of audits is to give confidence and provide assurance that the best possible quality of care is being delivered with the resources available.

In general, the focus of a radiotherapy audit should cover the following topics:

(a) Infrastructure, i.e. the availability of equipment and the organization of resources, including staffing;
(b) Process, i.e. the activities performed within the radiotherapy chain using the resources available;
(c) Outcome, i.e. the results of radiation treatment, including survival rates and various parameters related to quality of life.

Many guidelines and recommendations exist that describe the infrastructure and resources required for the organization and operation of radiotherapy services [20.5–20.9]. Similarly, the clinical and physical processes pertaining to the activities and decisions taken within the radiotherapy chain are described, including the parameters most relevant to radiotherapy outcomes. The criteria for auditing the radiotherapy process are typically established in accordance with evidence based medicine using quality assurance (QA) recommendations derived from a consensus of high level experts specializing in the different subfields of radiotherapy.

When auditing radiotherapy practices, it may be difficult to compare typical outcome parameters (survival, disease free survival, local control, toxicity, quality of life or population outcomes) among clinics because of the large number of complicating factors and uncertainties, such as geographical differences, patient selection, biological and therapeutic factors, and the time delay between the treatment and the audit of the outcome [20.10, 20.11]. Criteria for the audit of radiotherapy outcomes may be easier to define in the context of an individual clinic and implement through internal audit [20.12]. It is generally considered that the findings of the audit and its results are confidential between the auditing organization and the audited centre.

## 20.2. AUDIT FOCUS AND TYPES

There are several focus areas which are relevant to radiotherapy audits, and different ways of defining such areas. In general, quality audits can review the overall radiotherapy practice through a comprehensive audit, or selected parts of the practice that are important to achieve the desired treatment outcome, through a partial audit. Thus, radiotherapy audits can be comprehensive or partial. Audits can be external or internal, depending on whether the auditing organization is external to the audited centre or is part of the centre. Audits can be proactive or reactive, depending on whether the interest of the audited centre rests in continual improvement of its practices or the audit is invited as a reaction to specific problems or issues, such as suspected or reported radiotherapy incidents. Audits may also be a combination of the above. The different types and levels of radiotherapy audits are discussed briefly below.

A comprehensive audit in radiotherapy involves the entire clinical pathway of the patient, including all interrelated steps of radiotherapy. Typically, a comprehensive audit entails a review of infrastructure as well as of patient related and equipment related procedures, including radiation safety and patient protection. Staffing levels and professional training programmes are also reviewed. The audit of clinical outcomes may or may not be included in comprehensive audit systems. Certain audit systems include some measures of clinical outcome. As mentioned above, the audit of radiation treatment outcomes may be difficult to accomplish and the approach may vary between the various auditing systems, but the audit of outcomes should at least assess whether procedures to measure the outcomes are in place within the audited centre and the outcomes are regularly monitored.

A partial audit has a limited extent, and only selected important areas of the radiotherapy process are reviewed and assessed. The focus of a partial audit may be related to infrastructure, resources, process, specific QA procedures, documentation, and selected clinical or technical protocols. An example of an audit focusing on resources would be a review of staffing levels and their professional qualifications. A dosimetry audit verifying the correctness of beam calibration in external beam radiotherapy [20.13–20.15] is another example of a partial audit related to QA procedures and technical protocols. Audits may also measure the degree of compliance with particular clinical guidelines or protocols. Acquiring credentials for entry into cooperative clinical research studies [20.16, 20.17] is an example of an audit which checks the compliance of the centre's procedures with a specific clinical protocol for a selected group of patients.

Overall, a partial audit is useful in examining individual areas of the radiotherapy practice and defining targets to achieve in these areas which, when

achieved, would contribute to the overall improvement of quality in the centre. Partial audits may be performed remotely or through on-site review; sometimes they use surveys and questionnaires.

Internal and external audits normally have different interests and scopes, and they can complement each other. For example, an internal audit may be used as preparation for an external audit or to monitor the implementation of the external audit recommendations. Also, the internal audit rather than the external audit, especially in the international context, would be more suitable for reviewing radiotherapy outcomes in the audited centre. This is mostly because the current clinical outcome data reflect the treatment of patients at the audited centre a few years earlier, not at the time of the audit. The infrastructure and processes may have changed over the years, and the current practices at the time of the audit will be reflected in future outcomes. The relationship between the current outcomes and past practices may be difficult to assess by external auditors and they may not be able to formulate useful recommendations. Therefore, the external audit, in particular that by the international auditing body, should be considered an assessment or a snapshot of practices at the time of the audit. Consequently, such an audit would typically focus on infrastructure, including equipment, facilities and human resources, radiotherapy processes, and possibly research and training activities.

An internal audit is usually carried out by an audit team from within the centre, but outside the radiotherapy department, and typically reviews compliance with hospital procedures and protocols. In addition, it can be used for introducing improvements and preventive actions. For example, internal audits may systematically review different topical areas through a series of partial audits as per the internal audit programme, and the external audit may assess the complete clinical pathway in a comprehensive manner. Appropriate data collection forms can be developed for a specific part of the practice in order to collect data for analysis over a defined period of time. Using such data, the audit can then assess the effectiveness of the practice, draw conclusions and outline recommendations for improvement, where appropriate. Normally, internal audits are carried out on a regular basis, with a typical frequency of 12 months or less.

External audits are generally independent and are carried out by organizations external to the audited centre. Typically, external audits are carried out less frequently than internal audits. A programme of routine internal audits complemented by less frequent external audits is considered a practical and effective tool for quality improvement.

Quality audits may be proactive, i.e. consisting of a review of ongoing practices with the goal of quality improvement, or they may be reactive, i.e. focusing on analysis of a suspected or reported incident. A reactive audit can be associated with incident monitoring, which consists of reporting and analysing

clinical cases where there is concern regarding an adverse event or possibly adverse outcomes.

An example of a proactive quality audit is the IAEA/WHO thermoluminescent dosimeter (TLD) postal dose programme for radiotherapy [20.13–20.15]. An example of a reactive audit is to follow up the discrepancies in dosimetry discovered through TLD proactive audits using on-site review visits to radiotherapy institutions by experts in clinical dosimetry [20.18].

## 20.3. AUDIT PHASES: PLANNING, IMPLEMENTATION AND POST-AUDIT ACTIVITIES

The quality audit process consists of the following phases: the preparatory phase, including pre-audit activities, by both the audited centre and audit team; the audit implementation phase; the reporting of the audit findings and recommendations; and post-audit activities such as the analysis of audit recommendations, planning for addressing them and the management of implementation of recommendations. In some circumstances, a re-audit is foreseen in due time.

The audit objectives, scope and coverage have to be formulated at the beginning. Specifying the objectives of the audit is important for the audit preparation, the auditing process, its outcome and acceptance; therefore, the audit objectives have to be clearly defined. The time frame and programme of the quality audit also have an impact and must be carefully planned by the institution organizing an audit. As the audit is a collaborative process involving the staff of the audited centre and the audit team, both groups have their roles and responsibilities assigned.

A local team should be identified to interact with the auditors, representing appropriate professional groups, who will prepare the documentation necessary for the audit, inform relevant staff of the upcoming audit and arrange for practical aspects of the audit. Staff in the audited area should be aware of the audit, its objectives, its programme and the expected level of their engagement. Staff should feel comfortable with the audit process in order to fully engage with it. The quality audit should be an open and collaborative review of the radiotherapy practice, including any difficulties involved, with the intention of recognizing, understanding and addressing them. The local team should make available records and findings of previous external and internal audits, as appropriate, for the audit team to review. It may be necessary to collect some additional data sets or prepare statistics for review by the auditors, depending on the audit requirements.

The audit team should have specialist expertise in the areas covered by the audit, i.e. an adequate level of knowledge and professional experience, and a thorough understanding of the audited areas. In addition, a broader perspective, wisdom and good judgement would help to properly address issues that may arise in the audit and to carry out the audit activities in a tactful and sensitive manner. The audit team should communicate the audit rules to the local team and should follow the pre-agreed programme of the audit.

Typically, the audit starts with the entry briefing to introduce to the staff of the audited centre the auditors and the audit objectives, programme and logistics. For example, a comprehensive clinical audit will review the overall performance of the radiotherapy centre following the patient pathway. This will include diagnosis, decision to treat, treatment prescription, planning and preparation, delivery of the treatment and follow-up. The relevant services, departments, equipment and staff will be involved in the audit activities as per the audit programme. It is important that the audit team has access to all relevant areas within the centre and speaks with staff members involved in the radiotherapy process.

The IAEA Quality Assurance Team for Radiation Oncology (QUATRO) guidelines [20.4] contain a set of comprehensive audit checklists to assist the audit team in conducting the audit and preparing the audit report. The use of audit checklists is also recommended in the UK National Institute for Health and Care Excellence (NICE) report [20.19] for preparing, designing and carrying out a clinical audit and for the follow-up.

An exit briefing should take place at the conclusion of the audit to inform the staff of the audited centre about the audit findings, conclusions and recommendations. The auditors should invite comments, encourage open discussion and clarify any points raised. They must ensure that the audit findings, conclusions and recommendations are based on the facts, substantiated by accurate records of the audit documentation. To complete the audit, the auditors have to produce a report to the audited centre. Recommendations on actions to be taken should be specified. However, the auditors have no authority to enforce actions or requirements on the basis of the audit findings. It is up to the audited centre to follow up on the audit recommendations and to take up any relevant actions.

Following the receipt of the audit report, the audited centre should analyse the findings and decide on how to act upon the audit recommendations. It will be necessary to develop a concept for the management of the implementation of the audit recommendations, dedicate the appropriate time, allocate resources, assign responsibilities, and monitor and document the improvements. In particular, items that need to be changed should be classified and a timetable for implementing the changes drafted following a careful analysis of the resources needed. Apart from

infrastructure improvements involving direct investments, there may be other changes required, for example, work reorganization, with possible implications such as increased workload, greater responsibilities, and on some occasions a change of status or a reassignment of staff members to different tasks. Any obstacles and barriers in the process of improvement should be analysed and carefully addressed.

Occasionally, quality audits may not fully achieve their objectives. There may be various reasons and difficulties, such as inadequate communication, as well as organizational issues, for example insufficient information and feedback. Other problems may be related to the lack of an overall plan for the audit, or the auditors may make unrealistic recommendations or address issues of lesser importance to the audited centre. Mostly, difficulties with implementing the audit recommendations are related to a lack of resources [20.20], improper prioritization of tasks and the setting of unrealistic goals.

An important part of post-audit activities by the audited centre is the process of implementing changes and maintaining improvements. In order to achieve this, the centre should have in place a system for monitoring the quality of its practices, for example by regular internal audits of the various important areas of work. Also, an incident reporting system should be introduced in order to learn from incidents and near misses, identify gaps and improve internal procedures. The input from research and scientific developments cannot be underestimated in the process of improving the practices. The engagement of the centre in supporting staff development and motivation is also an important factor contributing to sustainable improvement of radiotherapy practices.

## 20.4. IAEA QUALITY AUDITS IN RADIOTHERAPY

### 20.4.1. Dosimetry audit

It has been over forty years since audits of radiation dose were introduced for radiotherapy centres [20.14, 20.15]. There are two audit systems existing in parallel, based on on-site visits and remote audits, often called postal dose audits. On-site visits are performed by a team of auditors that travels to radiotherapy centres with dosimetry equipment and QA accessories in order to review local dosimetry practices; check the quality of dosimetry work and operational characteristics of radiotherapy equipment; review treatment planning systems; and examine clinical dosimetry records. Several on-site review programmes operate at the national level. They typically serve a limited number of centres at a given period of time. In contrast, postal dose audit systems may provide cost effective audits for hundreds or thousands of radiotherapy facilities [20.13, 20.15,

20.21, 20.22]; however, because of their nature, they are restricted to checking fewer dosimetry parameters than the on-site audits. Generally, postal dose audit programmes verify a few selected dose points or beam parameters.

Dosimetry audits are useful for confirming good dosimetry practices, but they can also discover problems and errors and bring these to the attention of the clinical physicists involved. Follow-up of errors and discrepancies provides support in finding the reasons for deviations and helps to resolve them. As can be seen in Fig. 20.1, dosimetry audits have contributed to the improvement of practices in numerous radiotherapy centres over time, and they help in maintaining good practices. They also contribute to reducing uncertainties and to increasing consistency in radiotherapy results. At the same time, satisfactory audit results provide confidence to clinicians that the dosimetry supporting their practice is correct and outcomes for patients will not be affected by deficient physics practices. Audits of radiotherapy facilities have to be repeated on a regular basis as part of QA systems. It is required for any new radiotherapy facility to receive an external dosimetry audit before patient treatment starts.

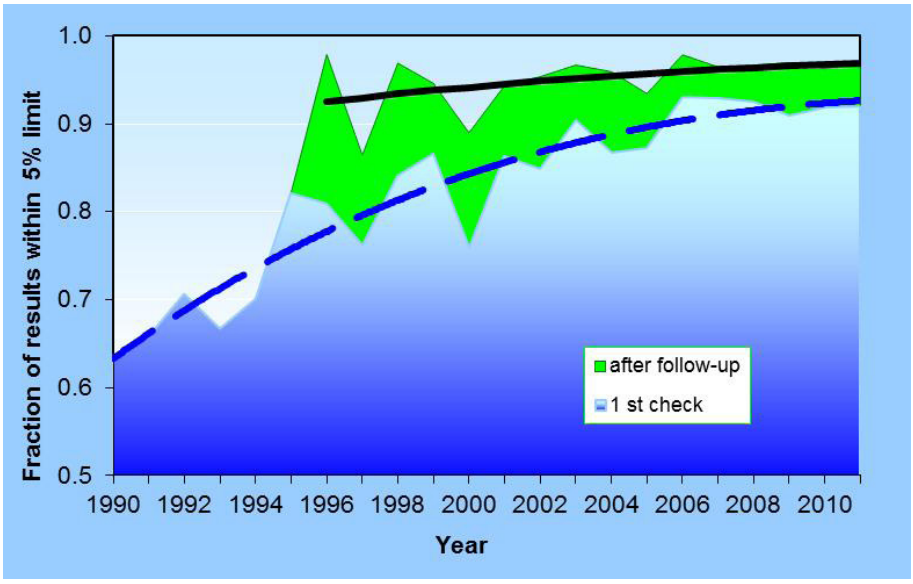


*FIG. 20.1. Fraction of TLD results within the 5% acceptable limit in the IAEA/WHO TLD postal dose audit programme. The regular follow-up of poor TLD results increased the fraction of acceptable results.*

Dosimetry audits can be of different scopes and complexity, from the basic audit of the beam output in reference conditions to the audit of more dosimetry parameters using simple or complex beam arrangements in static and dynamic dose delivery modes, including 'end to end' tests covering clinical imaging, treatment planning and dose delivery. The scope of dosimetry audits and their complexity should be adjusted to the complexity of radiotherapy technology as this may increase the potential benefits to the patient. However, the basic beam calibration audit should be made mandatory for all radiotherapy facilities; if the beam calibration is incorrect, all patients treated with this beam will receive incorrect doses, no matter how well the treatment prescription is made. It is estimated that, at present, only about two thirds of radiotherapy centres around the world have access to regular dosimetry audits [20.23].

### 20.4.2. Audits of treatment planning systems

One of the radiotherapy audit modalities available through the IAEA focuses on audits of TPSs [20.24]. The objective of such TPS audits is to ensure the optimal usage of TPSs, and hence safer radiotherapy. The TPS audit reviews the dosimetry, treatment planning and radiotherapy delivery processes in radiotherapy centres using the end to end approach, i.e. following a pathway similar to that of the patient, through imaging, treatment planning and dose delivery. It is a useful and efficient approach for verifying the agreement between TPS calculations and dose measurements, and it helps in identifying some shortcomings in the radiotherapy chain such as problems related to TPS data input, computed tomography to relative electron density conversion, and inaccurate beam calibration. In addition, it helps the clinical physicist to achieve a better understanding of the performance of the various TPS algorithms, including their limitations.

### 20.4.3. Comprehensive clinical audit

Accurate beam dosimetry and high quality of treatment planning are essential in the radiation treatment of cancer, but they cannot ensure the required patient outcome will be achieved without a correspondingly high level of clinical practice. Therefore, it is important to include both the medical and physics components of the radiotherapy chain in a comprehensive QA programme, and to audit both practice aspects. The comprehensive audit methodology has been described by the IAEA [20.4] and the European Commission (EC) [20.12]. The IAEA QUATRO audit methodology emphasizes radiotherapy structure and process. It consists of a review of radiotherapy infrastructure as well as of patient related and equipment related procedures, including radiation safety and patient

protection aspects, as appropriate. Staffing levels and professional training programmes for radiation oncologists, medical physicists and radiotherapists can also be reviewed.

The principles of the QUATRO and EC clinical audit guidelines [20.4, 20.12] are similar and are consistent with each other. The objective of comprehensive clinical audits is to review the quality of all aspects of the practice of radiotherapy in a cancer centre with a view to improving quality. The audit reviews and provides an assessment of the ability of a centre to maintain its radiotherapy practices at the level corresponding to the best clinical practices in the specific economic circumstances. The methodology incorporated in both sets of guidelines can be applied in a wide range of economic and cultural settings.

A few aspects of comprehensive clinical audits need to be highlighted in order to facilitate quality improvement in the audited centre:

(a) Clinical audits should promote the development and usage of internationally recognized, evidence based standards of radiotherapy practices taking into account the available resources.
(b) They should encourage the exchange of knowledge, experience and know-how to help achieve adequate standards of performance.
(c) They should foster an environment of good professional relationships and a multidisciplinary approach to patient care.

The IAEA QUATRO audits are carried out at the request of a radiotherapy centre by a team of international experts, including a radiation oncologist, a radiotherapy physicist and a radiotherapist. The audit follows the patient pathway from referral to follow-up. A detailed set of checklists is available to assist the audit team throughout the audit and to structure the audit report. These checklists are also made available to the radiotherapy centre prior to the audit so that its staff can become familiar with the auditing methodology and the details of audit procedures.

The QUATRO audit starts with an entrance briefing followed by the facility tour. Throughout the audit, the team reviews the working practices and procedures of the centre; interviews staff; checks and evaluates clinical and technical procedures, protocols and documentation; and performs practical dose measurements. Radiation treatments for typical anatomical sites treated in the centre are assessed for randomly selected patient files and treatment records. The audit concludes with an exit briefing.

The audit findings, recommendations and conclusions are formulated taking into account the criteria of evidence based good radiotherapy practices. Examples of such criteria are available from the IAEA [20.5, 20.6] and in a range of publications [20.25, 20.26]; several are referred to in EC clinical

audit guidelines [20.12]. The audit report specifies areas for improvement of practices in the audited centre and advice for further developments. Some audited centres have been recognized as operating at a high level of competence. The audit findings and recommendations help the audited centres to define targets and bring improvements to ensure optimal patient care and achieve the desired treatment outcome.

## 20.5. KEY POINTS

- It is widely recognized that quality audits constitute a vital component of a quality management system in radiotherapy.
- Quality audits differ fundamentally from regulatory inspections, i.e. they are not used as an enforcement tool, but they serve as an independent source of advice on quality improvement.
- It is generally considered that the findings of the audit and its results are confidential between the auditing organization and the audited centre.
- Comprehensive audits in radiotherapy involve the entire clinical pathway of the patient, including all interrelated steps of radiotherapy.
- Partial audits have a limited extent, and only selected important areas of the radiotherapy process are reviewed and assessed.
- Quality audits may be proactive, i.e. consisting of a review of ongoing practices with a goal of quality improvement, or they may be reactive, i.e. focusing on the analysis of a suspected or reported incident.
- Dosimetry audits are useful to confirm good dosimetry practices, but they can also discover problems and errors and bring these to the attention of the clinical physicists involved.
- The basic beam calibration audit should be made mandatory for all radiotherapy facilities; if the beam calibration is incorrect, all patients treated with this beam will receive incorrect doses no matter how well the treatment prescription is made.
- One of the radiotherapy audit modalities available through the IAEA focuses on audits of treatment planning systems (TPSs). The objective of such TPS audits is to ensure the optimal usage of TPSs, and hence safer radiotherapy.
- The IAEA Quality Assurance Team for Radiation Oncology (QUATRO) audit methodology emphasizes radiotherapy structure and process.
- The audit findings and recommendations help the audited centres to define targets and bring improvements to ensure optimal patient care and achieve the desired treatment outcome.

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# Part VI

# FOCUS TOPICS

# Chapter 21

# PAEDIATRIC RADIATION ONCOLOGY

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## 21.1. INTRODUCTION

Although cancer is a typical disease of ageing adults, it can be seen at any age and cancer diagnosis in a child is not a rare situation. Every day around the world, many teenagers, young children and even infants are diagnosed with cancer. Cancer in children is an important health care problem, not only for the individual patient and medical staff, but also for families, teachers, friends and society as a whole. In every culture, children are considered innocent human beings and the diagnosis of such an 'evil' disease in a young child always induces feelings of unfairness and anguish.

Most childhood cancers are curable; using the best treatment options, more than 80% of children with cancer may survive to adulthood. However, cure alone is not the ultimate goal for paediatric cancer treatment; late effects of treatment impact the quality of life of patients. Cure from cancer in a child means adding at least 50–60 years to his or her life, which is long enough to develop serious late effects of the treatment and the induction of secondary cancers. Thus, treatment should be tailored to minimize the exposure of healthy tissues to chemotherapy drugs and radiation.

Cancer treatment can be a painful process, often involving surgery, radiotherapy and chemotherapy, and requiring very long treatment periods, which impair the motor and mental development of the child, and his or her educational activities and relations with society. Childhood cancer survivors sometimes have modest to severe sequelae of the disease itself and the treatment used, which may disrupt their development to a healthy adulthood. These cancer survivors should be fully integrated into society and be allowed to live productive lives even when lifelong rehabilitation is required to keep them active.

## 21.2. INCIDENCE AND EPIDEMIOLOGY OF CHILDHOOD CANCERS

The incidence of childhood cancer displays great variability worldwide. In high income countries (HICs), the annual incidence in the population is 120–150 per million, whereas it is 80–120 in low and middle income countries

(LMICs). However, the incidence of childhood cancer is on the rise all over the world for various reasons [21.1, 21.2]. Despite the lower incidence, most of the world's children live in LMICs and 85% of cancers among children are diagnosed in these countries. Worldwide, children constitute approximately 1.4% of all cancer patients; however, this percentage varies from 0.5% in Europe to 4.8% in Africa (with most of the variation explained by differences in age composition and life expectancy) [21.3]. However, childhood cancer is not very visible and not considered a major health problem in many LMICs. The high number of children's deaths from poverty related diseases, malnutrition and communicable diseases, such as pneumonia, malaria, hepatitis and diarrhoea, outnumber those from childhood cancers, and neither local–national health authorities nor the international health institutions consider childhood cancer a priority on their agenda.

Every year, 175 000 children are diagnosed with cancer worldwide, and unfortunately, almost 100 000 of them die, mostly due to late diagnosis and difficulties in the evaluation and treatment of the disease due to social and economic problems. Almost 95% of all childhood cancer deaths occur in LMICs. Death from a childhood cancer is among the top three causes of death in many HICs; however, it is not even among the top ten causes of death in many LMICs, for the reasons described above.

In the twenty-first century, communicable diseases in LMICs are coming under control and the under-five mortality rate is dropping in almost all regions of the world due to national and international efforts. This means that more children in LMICs will be exposed to the development of cancer in the near future, which should compel national and international health authorities to take serious steps to handle the childhood cancer problem, as this is now being considered a 'silent crisis'.

In the past four decades, survival rates of almost all childhood cancer types increased dramatically, from 20–25% to 80–85%, with the help of advancements in diagnosis and treatment of cancer in general. Proper use of chemotherapy agents, new radiotherapy techniques, less invasive surgery, and advances in imaging and pathology all contributed to this success. Sadly, in many LMICs, where access to cancer treatment is limited, the cure for cancer among children is still exceptional and the 'survival gap' between rich and poor is increasing.

## 21.3. GENERAL CHARACTERISTICS OF CHILDHOOD CANCERS

The common cancers diagnosed among children (see Table 21.1) are quite different from most adult cancers, suggesting a distinct aetiology for some types [21.4]. Leukaemias and lymphomas, central nervous system (CNS) tumours

TABLE 21.1. MAJOR TYPES OF AND RELATIVE FREQUENCY OF CHILDHOOD CANCERS IN THE UNITED STATES OF AMERICA

| Diagnosis | Relative frequency (%) |
|---|---|
| Leukaemias | 27.5 |
| Central nervous system (CNS) tumours | 20 |
| Lymphomas | 11.3 |
| Neuroblastoma | 7.3 |
| Wilms' tumour | 6.1 |
| Rhabdomyosarcoma | 3.4 |
| Bone sarcomas | 4.7 |
| Other | 16.4 |

and solid tumours with embryological origin (neuroblastoma, nephroblastoma, retinoblastoma) are the most frequently diagnosed tumours in children.

Carcinomas, which are common in adults, are rarely diagnosed in the paediatric age group.

The reasons for developing a cancer in childhood are unknown in many cases. The microscopic appearance of embryonic tumours that affect very young children resembles tissues in the developing embryo and foetus, suggesting their origins from immature tissues. Defects in tissue growth pathways and their differentiation during the pre-natal and post-natal periods promote tumour genesis [21.5, 21.6].

Unlike those of adults, the organs and the immune systems of children are immature, growing and developing. They are less able to metabolize and excrete most toxins; consequently, they have a special vulnerability to acute, subacute and chronic effects of environmental chemical agents. Poverty, malnutrition and infectious diseases further contribute to vulnerability to environmental carcinogens.

Childhood cancers are mostly treated by various combinations of surgery, radiotherapy, chemotherapy and immunotherapy. The main principle behind this multimodal treatment approach is to reduce the dose and the intensity of each individual treatment modality in combination models that keep the side effects as low as possible while achieving a high cure rate. Thanks to joint efforts of

various paediatric cancer research groups starting in the 1970s, it is now possible to perform less surgery, reduce the dose of radiotherapy, use smaller radiation fields, and give lower doses of chemotherapy. This philosophy was later adopted in the treatment of many adult cancers as well. Risk based and response directed treatment is the backbone of the multimodal treatment approach in childhood cancers [21.7].

Supportive care is inevitably required for treatment success in childhood cancer. Small children require daily general anaesthesia to receive radiotherapy; emergency problems such as tumour lysis syndrome, acute paraplegia, superior vena cava syndrome, and brain oedema at diagnosis or during treatment may occur with the requirement for hospitalization in an intensive care unit for a certain period of time. Discomfort and side effects caused by the treatment itself should be minimized with proper supportive care management.

The management of patients in dedicated paediatric oncology centres and multidisciplinary expertise are necessary to cure the patient and handle the side effects successfully. Improved survival has been shown in childhood cancer patients receiving treatment in specialized centres compared with those receiving treatment in non-specialized medical institutes [21.8]. Unfortunately, there are very few paediatric cancer centres in many LMICs, and existing centres are usually located in big cities at long distances from many patients and their families, resulting in difficulties in accessing proper treatment or continuing prolonged therapy [21.9].

Inclusion of childhood cancer patients in national or international clinical cancer trials is important to standardize treatment and to enhance the level of care. All efforts should be made to maximize the utilization of the available resources and to enhance the capacity of the medical staff. The benefits of modern oncology should be easily accessible for all children with cancer around the world. Many cancer institutes, and national and international organizations, including the IAEA, have developed programmes to improve the status of paediatric radiation oncology in various regions and countries. These organizations provide educational support and grants for research. Improvement of paediatric cancer survival in LMICs may require alliances and partnerships involving national health care managers, the public and private sectors, and medical societies [21.10, 21.11].

## 21.4. OVERVIEW OF PAEDIATRIC RADIOTHERAPY

Childhood tumours are generally high grade with a rapid cell turnover. In view of their embryonic origin and high grade, most paediatric tumours have a propensity for rapid growth and early dissemination to neighbouring structures

and distant organs. Most childhood tumours are very sensitive to radiation, and there have been reports of long term disease control using moderate doses of radiotherapy alone. However, it is also very well known that radiotherapy, even at low doses, can result in significant normal tissue injury in a young child. Thus, it is essential to integrate radiotherapy into multimodal treatment models to reduce its dose, intensity and irradiated volume to a minimum level that is still sufficient to eradicate tumour cells. If possible, radiotherapy should be omitted from treatment protocols, or at least delayed until the growth and development of certain tissues are completed.

Every radiation oncology institute involved in the treatment of children should organize a dedicated paediatric oncology team consisting of well trained radiation oncologists who can manage paediatric cancers, oncology nurses specialized in paediatric patients, anaesthesiologists, social workers, paediatric psychologists and psychiatrists. All treatment decisions should be made in joint meetings, with paediatric oncologists and surgeons. Separate waiting rooms for children, anaesthesia equipment and radiotherapy fixation systems suitable for children are required.

## 21.5. RADIOTHERAPY TECHNIQUES IN CHILDREN

Advances in imaging and computer technology in recent decades have enabled radiation oncologists to plan and deliver sufficient radiation doses to tumours using sophisticated radiotherapy techniques while minimizing the radiation dose to normal tissues. In the first decade of the twenty-first century, conformal radiotherapy became the standard technique used to irradiate childhood cancers. Conformal radiotherapy offers the possibility of reducing the immediate and long term side effects of radiation without weakening the effect on the tumour. However, it is not an inexpensive treatment; expensive equipment such as a state of the art linear accelerator (linac), a good computer planning system, a computed tomography (CT) machine adapted for radiotherapy planning, patient immobilization materials and well trained staff are required to perform state of the art conformal therapy. Some of this equipment and qualified personnel are not available in many centres in LMICs. Indeed, there is no conformal therapy equipment in many countries. In many centres, radiotherapy is performed using simple radionuclide machines or basic linacs without the possibility to limit the dose to healthy structures. It is clear that those children treated with basic equipment and techniques are more prone to developing permanent side effects in the future [21.12].

New radiotherapy methods, such as intensity modulated radiation therapy (IMRT), image guided radiation therapy (IGRT), extracranial radiosurgery and

helical tomotherapy, have emerged in the last decade and offer possibilities for further refinement of radiotherapy. It is necessary to carefully evaluate the benefits of these new techniques in child patients, weighing their benefits against the long term effects of the higher integral radiation dose throughout the patient's body.

Another emerging technology is proton beam therapy. The physical properties of proton beams make it possible to concentrate the radiation dose on the target with delivery of fairly small doses to structures in front and behind the target. The physical dose distributions of protons are superior to those of photons. The early clinical results for several childhood tumours are promising. However, proton therapy equipment is very expensive and the number of proton facilities is limited, even in HICs. If ongoing research projects result in reducing the cost of proton therapy equipment, it is possible that protons will have wider use in the treatment of childhood tumours in the future.

## 21.6. ROLE OF RADIOTHERAPY IN THE MANAGEMENT OF SPECIFIC MALIGNANCIES

Radiotherapy is prescribed in a wide variety of childhood cancers. In some tumour types and sites, radiotherapy is the main treatment, used as an adjuvant to surgery, and it has an important role as a palliative therapy in all tumours (Table 21.2). The role of radiotherapy in major childhood cancers is summarized below.

### 21.6.1. Leukaemias and lymphomas

Leukaemias and lymphomas are haematological malignancies originating from the bone marrow, lymph nodes and reticuloendothelial system. Leukaemias are aggressive malignancies, and although leukaemic cells are extremely sensitive to radiation, these malignancies are systemic and are treated exclusively by chemotherapy. Radiotherapy is effective in preventing and treating CNS relapses, which is a common feature of leukaemia. Another use of radiotherapy in leukaemia is total body irradiation as part of the bone marrow transplantation schedule. Radiotherapy is effective in sterilizing the bone marrow, and reducing the immunological response against grafted marrow.

Lymphomas have several subtypes with different clinical features. They are mainly evaluated in two separate groups: Hodgkin's lymphoma and non-Hodgkin's lymphoma. Until the development of nitrogen mustard — the first effective chemotherapy drug — radiotherapy was used as the sole modality in the treatment of Hodgkin's lymphoma. Wide field irradiation to cover all

TABLE 21.2. ROLE OF RADIOTHERAPY IN CHILDHOOD CANCERS [21.11]

| Tumour | Annual incidence (per million population) | Peak age and range | Radiotherapy integral component | Additional essential modalities |
|---|---|---|---|---|
| Central nervous system (CNS) tumours | 16.5–32.5 | 0–7 (0–15) | Yes | Surgery |
| Retinoblastoma | 2.1–5.6 | 0–2 (0–4) | Yes; alternative modality | Surgery + chemotherapy |
| Leukaemias | 29.4–50.4 | 3–4 (1–8) | Special indications (total body, brain/testes relapse prevention) | Chemotherapy |
| Lymphomas | 13.5–37.7 | 14–15 (9–15) | Yes | Chemotherapy |
| Wilms' tumour | 5.1–9.2 | 3–4 (0–7) | Yes | Surgery + chemotherapy |
| Neuroblastoma | 6.1–15.8 | 0–2 (0–4) | Yes | Surgery + chemotherapy |
| Soft tissue sarcomas | 6.3–11.0 | 1–5 (0–15) | Yes | Surgery + chemotherapy |
| Bone sarcomas | 3.3–8.6 | 13–1 (11–15) | No; use in persistent disease under investigation | Surgery + chemotherapy |
| Head and neck carcinomas | 2.4–5.7 | 13–15 (10–15) | Yes | Chemotherapy |

lymph node areas on either side of the diaphragm using doses up to 45 Gy was standard treatment. Treatment was successful in most patients, with a price of serious late effects such as anatomic deformities, breast cancer at younger ages and secondary leukaemia. The development of CT and, recently, positron emission tomography with combination chemotherapy enabled a reduction in the doses to 15–20 Gy and limitation of the radiation fields to the involved node regions, and even to the involved nodes only. In a malignancy with a cure rate higher than 90%, it is extremely important to limit the radiation and volumes. Efforts to omit radiation in the very favourable cases are under way. Although radiation is used in most cases of Hodgkin's lymphoma, it is seldom prescribed in children with a diagnosis of non-Hodgkin's lymphoma; instead they are treated with chemotherapy alone.

### 21.6.2. Central nervous system tumours

CNS tumours are the most common tumour group after childhood leukaemias and lymphomas, and they are also the most common solid tumours in childhood. Approximately 15–20% of all childhood malignancies are CNS tumours. Usually they do not have any connections to the known aetiological factors, and their incidence is fairly similar in different regions of the world. It is not known why children are more prone to develop CNS tumours than adults.

There are several differences between children and adults related to the localization, types and management of CNS tumours. In adults, most CNS tumours are located at the cerebral hemispheres, although CNS tumours in children have the propensity to arise in the infratentorial region, with 60% of all brain tumours diagnosed around the cerebellum and brain stem. Low grade gliomas, medulloblastoma, ependymoma and craniopharyngioma are the common CNS tumours of childhood age, whereas high grade gliomas are the typical CNS tumours in adults (Table 21.3). Surgery performed by a skilled neurosurgeon is always the first choice to obtain diagnosis and to remove the tumour. Surgical resection has been shown to improve survival, but it is not possible to remove tumours with microscopically clear margins and recurrence is inevitable in many aggressive tumours. In principle, radiotherapy is indicated in almost all high grade tumours immediately after surgery and in low grade tumours after recurrence. Radiotherapy is usually postponed in younger children until they are 3–5 years old to allow complete myelinization. In certain situations, limited focal irradiation may be indicated.

Grade I pilocytic astrocytomas and grade II astrocytomas and oligodendrogliomas are the common low grade gliomas of childhood. In low grade gliomas, radiotherapy is usually delayed and not used as the first line treatment until tumour progression. High grade gliomas (anaplastic astrocytoma

TABLE 21.3. TYPES AND RELATIVE FREQUENCY OF CENTRAL NERVOUS SYSTEM TUMOURS

| Diagnosis | Relative frequency | Peak age group (years) |
|---|---|---|
| Astrocytoma | 35% | 2–10 |
| Supratentorial | 22% | >6 |
| Infratentorial | 13% | 2–10 |
| Malignant glioma (AA and GBM) | 8% | <1, >6 |
| Brain stem glioma | 8% | 3–9 |
| Oligodendroglioma | 2% | <6 |
| PNET (Medulloblastoma and supra PNET) | 20% | 1–10 |
| Ependymoma | 8% | |
| Supratentorial | 3% | >6 |
| Infratentorial | 5% | 1–5 |
| Craniopharyngioma | 7% | 8–14 |
| Pineal region and germ cell tumours | 4% | <2, >6 |
| Choroid plexus tumours | 2% | <1 |
| Other: ganglioglioma, meningioma, primitive embryonaltumours | <2% each | |

**Note:** AA — anaplastic astrocytoma; GBM — glioblastoma multiforme; PNET — primitive neuroectoderma.

and glioblastoma multiforme) are rare and the management is similar to that used in adults, where immediate post-operative radiotherapy with chemotherapy is used. Despite these combined efforts, local tumour progression occurs in almost all patients with high grade gliomas, and long term survival rates are less than 20%. Diffuse glioma of the brain stem, sometimes referred to as pontine glioma, is a unique tumour of childhood. Surgery is not possible due to its location, and radiotherapy alone or combined with chemotherapy is the only choice in the treatment. Unfortunately, this is one of the most aggressive tumours among children; less than 10% of the patients survive more than two years.

Medulloblastoma is the most common embryonic CNS tumour in childhood. This tumour arises exclusively from the posterior fossa and grows into the fourth ventricle. It is a highly aggressive tumour which may spread to the whole brain and spinal cord via the cerebrospinal fluid. It is sensitive to radiation, and therefore the entire brain and spinal cord, not only the posterior fossa, should be treated using the craniospinal irradiation (CSI) technique to prevent spread of the tumour. CSI is one of the most complicated radiotherapy treatment techniques. It requires careful planning and precise treatment delivery in order to keep radiation dose to the spinal cord and brain below tolerance limits.

### 21.6.3. Neuroblastoma

Neuroblastoma is a neuroendocrine tumour arising from neural crest elements of the sympathetic nervous system. It is the most common extracranial solid tumour in childhood, and the most commonly diagnosed malignancy among infants. Neuroblastoma usually arises in one of the adrenal glands, but can also develop in nerve tissues in the neck, chest, abdomen or pelvis. Maturation and spontaneous regression of neuroblastoma are possible, especially among infants. However, neuroblastoma frequently disseminates to bone marrow, bones, liver and lungs. Surgery and chemotherapy are effective in controlling this disease even in advanced stages, and today radiotherapy is used only in high risk patients with unresectable tumours.

### 21.6.4. Wilms' tumour

Wilms' tumour (nephroblastoma) is the most common renal malignancy seen in children. This is an embryonic tumour of the renal parenchyma predominantly affecting children under five years of age, most commonly during the first two years of life. Wilms' tumour is highly radiosensitive: it can be controlled with radiation doses of as low as 20 Gy. However, patients are usually too young for large fields of abdominal irradiation, so radiotherapy is used after surgery with reduced doses of approximately 10 Gy to control microscopic disease. With contemporary treatment, the survival of patients with Wilms' tumour is over 85%.

### 21.6.5. Rhabdomyosarcoma

Rhabdomyosarcoma is a malignant tumour of the skeletal muscle originating from embryonic cells. Since skeletal muscle is distributed throughout the whole body, rhabdomyosarcoma may arise anywhere. It has different subtypes, with embryonal rhabdomyosarcoma being the most common. The

therapeutic approach to a patient with rhabdomyosarcoma depends on various factors such as age, location and size of tumour, stage and histological subtype, and requires careful pre-treatment evaluation of the patient and individualization of the treatment. The role of radiotherapy depends on the treatment protocol used. North American treatment protocols using radiotherapy in most patients are quite different from the European approach, where radiotherapy is reserved for unresectable tumours and recurrences.

### 21.6.6. Retinoblastoma

Retinoblastoma is a malignant tumour of the eye arising in the foetal retinal cells. It affects children under five years of age and may affect both eyes, suggesting a hereditary aetiology. Retinoblastoma, when diagnosed early, can be treated effectively, with very high rates of disease control with preservation of useful vision. There are several options for the early stage disease, including cryotherapy, laser ablation, surgery, radioactive plaque implantation and external irradiation. The role of radiotherapy in the primary management of retinoblastoma has decreased recently due to the effective use of other local treatment methods and concern about increased risk of secondary osteosarcoma among survivors.

### 21.6.7. Bone sarcomas

Osteosarcoma and Ewing's sarcoma are the second most common bone tumours seen in children. While osteosarcoma is renowned for its resistance to radiation, Ewing's sarcoma, which is a tumour of embryonic origin, is highly radiosensitive. Limb sparing surgery and chemotherapy are the first choice for treatment of both types of bone tumour. Although radiotherapy is effective in the treatment of Ewing's sarcoma, its side effects may be serious; thus irradiation is usually limited to the non-extremity tumours (mostly in the pelvic bones) where surgical excision with clear margins is not possible. The outcome for patients with Ewing's sarcoma has improved over the past decades. However, approximately 45–55% of patients still fail locoregionally with or without distant failure, where radiotherapy plays an important role as a salvage treatment.

## 21.7. LATE EFFECTS OF RADIOTHERAPY

As a result of the increasing incidence of childhood cancer and the significant improvement in the survival rate, 1 out of every 400–500 adults will be a childhood cancer survivor in HICs in the near future, and survivors will be found in LMICs as well. Thus, the late treatment effects and squelae have

become a significant problem among the increasing number of survivors [21.13, 21.14].

Although currently it is possible to reduce the radiation dose to healthy tissues around the tumour using state of the art radiotherapy techniques, a considerable amount of healthy tissue is inevitably exposed at a minimal to moderate radiation dose. The result of this exposure is acute and late radiotherapy toxicity. Acute toxicity occurs from the first weeks of the treatment period until several weeks after the completion of radiotherapy. These effects are site specific and usually well tolerated by patients. However, occasionally they can be serious enough that various medications and a break of a few days of treatment may be needed for healing. Acute effects are mostly temporary and do not cause permanent impairment of tissues and organs.

Late effects of radiotherapy are more serious than acute effects; they are usually progressive, irreversible and permanent, may cause organ insufficiency and may even be life threatening. They may develop months to years after the completion of irradiation. The backbone of late effects is the thrombosis of small arterioles and capillaries, followed by fibrosis and hyalinization of the tissues and organs. Since children's organs are still growing, they are more vulnerable than adults' to the late effects of radiation.

Late effects develop in the irradiated volumes of tissue, and other organs may be affected as well as whole organ systems. Growth impairment, skeletal deformities, endocrine insufficiencies, infertility, and impaired mental and motor development are common. Organ insufficiencies such as renal failure, lung fibrosis and cardiomyopathy may occur, which may be life threatening. Surgical excisions and some chemotherapy drugs may worsen the situation as well.

Secondary cancers are considered the most serious late effect of cancer treatment. Both radiotherapy and chemotherapy contribute to the development of secondary cancers. They may occur many years after the completion of therapy. Since children live much longer than adults after radiotherapy, they are at a high risk of secondary cancers. The mortality rate beyond five years from the end of treatment was estimated to be 13 times higher than that of the age and sex matched population in the United States of America. The time of highest risk is between five and nine years from the diagnosis period, with decreasing risk thereafter. However, even at 30–34 years from diagnosis, standardized death rates are elevated [21.15].

## 21.8. CONCLUSIONS

The role of radiotherapy in the management of childhood tumours has undergone significant refinement over the years. From the time that radiotherapy

was used as the sole modality for achieving local control, current treatment protocols have evolved as multimodal approaches integrating all three modalities in the optimal sequence for achieving the best therapeutic ratio. Radiotherapy still remains an integral part of most current treatment protocols for childhood solid tumours.

Recent technological advances in imaging, radiotherapy planning, treatment delivery and verification have made it possible to further optimize dose distributions to the target tissues, while significantly reducing the dose to surrounding normal structures.

## 21.9. KEY POINTS

— The incidence of childhood cancer is increasing throughout the world.
— Most childhood cancers are curable with proper treatment.
— Childhood cancers are mostly treated by various combinations of surgery, radiotherapy, chemotherapy and immunotherapy. The main principle behind multimodality treatment is to reduce the toxicity of each individual modality while keeping the cure rates at a high level.
— Management of paediatric cancer patients in dedicated oncology centres by well trained multidisciplinary teams is necessary to cure patients and manage the side effects successfully.
— Advances in imaging and computerized radiotherapy technology have enabled radiation oncologists to plan and deliver sufficient radiation doses to tumours while keeping the radiation dose to the normal structures at a minimum.
— New radiotherapy methods (intensity modulated radiation therapy, image guided radiation therapy, stereotactic body radiotherapy and helical tomotherapy) offer possibilities of further refinement of radiotherapy quality.
— The physical properties of the proton beam make it advantageous in selected paediatric cancers.
— Since children's organs are still growing, they are more vulnerable than adults to the effects of radiation.
— Late radiotherapy toxicities have become a significant problem among long term childhood cancer survivors.
— Secondary cancers are considered the most serious late effect of childhood cancer treatment.

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# Chapter 22

# RADIOTHERAPY FOR HIV/AIDS RELATED CANCERS: A SOUTH AFRICAN PERSPECTIVE

**V. Sharma, J. Kotzen**

## 22.1. INTRODUCTION

Cancer is a significant cause of morbidity and mortality in people infected with the human immunodeficiency virus (HIV) [22.1]. In fact, 30–40% of people with this condition will develop a malignancy during their lifetime [22.2]. The majority of cancers affecting HIV positive people are those established as AIDS defining: Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL) and invasive cervical cancer [22.3, 22.4]. However, other types of cancer also appear to be more common among those infected with HIV. While not classified as AIDS defining, these malignancies are affecting the HIV/AIDS community greatly and have been referred to as 'AIDS-associated malignancies' [22.1, 22.5] or 'opportunistic' cancers. Two analyses have revealed a two to three fold increase in the overall risk of developing these cancers [22.3, 22.5, 22.6]. The introduction of highly active antiretroviral therapy (HAART) has resulted in decreased mortality and morbidity [22.7], and the majority of people in developed countries infected with HIV are living with only mild to moderate immunosuppression because of wide access to antiretroviral therapy [22.8].

HIV positive persons have a markedly elevated risk for two malignancies: KS and NHL, which are themselves considered sufficient to signify progression to AIDS [22.9]. KS and NHL are caused by a loss of immune control of latent infection with oncogenic viruses (human herpes virus 8 (HHV-8) for KS, Epstein–Barr virus for certain NHL subtypes) [22.10]. Other cancers caused by viruses (e.g. cervical and anal canal cancers caused by human papillomavirus (HPV), liver cancer caused by hepatitis B and C) also occur with increased frequency in this population, although for them, the importance of immune suppression is less clear [22.11, 22.12].

## 22.2. HIV VIRUSES

HIV belongs to the *Lentivirus* genus of the Retroviridae family. It is 100 nm in diameter. The main routes of transmission in sub-Saharan Africa are through

sexual intercourse, blood transfusions and mother to infant transmission. Two HIV types are relevant to the epidemic (HIV-1 and HIV-2), but one type (HIV-1) is responsible for 95% of HIV infections globally. HIV-1 is classified into ten subtypes (A–H, J, K). HIV-1 Subtype C, which accounts for about half (48%) of all global infections [22.13], is the major subtype in South Africa.

HIV infects cells that have CD4 antigen molecules on their surface. These cells are principally the helper subset of T lymphocytes, which are central to cell mediated immunity and are called CD4+ lymphocytes. HIV also needs chemokines on the cell surface to gain entry into the cell. The critical abnormality resulting from HIV infection is a progressive decline in the number of CD4+ T lymphocytes. The surviving cells also do not perform the function of cell mediated immune response. Progressive infection by the virus therefore causes a progressive decline in immunity.

Various tests for checking HIV infection exist, including antibody tests and simple/rapid tests. Full blood count findings suggestive of HIV infection are unexplained anaemia, leucopenia or thrombocytopenia.

*Antibody tests.* HIV infection is usually diagnosed through detection of antibodies to the virus. Production of these antibodies usually begins three to eight weeks after infection. The period following infection, but before antibodies become detectable, is known as the 'window period'.

The most widely available method for identifying HIV infected individuals is the detection of HIV antibodies in serum or plasma samples. The two main methods of testing for HIV antibodies are the enzyme-linked immunosorbent assay (ELISA) and the rapid immune binding assay. These tests can detect both HIV-1 and HIV-2. They are extremely reliable and highly sensitive and specific. The ELISA test is the most efficient for testing large number of samples per day. It is less expensive than immunoblot, but needs specialized laboratory equipment.

*Simple/rapid tests.* Several antibody tests, such as agglutination, dipstick, and flow through membrane can perform enzyme immunoassay. They can take less than 10 minutes (rapid) or longer (simple) and have internal controls. The first assays capable of detecting free circulating HIV particles were the HIV p24 antigen enzyme immunoassays. The quantitative measurement of plasma HIV RNA (viral load) is based on amplification of viral nucleic acids or of the probe binding signal.

South Africa had an estimated 5.9 million people (17.8% of the population) living with HIV in 2009, accounting for 17% of the global HIV/AIDS population. In the same year, 310 000 South Africans died due to AIDS related complications and 500 000 people were newly infected with HIV [22.14]. Figure 22.1 shows the prevalence of HIV infection in different African countries according to 2010 data from UNAIDS. Another UNAIDS report from 2006 stated that 63.5% of patients with HIV infections were living in sub-Saharan Africa [22.15]. Africa

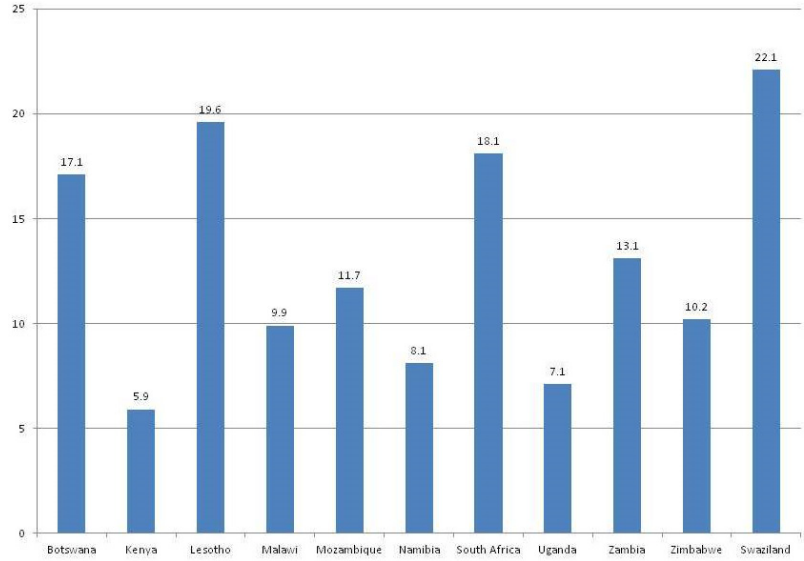


*FIG. 22.1. HIV prevalence (%) in African countries. Source: UNAIDS 2010 data.*

has the highest prevalence of HPV infection in the world, with 25.6% of women between 15 and 74 years old infected, followed by Latin America (14.3%) and Asia (8.7%).

The treatment guidelines for antiretroviral therapy have been amended in South Africa so that it can be initiated at a cell count of <350 cells/μL as opposed to the earlier figure of <200 cells/μL. Failure to begin or late initiation of treatment is usually attributed to lack of HIV testing and problems accessing treatment.

People living with HIV are at a far higher risk of developing active tuberculosis because their weakened immune system facilitates the development of this disease. Similarly, tuberculosis can accelerate the course of HIV disease. South Africa accounts for 28% of the world's people living with both HIV and tuberculosis.

## 22.3. AIDS DEFINING MALIGNANCIES

Despite a decreasing incidence since the use of combined antiretroviral therapy became widespread, AIDS defining malignancies, and particularly NHL, remain a leading cause of death in HIV infected patients [22.16].

### 22.3.1. Invasive cervical cancers

HPV infection is associated with a higher risk (increased tenfold) of invasive cervical cancer than observed in the general population [22.17]. A rapid progression to more advanced stages of cervical carcinoma, a higher rate of treatment failure, more recurrences and metastases to unusual sites and poor general condition of the patient have been associated with HIV infection [22.18–22.27].

Patients with cervical cancer and HIV positive status are 5–10 years younger in age than those with cervical cancer and HIV negative status [22.28, 22.29]. This conforms to the trend in other parts of the world and to the hypothesis that HIV infection shortens the latent period observed in progression from pre-malignant cervical lesions to invasive cancer [22.22, 22.30].

HIV positive cervical cancer patients are known to have poor response to radiotherapy and early recurrence, resulting in poorer overall survival [22.22, 22.31]. In the study by Shrivastava et al. [22.32], only 50% of patients had a complete response to radical radiation and the overall compliance was poor. The authors suggested that definitive radiotherapy should be offered to a selected group of patients.

A total of 7022 patients with cancer of the cervix were seen at the Department of Radiation Oncology of the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH, Johannesburg) over a ten year period from 1999 to 2008. Carcinoma of the cervix comprised on average 20% of all the cancer cases seen during that time. A retrospective analysis showed 1529 (21%) patients to be HIV positive, with an increase from 80 (12%) in 1999 to 272 (34%) in 2008. Stage III/IV patients represented 50%, and another 10% of patients could not be staged. Between 13.6% and 33.6% of the HIV positive patients did not receive any treatment as per the records and 64–91% of them were either staged as stage III/IV or the stage was not determined (Table 22.1). Most of the HIV positive patients received radiation therapy alone (52%–81%) over the study period.

### 22.3.2. AIDS related lymphomas

Analysis of data from an international database of 48 000 HIV seropositive individuals from the USA, Europe and Australia [22.4] found a 42% decline in the incidence of NHL among these individuals from 1997 to 1999 compared with 1992 to 1996, both for primary central nervous system lymphoma and for systemic lymphoma. The introduction of HAART is the explanation proposed for this decline. The diagnosis of AIDS precedes the onset of NHL in approximately 57% of patients, but in 30% of patients the diagnosis of AIDS is made at the

time of the diagnosis of NHL and HIV positivity. The geographical distribution of these lymphomas is also similar to the geographical spread of AIDS. Unlike KS, which is more common in homosexual men and appears to be on the decline in incidence, all risk groups appear to have an excess number of NHLs; these risk groups include intravenous drug users and children of HIV positive individuals.

In general, the clinical setting and response to treatment of patients with AIDS related lymphoma is very different from that of non-HIV patients with lymphoma. The HIV infected individual with aggressive lymphoma usually presents with advanced stage disease that is frequently extranodal [22.33]. The clinical course is more aggressive, and the disease is both more extensive and less responsive to chemotherapy. Immunodeficiency and cytopenias, common in these patients at the time of initial presentation, are exacerbated by the administration of chemotherapy. Treatment of the malignancy increases the risk of opportunistic infections that, in turn, further compromise the delivery of adequate treatment.

In the HAART era, there is a 62% five year survival rate for people with Hodgkin's lymphoma and HIV. Half the patients with Burkitt's lymphoma are expected to be alive five years after diagnosis, as are 44% of those with diffuse large B-cell lymphoma, 43% of people with other forms of NHL and 22% of individuals diagnosed with primary lymphoma of the central nervous system [22.34]. Attention to infection prophylaxis and antiretroviral therapy is important. Evidence suggests that HAART has resulted in a decreased incidence of lymphoma, and that patients with systemic lymphoma treated in the post-HAART era have a better prognosis.

TABLE 22.1. NUMBER OF HIV POSITIVE PATIENTS PER STAGE IN CERVICAL CANCER PATIENTS (*source: CMJAH data 1999–2008)*

| Year | Stage I | Stage II | Stage III | Stage IV | Unstaged | Total |
|---|---|---|---|---|---|---|
| 1999 | 4 | 25 | 36 | 6 | 9 | 80 |
| 2000 | 9 | 23 | 29 | 6 | 6 | 74 |
| 2001 | 6 | 30 | 44 | 12 | 8 | 100 |
| 2002 | 9 | 33 | 63 | 10 | 16 | 131 |
| 2003 | 16 | 45 | 56 | 14 | 13 | 144 |
| 2004 | 8 | 56 | 73 | 11 | 10 | 159 |
| 2005 | 10 | 55 | 80 | 15 | 23 | 183 |
| 2006 | 14 | 65 | 74 | 20 | 22 | 196 |
| 2007 | 20 | 60 | 80 | 7 | 23 | 190 |
| 2008 | 33 | 78 | 114 | 19 | 28 | 272 |

As per the South African cancer registry from 2005, lymphomas comprised 2.94% of all male cancers and 2.56% of all female cancers. NHL comprised 2.39% and 2.21% of all cancers in males and females, respectively. According to departmental records, 438 patients with lymphomas were seen at the Department of Radiation Oncology between the years 2001 and 2009. The median age was 37 years. Three hundred and eleven patients (71%) were black South Africans. Three hundred and twenty-eight patients (75%) were diagnosed with NHL and the remaining 110 patients (25%) had Hodgkin's lymphoma on histological evaluation. One hundred and fifty-one patients (34%) were HIV positive and 133 (88%) of these patients had NHL. One hundred and eighty-two patients (41%) received radiation therapy.

### 22.3.3. Kaposi's sarcoma

KS is an AIDS defining cancer and was one of the first HIV related illnesses recognized in the early 1980s. Unlike most cancers, which start in one site and may then spread to other parts of the body, KS can simultaneously appear at several sites. KS results in visible purplish patches, or lesions, on the skin, mucous membranes or internal organs.

KS has been shown to be caused by HHV-8, which is also known as KS associated herpes virus. In the presence of other factors — such as immune suppression or other effects of HIV in the body — HHV-8 is thought to encourage normal cells to change into tumour cells. It can affect people at all stages of HIV infection, but it is unlikely to be life threatening as long as the CD4 cell count is above 250 cells/μL. Since the introduction of effective HIV treatment, KS is seen much less often. People with lower CD4 counts are more likely to develop KS that affects internal organs, such as the lymph nodes or the lungs, with potentially life threatening consequences. KS can also affect HIV negative patients; the first cases reported as far back as 1872 were a form of the cancer in older people of eastern Mediterranean origin.

Both HHV-8 and KS itself are more common among HIV positive gay or bisexual men, women who were infected with HIV through sex with bisexual men, and HIV positive people from African communities, than other groups with HIV. Earlier ideas about the cause of KS, such as the theory that it was linked to the recreational use of poppers (inhaled nitrites) have now been shown to have no foundation in fact.

HHV-8 appears to be sexually transmitted, although it could also be transmitted in other ways. Studies have shown that transmission of HHV-8 increases with the number of years of regular sexual intercourse, the number of past male sexual partners and a past history of several sexually transmitted infections.

Results from a case control study published by Stein et al. [22.35] suggested that 89% of 333 patients with KS were HIV positive and were infected by the HIV-1 type virus. Singh et al. [22.36] have reported results of a comparative study of hypofractionated radiotherapy in 60 patients with epidemic KS with an overall response rate of 96%, median survival of 5.5 months and overall survival of 37% at 1 year. The retrospective review done by the authors found 117 patients between 2001 and 2008, 37% of oral KS treated with a median survival of 3.5 months.

## 22.4. NON-AIDS-DEFINING MALIGNANCIES

Non-AIDS-defining malignancies taken as a group are two to three times more frequent in HIV infected patients than in the general population [22.8, 22.37–22.44], although a wide variation may be observed according to the type of cancer and gender. The reasons for the higher incidence of non-AIDS-defining malignancies include prolonged overall survival, ageing and decrease in fatal opportunistic infections. In addition to tobacco smoking (45–50%) or excessive alcohol consumption (10–15%), co-infection with the hepatitis B virus or hepatitis C virus in HIV infected individuals contribute to high frequencies [22.16, 22.45]. A recent meta-analysis suggested that immunosuppression rather than risk factors might explain the higher risk of non-AIDS-defining malignancies in HIV/AIDS patients [22.46].

### 22.4.1. Head and neck cancers

The incidence of head and neck cancers is higher in HIV infected patients than in the general population, and could be related to the Epstein–Barr or HPV viruses [22.40, 22.47]. Figures 22.2 and 22.3 show the prevalence of HIV disease in patients with head and neck cancers in Johannesburg between 2001 and 2010. A clear increase over time is evident.

Kakande et al. [22.48] reported on 219 patients with head and neck squamous cell carcinoma in Uganda with a mean age of 58.8 years. The tongue was involved in 17.4% patients, followed by the palate in 12.3%. Seven of 219 (3%) patients were HIV positive and 6 of these 7 were between 24 and 30 years of age. Nwaorgu et al. [22.49] reported a series of 521 patients with head and neck cancers from Nigeria between 1996 and 2006 with only 10 (1.9%) being HIV positive and with 70% of these HIV positive patients in the 17–45 age range. They reported that salivary gland malignancy was the most common tumour in patients who were HIV positive in the southwest region, whereas Otoh et al. [22.50] reported KS as the most common in the northeast

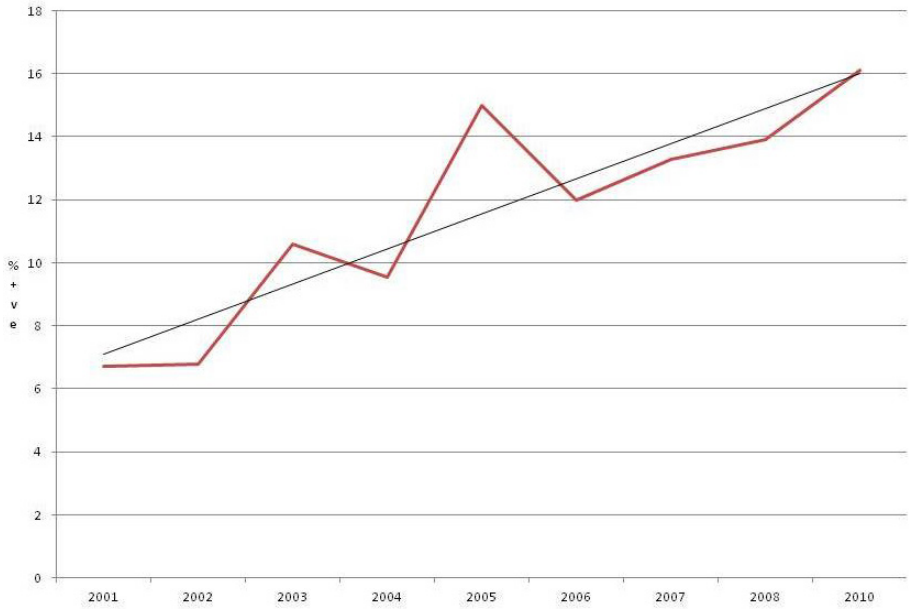


*FIG. 22.2. HIV positive prevalence in patients with head and neck cancers between 2001 and 2010.*

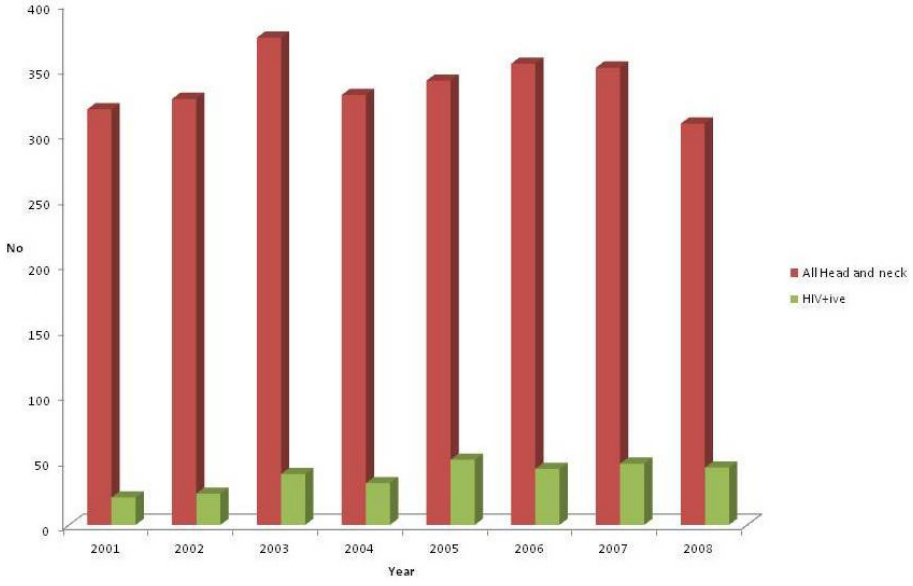


*FIG. 22.3. Relation between total head and neck cancer and HIV positive patients from 1999 to 2008. Source: CMJAH, Johannesburg, South Africa.*

TABLE 22.2. INCIDENCE OF HEAD AND NECK CARCINOMAS ARISING IN PATIENTS WHO ARE HIV POSITIVE AND HAVE AIDS

| Author, year | Country/ region | No. of patients with H&N cancer | No. of HIV+ cases | Head and neck sites | HIV or AIDS | Ref. |
|---|---|---|---|---|---|---|
| Melbye, M., et al., 1996 | United States of America | 50 050 | 4 | Nasopharynx | AIDS | [22.54] |
| Serranio, D., et al., 1999 | Southern Europe | 5 281 | 3 | Supraglottic larynx, nasopharynx | AIDS | [22.55] |
| Li, Y., et al., 2002 | Australia | 8 118<br>7 061<br>2 112 | 6<br>4<br>3 | Lip<br>Lip<br>Lip | HIV<br>HIV<br>AIDS | [22.56] |
| Powles, T., et al., 2004 | United Kingdom | 8 640 | 7 | Nasopharynx<br>Oral cavity<br>Larynx | AIDS<br>HIV | [22.49] |
| Clifford, G., et al., 2005 | Switzerland | 7 304 | 11 | Lip, tongue<br>Oral cavity<br>Pharynx | Not specified | [22.41] |
| Mbulaiteye, S.M., et al., 2006 | Uganda | 12 607 | 9 | Thyroid<br>Conjunctiva | Not specified | [22.57] |
| Chaturvedi, A., et al., 2009 | United States of America | 499 230 | 59 | Oropharynx | AIDS | [22.58] |

region. Butt et al. [22.51] have reported on the patterns of head and neck malignancies in Kenya and noted that of 200 patients, 58% were males and 42% females. Females were significantly younger (mean 33 years) than males (mean 37 years) ($p = 0.001$). Of the malignant lesions, 68% were KS, 17% squamous cell carcinomas and 13% NHL. Ninety-seven per cent of patients had stage III/IV disease. Table 22.2 shows the incidence of HIV/AIDS and head and neck cancer reported in various countries [22.39, 22.47, 22.52–22.56].

A retrospective review at the Charlotte Maxeke Johannesburg Academic Hospital showed that head and neck malignancies represented 9% of all malignancies seen per year from 2001 to 2008. Of the 2782 patients seen during the period, 319 patients (11%) tested positive for HIV infection (5.6–15%) (Fig. 22.2). The mean age of the group was 38.7 years (range 5–86 years). Squamous cell carcinoma histology was observed in 128 (40%) of patients, with 117 patients (37%) diagnosed with KS. Table 22.3 shows the characteristics

TABLE 22.3. HIV AND HEAD/NECK LESIONS
*(source: CMJAH data 2001–2008)*

| Patient characteristics and treatment parameters (No. = 319) | |
|---|---|
| Gender — Male : Female | 167:152 (1.1:1) |
| Age group 5–86 years | Median = 37 years |
| ECOG | No. (%) |
| 1 | 161 (50) |
| 2 | 90 (28) |
| Histology | No. (%) |
| Squamous cell carcinoma | 128 points (40) |
| Kaposi's sarcoma | 117 points (37) |
| CD4 count: 187 points | Range (3–1215 cells/μL) |
| Squamous cell carcinomas: median 150 cells/μL | Range (3–772 cells/μl) |
| Kaposi's sarcoma: median 332 cells/μL | Range (3–1215 cells/μL) |
| Main sites involved | No. (%) |
| Hard/soft palate | 80 (25) |
| Conjunctiva/orbit | 53 (17) |
| Oral tongue/base tongue | 30 (9) |
| Parotid gland | 24 (8) |
| Larynx | 23 (7) |
| Treatment with radiotherapy | 163 points (51%) |

of the patients and tumours. One hundred and sixty-three patients (51%) were treated with radiation therapy without chemotherapy.

Enhanced mucosal reactions in AIDS patients receiving radiotherapy for oropharyngeal cancer [22.57] and KS have been reported [22.58, 22.59]. This increased radiosensitivity has been attributed to intrinsic cell radiosensitivity [22.60] and glutathione deficiency [22.61].

Cancer of the conjunctiva has a prevalence ten times higher in HIV positive patients than in the general population. It is probably related to HPV infection and exposure to ultraviolet radiation. Conjunctiva carcinoma used to be an uncommon slow growing tumour found in elderly males [22.62, 22.63], but in Africa it is becoming more aggressive and more likely to affect young females [22.64]. This pattern is related to the coexistence of the HIV/AIDS pandemic with high HPV exposure and solar radiation in the region.

Ateenyi-Agaba et al. from Uganda [22.64] recorded a sixfold increase in the incidence of carcinoma of the conjunctiva from 6 per million per year in 1970 and 1988 to 35 per million per year in 1992 (over a four year period). Lee et al. [22.62] reported that 78.5% of the patients affected were elderly males with a mean age of 60 years in Australia. Pola et al. [22.65] reported that 70% of the patients in Harare, Zimbabwe were females, with a median age of 35 years. In South Africa, the mean age was 37 years [22.66]. The majority of affected persons in Africa are HIV positive: 71% in Uganda, 86% in Malawi [22.67] and 70.6% in South Africa [22.66]. In the present series, 53 patients (41%), with a median age of 37 years, had conjunctival tumours; 90% presented with advanced disease and all were HIV/AIDS positive.

The morbidity from squamous cell carcinoma of the conjunctiva relates to the effects of the disease and its treatment. It may extend into the eyeball, orbit, regional lymph nodes, surrounding paranasal sinuses and brain [22.68]. Advanced disease, where the tumour has spread, requires removal of the eyeball (enucleation) or the entire orbital contents (orbital exenteration) in an attempt to save life [22.69]. Despite therapy, 43% of treated patients experience recurrence at variable times (most within two years) [22.70–22.72].

The recurrence rate may be higher in Africa due to late presentation, exposure to solar radiation and lack of adjunctive therapies. There is a need to conduct randomized controlled trials to provide unbiased evidence for the effectiveness of currently used interventions for treating conjunctival squamous cell carcinomas. Treatment of opportunistic tumours in HIV/AIDS patients, such as squamous cell carcinoma of the conjunctiva, is part of HIV care. Untreated squamous cell carcinoma of the conjunctiva threatens survival, and not paying due attention to this disease may compromise gains from other care administered to affected individuals.

### 22.4.2. Anal cancer

The incidence of anal cancer is 176 times higher in HIV infected patients than in the general population in age and gender matched groups [22.73]. Dhir et al. [22.74] reported results from 251 patients identified as HIV positive during 2001–2005: 141 (56%) had non-AIDS-defining illnesses. In males, the projected incidence rate (PIR) was increased for anal cancers (PIR = 10.3), Hodgkin's disease, testicular cancer, colon cancer and some sites of head and neck cancers. Among females, a PIR for anal cancer of 6.5 was noted. This high incidence could not be confirmed from the data available from CMJAH.

The use of definitive radiotherapy doses (60–70 Gy), combined with cisplatin and 5-Fluoruracil chemotherapy, yield similar results as in HIV negative patients [22.23, 22.75].

### 22.4.3. Oesophageal cancer

The prevalence of HIV in cancer of the oesophagus has ranged from 4% in 1999 to 11% in 2008 according to the Cancer Epidemiology Study Group [22.76]. Twelve (21%) patients were reported to be reactive to the ELISA test for HIV-1 infection during the retrospective review of the charts of 58 patients diagnosed with carcinoma of the oesophagus who were attending CMJAH in 2009 (Fig. 22.4). Their age ranged from 36 to 61 years. The CD4 count ranged between

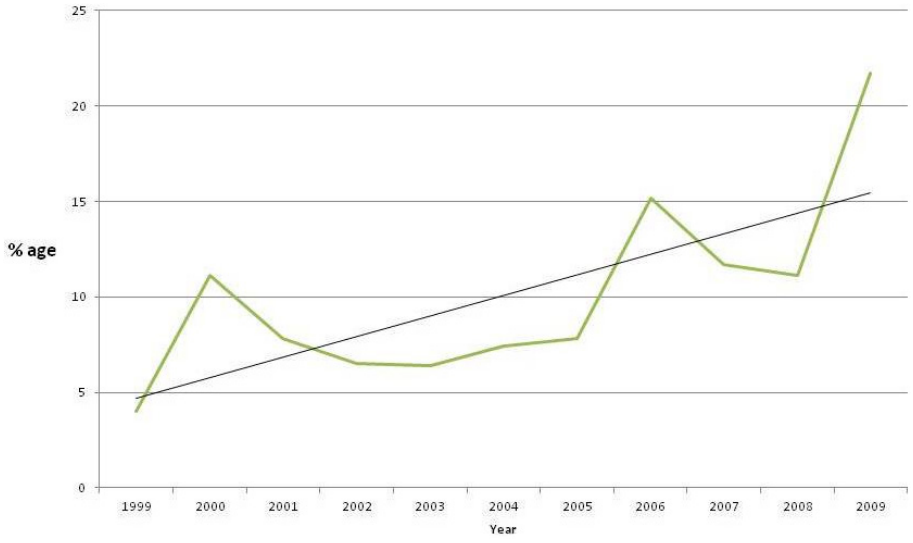


*FIG. 22.4. HIV positive prevalence in patients with carcinoma of the oesophagus between 2001 and 2010.*

43 and 298 IU/mL. The median survival for HIV positive patients was 46 days as compared with 105 days for patients treated during the same period with HIV negative status.

Primary oesophageal carcinoma is another non-AIDS-defining cancer associated with moderate immune suppression and lifestyle habits, including tobacco and alcohol use [22.77]. Dysphagia, odynophagia and retrosternal pain are common symptoms associated with oesophageal compromise in patients with HIV-1 infection, with HIV being responsible for ulcerative esophagitis [22.78]. Patients may present with atypical clinical, radiographic and endoscopic findings in the AIDS setting, and a changing radiographic or endoscopic pattern should make a biopsy necessary to rule out superimposed squamous cell cancer [22.79]. A study from Uganda by Parkin et al. [22.80] has reported that the incidence of oesophageal cancer has remained relatively constant. The incidence is increasing at CMJAH as compared with earlier years [22.76] and compared with the rates reported in the publication by Parkin et al. [22.80]. The biological behaviour and outcome of HIV related oesophageal cancer also appears different than that in the general population, as reported by Stebbing et al. [22.77].

## 22.5. FINAL CONSIDERATIONS

With the use of combination antiretroviral therapy, malignant tumours have become the most frequent cause of death [22.45] and a frequent cause of hospitalization [22.81] in HIV positive patients. Infection by HIV is associated with a high risk of high grade systemic NHL (i.e. Burkitt's and immunoblastic lymphoma), primary brain NHL, KS and invasive cervical cancer. These diseases are considered AIDS defining conditions [22.9]. The prognosis seems poorer in HIV infected patients than for similar diseases occurring in uninfected individuals. There is no evidence at present for a different treatment approach in patients with NHL, Hodgkin's lymphoma or lung cancer in HIV positive and HIV negative patients.

The study of cancer in HIV positive people in Africa is valuable for two reasons [22.82]. First, the large size of the HIV epidemic underscores its public health significance, including its impact on cancer incidence and morbidity. Second, Africa has an extraordinary genetic diversity of pathogens and hosts.

Two approaches are being used for understanding and developing mechanisms for the better management of HIV/AIDS cancer groups. The African Organisation for Research and Training in Cancer (AORTIC) provides resources that could be leveraged to initiate, implement and report on Africa wide studies of cancer. In contrast to a *resource focused* approach, a *disease focused* approach will help understand the association between HIV and cancers, especially lung,

breast and anal cancers, because of the specific habits prevalent in African countries compared to the West.

The treatment strategies for cancers in HIV infected patients should not be different from those for non-HIV-infected individuals. The case management should take into account the immune status, prophylactic measures, potential interaction with antiretroviral treatment, and drug combination toxicity.

It is highly desirable that the scientific community also accept the challenge of including these patients into clinical trials to allow them to benefit from innovative treatments for cancers as other patients do [22.83].

## 22.6. KEY POINTS

— Thirty to forty per cent of people infected with HIV will develop a malignancy during their lifetime.
— The majority of cancers affecting HIV positive people are those established as AIDS defining: Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL) and invasive cervical cancer.
— Two HIV types are relevant to the epidemic (HIV-1 and HIV-2), but one type (HIV-1) is responsible for 95% of HIV infection globally.
— The majority of people in developed countries infected with HIV are living with only mild to moderate immunosuppression because of wide access to antiretroviral therapy.
— Despite a decreasing incidence since the use of combined antiretroviral therapy became widespread, AIDS defining malignancies, and particularly NHL, remain a leading cause of death in HIV infected patients.
— HIV positive cervical cancer patients are known to have a poor response to radiotherapy and early recurrence, resulting in poorer overall survival.
— KS has been shown to be caused by a virus called human herpes virus 8 (HHV-8), which is also known as KS associated herpes virus.
— Non-AIDS-defining malignancies include several forms of head and neck cancer, anal cancer and oesophageal cancer.
— There is no evidence at present for a different treatment approach in patients with NHL, Hodgkin's disease or lung cancer in HIV positive and HIV negative patients.
— The patient's management should take into account the immune status, prophylactic measures, potential interaction with antiretroviral treatment, and drug combination toxicity.

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# Chapter 23

# INTEGRATION OF RADIOTHERAPY IN PALLIATIVE CARE

**R. Drummond, E. Rosenblatt, B.J. Allen, S.A. Hussain**

## 23.1. INTRODUCTION

The goal of palliative care is to achieve the best quality of life for a patient with an incurable disease. The essential elements are:

(a) The patient has an incurable disease.
(b) Care focuses on helping the patient live as actively and independently as possible until death.

Treatment is aimed at the relief of pain and other distressing symptoms, with the primary aim of optimizing the patient's quality of life. Prolongation of life is not an aim, although good symptom control may prolong survival.

Hence, palliative care is individualized, patient focused care which includes treatment aimed at symptom control, but also includes psychological, spiritual and social care for the patient and his or her family. A multidisciplinary team of medical specialists and paramedical staff is required to achieve this.

The World Health Organization (WHO) [23.1] and the American Society of Clinical Oncology (ASCO) [23.2] recommend early integration of palliative care into cancer management. This is to ensure:

(a) The best possible symptom control and quality of life;
(b) Attention to psychosocial and spiritual issues;
(c) The prevention of feelings of abandonment after curative treatment ceases.

Patients undergoing curative radiotherapy treatment will benefit from the symptom control measures used in palliative treatment. High quality palliative care cannot be achieved without excellent symptom relief. Radiotherapy treatment has a major role in symptom relief [23.3] and hence is an essential element of palliative care in cancer patients.

Palliative cancer care plays an increasingly important role in global health care for two main reasons [23.4]:

(a) Although the cure rates of cancer are improving in high income countries, cancer continues to be one of the world's leading causes of death.
(b) Despite a rise in cancer deaths, survival rates are also steadily increasing. This leads to a population of patients who may be short term or long term survivors, but still need to cope with the symptoms and clinical problems caused by cancer and its treatment.

*Palliative care* is defined as the physical, social, psychological and spiritual care of patients with life limiting illnesses that is delivered by a multidisciplinary team. Palliative care is an approach to improving the quality of life of patients and their families facing problems associated with life threatening diseases through the prevention and relief of suffering by early identification and accurate assessment and treatment of pain and other problems of a physical, psychological and spiritual nature.

*Supportive care* is defined as treating the adverse effects of cancer treatment, such as nausea, vomiting, infections, cytopenia, mucositis, malignant effusions, paraneoplastic syndromes and oncological emergencies, and providing nutritional support. It aims to optimize the comfort, function and social support of patients and their families at all stages of disease.

Radiotherapy is one of the most effective means of providing palliation of cancer symptoms. The symptoms most commonly relieved with palliative radiotherapy are pain, bleeding and organ obstruction caused by tumours. Recognizing the importance of radiotherapy in palliative care, this topic is and should be included in the curriculum for the training and education of radiation oncologists. Trainees should be familiar with the principles of both palliative and supportive care, together with the principles of radiation biology, the indications for the use of radiotherapy as a curative and palliative modality, the control of cancer related symptoms and the adverse effects of treatment.

## 23.2. PRINCIPLES OF PALLIATIVE RADIOTHERAPY

In contrast to curative cancer therapy, complete eradication of the cancer is not required from palliative radiotherapy to achieve symptom relief. So moderate therapeutic doses can be employed and tumour regression may not always be seen.

### 23.2.1. Accurate anatomical localization of the symptomatic tumour deposit

The tumour mass which is producing the symptom must be irradiated to achieve a response. Adequate diagnostic imaging is required to anatomically locate the site of the symptomatic metastasis. Plain X rays will provide this information for most symptomatic bone metastases and are usually readily available. More sophisticated imaging methods (computed tomography (CT) scan or magnetic resonance imaging (MRI)) may be required to determine the location of soft tissue metastases causing obstruction and compression symptoms.

### 23.2.2. Simple techniques and field arrangements

#### *23.2.2.1. Patient positioning*

A comfortable position for the patient should be used, with consideration for the patient's symptoms. Patients who have difficulty breathing can be treated in a sitting position. Restrictive patient immobilization devices are not required.

#### *23.2.2.2. Simulation*

The criteria for simulation are not formalized in palliative radiotherapy. In keeping with the goals of effective palliation, simulation and palliative radiotherapy techniques should be simplified to maximize the patient's comfort. Simulation and portal imaging are beneficial when treating spinal cord compression or vertebral metastases to ensure the proper coverage of the vertebral bodies. Simulation and imaging are important when palliative radiotherapy fields must account for prior radiotherapy portals, particularly over the spinal cord or other critical structures.

While simulation is usually a standard of care in high income and middle income countries, it is not always mandatory for palliative radiotherapy, especially for the treatment of long bones such as the femur and humerus. The site and volume of tumour involvement are the most important considerations in the development of a palliative radiotherapy treatment plan because of the radiation tolerance of adjacent normal tissues. Unlike the comprehensive radiation treatment portals used in curative therapy, palliative radiotherapy usually only aims to encompass the tumour volume relevant to symptoms. Treatment planning must minimize possible toxicities and account for prior courses of radiation. Toxicity is reduced by limiting the irradiated volume and through the application of dosimetric principles that minimize integral dose.

#### *23.2.2.3. Clinical marking of treatment fields for surface lesions*

A good knowledge of surface anatomy facilitates clinical field marking for treatment of bone metastases in an emergency situation or when simulation imaging is not available. Plain radiographs of the area to be treated, taken in the treatment position, to verify or mark the treatment field are adequate for most palliative radiotherapy. CT based field arrangement and treatment planning is not often required. There is little evidence that these more sophisticated planning methods provide any clinical benefit in palliative treatment, but they do add to the cost of and time required for the planning of treatment.

#### *23.2.2.4. Treatment fields*

Single fields or parallel opposed fields are primarily used in palliative treatment. There is no place for very small treatment fields or complex field shaping. Fields need to be of adequate size to cover the known tumour, a margin for microscopic cancer infiltration and an adequate margin to account for patient movement, both day to day and during treatment. This is particularly important in palliative treatment, as the patient is not restrictively immobilized.

#### *23.2.2.5. Dosimetry*

Unlike radical treatment where high doses of radiation are being delivered to the target volume with the aim of complete cancer eradication, in palliative treatment, where more modest doses are used, achieving a homogeneous dose distribution is not essential. Detailed dosimetry is rarely required. It is of course important to clearly designate where the treatment dose is prescribed.

### 23.2.3. Short hypofractionated treatment regimes

Patients with metastatic cancer have a reduced life expectancy, possibly only months, so the treatment itself should not consume a major portion of the remaining life span. However, patients with some metastatic cancers (e.g. breast or prostate cancer) can have a long survival. In these cases, a higher dose and a more fractionated course of radiotherapy may be justified to produce more durable symptom control and reduce the need for re-treatment.

In contrast to the low daily radiotherapy doses given in conventional curative fractionation of 1.8–2.0 Gy per fraction administered over five to seven weeks for total doses of 50–70 Gy, hypofractionation is recommended for most palliative clinical situations. Hypofractionation consists of larger than standard doses per fraction and shorter overall treatment times. Hypofractionated

radiotherapy schedules can range from 2.5 Gy per fraction administered over three weeks for a total dose of 35 Gy to a single 8.0 Gy dose of radiation for solitary painful bone metastases. A single 8.0 Gy fraction is routinely given in most European countries and Canada for uncomplicated painful bone metastases given the equivalent outcomes in a wide range of clinical trials [23.3]. A single large radiotherapy dose is as effective in relieving pain as other more protracted schedules. Re-treatment with the same dose is possible, if necessary [23.5].

### 23.2.4. Moderate doses of radiation

Moderate radiation doses are generally used to achieve a good, predictable response and keep toxicity to a minimum. The aims of palliation of symptoms and improved quality of life will not be achieved if the treatment itself has significant toxicity.

A sufficient radiation dose must be given to ensure that the symptoms respond and that the symptom relief will last for the rest of the patient's life. Too low a dose means that re-treatment at some later time will be required. Too high a dose may result in increased toxicity, and both will adversely affect quality of life.

### 23.2.5. Tailoring the treatment

Treatment aim and treatment duration should be tailored to the patient's overall life expectancy. Palliative radiotherapy may be an unnecessary burden for patients whose death is imminent, and it should be avoided in terminal patients. However, physicians' estimates of survival of patients with metastatic cancer are not always accurate. Even with patients with a short life expectancy, a single dose of radiotherapy for a painful metastasis will result in improved quality of life, whereas a multiple fraction course of treatment would result in deterioration in the quality of life. Prognostic models for estimating survival time in patients with advanced cancer may have a useful role. Major benefits of the use of radiotherapy are the speed with which symptoms respond and the relatively high response rates.

## 23.3. CLINICAL OVERVIEW

Surveys of radiotherapy utilization rates suggest that 30–50% of all radiotherapy courses are administered with palliative intent. Table 23.1 presents the predominant cancer types referred for palliative radiotherapy [23.6].

TABLE 23.1. TYPES OF CANCER REFERRED FOR PALLIATIVE RADIOTHERAPY

| Cancer type | % of all cancers referred to palliative radiotherapy |
|---|---|
| Lung cancer | 27 |
| Prostate cancer | 21 |
| Breast cancer | 8 |
| Bladder cancer | 7 |
| Kidney cancer | 4 |
| Large bowel cancer | 4 |
| Head and neck cancer | 3 |
| Pancreatic cancer | 3 |

The figures in Table 23.1 reflect the relative incidence of the cancer type, the frequency with which the cancer is incurable at diagnosis and the relative efficacy of radiotherapy in controlling symptoms compared with other available treatments.

## 23.4. CLINICAL ROLES FOR PALLIATIVE RADIOTHERAPY

### 23.4.1. Painful bone metastasis

The most common indication for palliative radiotherapy is painful bone metastasis. Bone metastasis may cause significant morbidity including pain, pathological fractures, spinal cord compression and hypercalcaemia. Radiotherapy is an effective treatment, with up to 80% of patients experiencing significant pain relief.

The exact mechanism underlying the effect of pain relief is unknown. Onset of pain relief starts within ten days, but may take up to one or two months to be complete (Fig. 23.1).

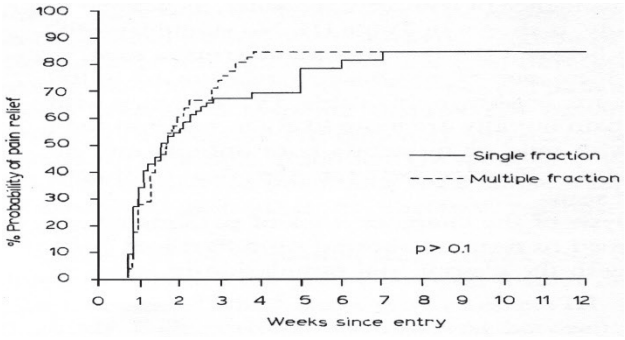


*FIG. 23.1. Onset of pain relief by treatment allocation.*

Randomized clinical trials show that a single dose of 8.0 Gy is as effective as more fractionated treatment regimes of 30 Gy in ten fractions or 20 Gy in five fractions. However, patients treated with a single fraction require re-treatment more often than those treated with more fractionated regimes (25% require re-treatment) [23.5].

### 23.4.2. Mechanical strength

While radiotherapy is effective for pain relief, it does not immediately improve bone strength. Lytic bone metastases, particularly in weight bearing bones, are at risk of fracture if they are greater than 2.5 cm in size or encompass more than 50% of the cortical bone. If the patient has a pathological fracture, surgical stabilization should be performed. Although surgical stabilization will often produce good pain relief, post-operative radiotherapy is recommended to gain tumour shrinkage and facilitate bone healing.

### 23.4.3. Bisphosphonates

Bisphosphonates are drugs which reduce osteoclast activity in bone metastases and reduce calcium resorption from the bone. They have a major role in treating hypercalcaemia, but have also been shown to reduce the risk of complications (pathological fractures, spinal cord compression and bone pain) in patients with bone metastasis. They are not useful in treating fracture risk or spinal cord compression, but are a useful follow-up treatment after palliative radiotherapy for bone metastases.

### 23.4.4. Bone-seeking radioisotopes and hemibody radiotherapy

Bone-seeking radioisotopes such as strontium-89 and samarium-153 are selectively taken up at sites of osteoblastic activity, where they are retained and deliver a significant dose of beta irradiation to a metastasis at that site. This treatment is delivered with a single intravenous injection. It is suitable for a selected group of patients with multiple sites of pain from osteoblastic bone metastasis (predominantly metastatic prostate cancer and some breast cancer metastases). Onset of pain relief can take three to four weeks. Response rates of up to 63% have been reported. The main toxicity is bone marrow depression, which may limit the scope for repeat treatment [23.7].

Hemibody radiotherapy is also an effective treatment for multiple sites of pain from widespread bone metastasis. This is a single dose of radiotherapy given to the upper or lower half of the body. An improvement in pain may be seen within 24 hours or take up to six weeks. The response rate to hemibody radiotherapy and the duration of benefit are similar to those obtained with radioisotopes. This treatment can be delivered on any megavoltage radiotherapy machine [23.7].

### 23.4.5. Brain metastasis

Brain metastases cause neurological symptoms, raised intracranial pressure and severe disability. Treatment options include corticosteroids, whole brain radiotherapy, stereotactic radiotherapy, stereotactic radiosurgery and surgical resection. The median survival for a patient with brain metastasis varies from one month to several years, depending on the primary cancer, the extent of neurological deficit at diagnosis and the extent of metastatic disease outside the brain. For the most common clinical presentation of multiple brain metastasis, corticosteroids will provide short term symptom relief. A short course of whole brain irradiation will consolidate and maintain this symptom relief, with improvement in neurological function for a reasonable period of time [23.8]. For patients with a solitary metastasis and no extracranial cancer, surgical excision with or without radiotherapy should be considered.

### 23.4.6. Obstruction/compression symptoms

A range of different symptoms arise when a cancer mass within or around a hollow organ causes compression or obstruction. Examples are:

(a) Airway obstruction from bronchogenic carcinoma;
(b) Dysphagia from oesophageal cancer;

(c) Superior vena cava obstruction;
(d) Urinary outlet obstruction;
(e) Spinal cord compression.

As cancer shrinkage is required to achieve reliable and durable symptom relief, more fractionated palliative treatment regimes are preferred. Locally advanced lung cancer has been extensively studied: there is a trend towards improved survival and decreased re-treatment in biological equivalent doses of 35 Gy or higher. Higher doses are followed by higher rates of oesophagitis and risk of myelopathy. Treatment programmes must take into account the patient's co-morbidities and life expectancy, when selecting a treatment regime [23.9]. When higher dose treatment regimes are used, more advanced treatment techniques are justified to lessen treatment toxicity and achieve optimum quality of life.

### 23.4.7. Bleeding, tumour ulceration and fungation

Bleeding from a cancer can occur as haemoptysis from a bronchogenic cancer, haematuria from bladder cancer, vaginal bleeding from advanced gynaecological cancers or from local recurrence of breast cancer, skin metastasis from breast cancer, melanoma or head and neck cancers. Bleeding is frightening for the patient and can be significant, necessitating a blood transfusion. Local radiotherapy is often effective in achieving haemostasis. A single dose of 6–8 Gy will stop bleeding, but a more fractionated course of treatment is usually used to achieve tumour regression and encourage healing of the epithelial surface [23.9, 23.10].

## 23.5. PALLIATIVE MANAGEMENT PLAN

Control of physical symptoms is the basic requirement of palliative medicine, but it is only one element of holistic care of a patient with incurable cancer. Other treatments used in palliative medicine include symptom controlling drugs (analgesics, antiemetics), anticancer systemic therapy (cytotoxic drugs, endocrine therapy), physical aids (crutches, walking frames) and palliative surgery (laminectomy, stents, orthopaedic surgery). Thus, the care of patients with metastatic cancer requires a multidisciplinary team just as much as the curative treatment of cancer does [23.8].

To achieve control of physical symptoms requires:

(a) Accurate diagnosis;

(b) Good clinical judgement;
(c) Patient focused and individually tailored treatment;
(d) Comprehensive knowledge of cancer and its available treatment;
(e) Appropriate follow-up and reassessment.

## 23.6. UNDERUTILIZATION OF RADIOTHERAPY

Palliative radiotherapy is effective in reducing symptoms and increasing subjective well being with minimal side effects. However, there is much evidence that many patients do not receive the benefit of this treatment [23.6]. In some countries this is due to lack of radiotherapy facilities. In others, lack of awareness of the benefits of palliative radiotherapy by the patients' medical practitioner is the cause.

## 23.7. OPTIMIZING RESOURCES IN PALLIATIVE RADIOTHERAPY

Differing patterns of cancer epidemiology around the world influence the need for radiotherapy resources. In low and middle income countries (LMICs), radiotherapy is often an important resource in cancer therapy, given the large numbers of patients diagnosed with advanced and metastatic disease. Radiotherapy may be used in more than two thirds of cancer patients in high income countries for curative intention, and for palliation when systemic therapies fail to control metastatic disease. For all countries, however, lung cancer, a partly preventable disease, is the greatest cause of cancer related deaths. Even with the most aggressive therapies in high income countries, lung cancer survival rates remain low, with recurrent or metastatic lung cancer survival being measured in months. Often, radiotherapy is the only effective therapeutic modality to palliate symptoms.

Palliative radiotherapy is essential in every country. When cancer screening is limited and most patients present with advanced/metastatic tumours, palliative radiotherapy can provide effective and efficient symptom relief, and be a part of ongoing palliative care. Palliative radiotherapy also remains an essential part of cancer care in high income countries.

Clearly, with such an overwhelming need for palliative radiotherapy, it is imperative that the available resources be optimized and used to their full potential. There are, however, several factors that prevent such resource optimization:

(a) Palliative radiotherapy and palliative care are often delayed in pursuit of aggressive therapies, even when a cure is beyond attainment.

(b) Radiotherapy resources are concentrated unequally throughout the world. While LMICs represent about 85% of the world population, high income countries, including countries in North America, western Europe, Australasia, and Japan, have two thirds of all radiotherapy facilities. This includes 80% of all medical linear accelerators and over 25% of all cobalt units. Only 3300 teletherapy machines, mainly cobalt-60 units, are installed in LMICs.

(c) With cancer cases set to rise dramatically in the future, it is also clear that there is an insufficient number of radiotherapy machines. Assuming that one machine is required for 500 new cancer cases per year, more than 10 000 radiotherapy machines are currently needed in the developing world. The introduction of new radiotherapy equipment, including linear accelerators and computer based treatment planning systems, also requires calibration and training of staff for the specific units installed. Trained staff is needed, along with the radiotherapy equipment, to provide safe and effective treatment. Ongoing quality assurance measures are also necessary to maintain the equipment.

(d) A lack of local radiotherapy infrastructure and an inadequate health care structure can negatively impact the effectiveness of palliative care resources. Even limited health care resources, especially in the case of radiotherapy provision in LMICs, require a fixed and expensive infrastructure to allow access to care. Access to palliative radiotherapy is also affected by a lack of infrastructure (e.g. lack of public transport), logistical problems due to long distances to treatment sites, adverse weather conditions, inadequate health insurance, the overall expense of radiotherapy treatment and failure to refer patients for palliative radiotherapy in the first place when more costly, toxic and often less effective systemic therapies are preferred.

(e) Perhaps most importantly, patient socioeconomic status is the greatest determinant governing access to care. Problems relating to access to health care are pervasive in LMICs with limited health care resources and large rural areas. Access is also a problem for uninsured patients in high income countries. New therapeutics derived from cancer research are often the least accessible to people of low socioeconomic status because of system barriers.

## 23.8. RESOURCE PLANNING AND PRIORITIES

### 23.8.1. Funding a national policy

Cancer care plans for palliation often fail to address accessibility of palliative radiotherapy, and most palliative care guidelines include only a limited description of the role of palliative radiotherapy. This description also often offers limited guidance for evaluating the level of resources necessary to provide this critical component of palliative care.

Because radiotherapy is available for curative cancer treatments, it is often assumed that capacity automatically exists for radiotherapy units to also administer palliative care, especially since fewer radiotherapy fractions are generally prescribed for palliative radiotherapy. However, this assumption is too simplistic and leads to an underestimation of the number of radiotherapy machines required, their levels of capacity and the number of staff required to operate them. The magnitude of this underestimation can be profound, particularly if a large proportion of patients present with locally advanced or metastatic disease that requires palliation. Palliative care plans should include the resources needed to administer palliative radiotherapy based on regional demographics that reflect the presenting stage of the disease. Without such evidence of compelling need for palliative radiotherapy, it is often more attractive to fund new technologies and therapeutics that have lower and less sustainable rates of response than palliative radiotherapy.

### 23.8.2. Funding radiotherapy units

Radiotherapy needs to be recognized as an integral aspect of cancer care. Funding of radiotherapy units is a challenge to government based health care systems in both high and low income countries. For advanced/metastatic disease especially, radiotherapy is an efficient and cost effective modality. Resource allocation at the governmental level needs to account for the use of radiotherapy in multimodality cancer therapies with curative intent and the need for palliative radiotherapy in cancer patients for whom cure is not feasible. Lack of radiotherapy resources can result in delays in the initiation of curative cancer treatment, which can adversely affect outcomes, or failure to provide urgent symptom relief needed by a patient dying of cancer.

## 23.9. KEY POINTS

— Palliative radiotherapy should be integrated into a broader palliative care system.
— Radiation oncologists should be trained in palliative cancer care. Specific training in palliative radiotherapy is highly recommended as part of radiation oncology training programmes.
— Palliative radiotherapy resources should be optimized. The most cost effective planning processes and fractionation schedules should be used.
— Health policy makers should ensure access to palliative radiotherapy for cancer patients with advanced symptomatic disease and treatable symptoms. Palliative cancer care should be delivered with minimal treatment burden and financial costs to the patient.
— Research on palliative radiotherapy is a high priority, especially in low and middle income countries, since available data mostly come from developed countries.
— Palliative care, and palliative radiotherapy in particular, are too often delayed in pursuit of aggressive therapies, even when cure cannot be realistically achieved.
— Access to care is a significant problem for individuals of low socioeconomic status, those living in rural areas and the uninsured in high income countries.

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# Chapter 24

# RESEARCH IN RADIATION ONCOLOGY

**G.W. Jones**

This chapter provides a justification for more research in radiation oncology, identifies essential aspects of good research, and promotes a strategy for more rapidly improving research capacity and evidence based practice.

## 24.1. PERSPECTIVES ON RESEARCH

### 24.1.1. Evidence generating research

The primary objectives of any health care activity are to improve well-being and reduce suffering. Reliance on scientific principles and systematic measurement to establish new technologies was a philosophical cornerstone of the European enlightenment. These led to the ascendancy of the natural sciences and engineering in Europe. Eventually, medicine departed from folk and popular remedies in the nineteenth century, and in the mid- to late twentieth century clinical epidemiology and biostatistics became the best methods for generating evidence in support of clinical–medical decisions [24.1]. Clinical research is a systematic approach to collecting evidence through careful observation and measurement. Evidence for treatments consists of findings from a suitable pattern of research studies demonstrating the superiority or suitability of such treatments. Such research is increasingly conducted as partnerships within networks of research methodologists, statisticians, sponsors, agencies and investigators [24.2].

Clinical research requires access to patients and excellent patient care. Consequently, the availability of frontline clinical staff is an essential element of this research, and the fundamental, indeed privileged, relationship between a primary care provider and a patient remains. Many clinicians now practise at the interface between evidence and medicine, with information flowing mostly from external research and prior experience through to informed consent and patient specific value claims (i.e. ‘this patient should receive, and prefers to have, the best treatment as determined by research’). To conduct quality research, clinicians require research oriented training and supporting infrastructure to become clinical investigators who practise at that interface and who provide

trial information from clinical encounters through data management resulting in knowledge claims.

Clinical decisions should be influenced by, and in some cases may be determined by, all available evidence. Greater weight is assigned to results from randomized clinical trials and meta-analyses. Evidence can affect patient informed consent — consent should now be truly 'informed' (meaning detailed in terms of benefits and adverse effects relative to alternative choices) and also 'in formation' (meaning logically consistent for all stakeholders and aligned with efficient and effective uses of personal and system resources, relative to other uses) [24.1]. Through research evidence, greater well-being and less suffering are realistic objectives.

### 24.1.2. Radiation oncology

The use of radiation as a modality to treat disease began almost immediately after its discovery in 1895, at the beginning of a 'century of physics'. Early animal and clinical research consisted of systematic studies to optimize dose fractionation scheduling based on biological effects [24.3], especially adverse events (radiobiological tolerance) for external beam radiotherapy (e.g. breast cancer) and brachytherapy (e.g. cervical cancer). In the mid-twentieth century, the envelope of regimens with a positive therapeutic ratio was extended with advances in engineering, as accelerators provided treatment beam energies of 3–35 megavolts (MV). These increased dose at depth by better aligning high dose volumes and deep seated tumours, with relative sparing of superficial tissues.

Randomized clinical trials in radiation oncology gained favour between the 1960s and 1980s [24.4]. Over several decades, trials refined methods (e.g. dose levels, target volumes, beam arrangements, fractionation patterns), established combined modality strategies (e.g. radiation sensitization that leveraged chemotherapy agents), added adjuvant regimens to reduce the risks of recurrence following surgical resection and developed strategies for organ conservation.

Local economic development and globalization are resulting in greater sharing of technologies — increasing homogenization — while large population migrations [24.5] and greater emphasis on patient autonomy and preference in making decisions are diversifying clinical practice — increasing apparent heterogeneity. These developments highlight a controversy over the extent to which findings from clinical trials in high income countries apply to low and middle income countries (LMICs). Putative distinctions include genetic and nutritional factors, levels of co-morbidities including infections, modes of decision making, and differing socioeconomic priorities [24.6]. Are these shades or worlds of difference? Unfortunately, some regions of the world lag well behind high income countries in conducting research, and more evidence is needed to

resolve this controversy [24.7]. Two of the best ways to explore homogeneity–heterogeneity [24.8] are to establish real time prospective cancer outcomes registries [24.2, 24.9, 24.10] for health service and epidemiology research, and to conduct international multicentre randomized clinical trials such as those of the IAEA and other groups.

Meanwhile, the combination of newer, improved imaging modalities for staging disease and localization of target volumes with excellent image and computer based treatment planning algorithms and systems brings radiation planning and delivery within reach of the goal of very high accuracy and precision to maximize the therapeutic ratio [24.11]. Strategies include intensity modulation with dynamic collimation for dose painting and sculpting, tomotherapy and dynamic rotating beams, stereotactic hypofractionation, and adaptive–responsive methods (tracking organ motion, repositioning isocentres and replanning). Clearly, therapeutic radiation as a modality has not been exhausted; instead it has entered another period of discovery. Radiation will remain the most important modality to treat cancer for another generation [24.12]. Therefore, studies need to optimize new radiation strategies into solid radiation platforms so that radiation can be safely combined with the range of emergent technologies from genomic and epigenetic therapies, 'personalized' cancer characterizations, new targeting systems for diagnostic imaging and drug delivery, and nanomaterials and nanomedicine [24.13].

### 24.1.3. Opportunities

The difficulty with research in radiation oncology today is not finding enough good questions but having sufficient available infrastructure to obtain answers. There are limits to: investigator training, levels of research experience and time allotted to research; support equipment and staff for local data handling; responses to geographies, cultures and systems that hamper patient follow-up; and regional to global data management and statistical capacities to support registries, studies and trials. How limited these are ranges by orders of magnitude across high, middle and low income countries, with very serious shortfalls in lower income countries. An international strategy is needed to overcome limitations in LMICs [24.14], where the majority of cancer cases occur [24.15].

Implementation of a strategy is also an urgent matter. Fortunately, rapid adoption of research methods is possible because these are well developed, and international collaboration is far easier with today's global electronic integration. Research in radiation oncology is urgently needed because it takes time to acquire mature findings, to conduct a sequence of trials, if required, and to change practice and acquire supporting resources for clinical policies. Significantly influencing the trajectory of oncology over the next decades will

require investing in infrastructure and clinical trials in this decade. Research is also becoming an imperative for political and economic reasons. Research infrastructure and products must grow faster than the pace of economic development and health care budgets in order to accommodate the rapid rate of change in radiation oncology and strong shifts in social demographics. Significant population ageing [24.16] and lifestyle changes are forcing a global epidemic of cancer centred in middle income countries [24.17]. Providing radiotherapy to the more than one hundred million patients with cancer over the next decades will require safe and effective methods that must be appropriate to the context, where context is proven to make a real difference. Immediate investments in research can produce short and intermediate term research findings that are 'just in time' and are thus of maximum benefit to countries where coping with the epidemic of cancer is a salient concern. Findings will be vital to ensure that rising health care expenditures are technically and socially efficient relative to alternative uses of personal and national resources under growing but narrowly defined budgets [24.18]. Prospective local and regional studies, treatment and outcomes registries, and international clinical trials can determine how best to apply radiotherapy alone, and in combination with other modalities, for the benefit of all humankind.

## 24.2. METHODS OF RESEARCH

### 24.2.1. Good questions

A good question regarding research is discovery. Research must be relevant, ethical and motivating. A good question about treatments must specify the target population, the contrasting treatment options and the clinical outcome measure. Population definition characterizes the patient–disease cohort (i.e. the cases). Treatment options must be well defined and optimized for definitive testing. And outcome measures must be of sufficient scope and precision to capture clinically relevant differences. Beneficial outcomes include greater biological efficacy and clinical disease control, lower rates and severities of adverse events, less need for or lower intensity of supportive care and psychosocial support, simpler monitoring, improved quality of life and survivorship, and a lower economic cost or an increased expenditure that is considered to be worthwhile.

The research question is aimed at affirming and strengthening belief in one form of care or changing care to an alternative form. The fundamental issue is preference. Findings from research strengthen or change preference, and hence agreement, among stakeholders [24.19]. Preference is typically ex ante, or before the event, and under uncertainty, meaning outcomes for a patient are stochastic and not yet achieved when making a treatment decision. Informed consent

emerges by envisioning possible futures (i.e. experiences) under uncertainty (i.e. probabilities), with stakeholders constructing preferences for a course of action over the next best alternatives [24.1, 24.18]. Since clinical research alters preference and choice, such research is 'economic' and operates within the health economics framework.

There are an overwhelming number of research questions in radiation oncology relative to resources for studies, registries and trials. Priorities must favour core issues where answers can make real differences in the lives of patients. Priorities can optimize resource allocations for research and strike a balance with clinical practice. Research must be intrinsically economical, not wasting resources on less important, overly lengthy or impossible projects. Also, overly narrow research projects in high income countries are sometimes far removed from clinical application — they may be nice to do, but are rightly criticized as being inappropriate in the context of pressing global concerns [24.20]. Further, broader clinical projects can better address heterogeneities and adapting research findings, while providing research experience to the many clinicians who work in LMICs. These can help build infrastructure and evidence based practice around the world.

### 24.2.2. Good methods

Not all questions require large and expensive randomized controlled trial designs. Some questions will never be answered through randomized trials, specifically: questions involving very small target populations; questions that require qualitative and mixed research designs; questions about underlying and uncontrollable heterogeneity; and questions where randomization may be unethical. Careful implementation and documentation are essential for charting some of the advances in radiation technology, in classification and measurement (e.g. for adverse events), and in supportive and psychosocial care. Lower levels of evidence than randomized trials may be sufficient to answer many types of research questions using designs such as case series, cohort studies, cross-sectional analyses, case control, before–after and comparative studies. It is vital that the best study design and excellent methods and measures be selected to address a research question. Controversies can then be resolved more quickly with definitive answers, so everyone can move on to other research questions. Research that is without sound science and a justified and attainable sample size is unethical because it cannot hope to answer the question. With a favourable scientific review of a research protocol, an ethics review can then address: the embodiment of human values in the research; consent and modes of participation (e.g. voluntary); the burden of the study on a patient; confidentiality and data

security; processes to ensure data quantity and quality; investigator training and 'time on task'; the level of local institutional commitment; and so on.

Many research protocols are excellent. With a good sponsor or research network, developing a good question into a protocol, consent template, plans for data management and statistics, operational documents, study forms, and budget is less effort than conducting the study properly and finishing it well. Experience indicates that international trials have greater startup problems, including delays arising from peculiarities in regulations and approval mechanisms. Some countries require both local and national committee approvals, with multiple translated consent documents and even translations of the source protocol. The burden on local investigators to obtain approval can be considerable and may take more than a year, delaying accrual and dampening the enthusiasm of investigators. Further, investigators typically overestimate rates of actual accrual. Often they have not analysed their present caseload to see what proportion is eligible, and they tend to accrue up to a limit per unit of time (e.g. ten cases per year) so that their mean accruals are lowered by not accruing all eligible cases in some months to compensate for months in which few, or no, cases are accrued. Larger networks of trained and engaged investigators would overcome the basic accrual problem.

Barriers to randomized trials, such as those that were noted decades ago and which have been reduced in high income countries, are often active and significant in LMICs. These include: resistance of patients or family members to participating in research; referring physicians not accepting equipoise for trial arms, and so subverting accrual; patients not seeing the benefit of close follow-up after treatment; investigators not adhering closely to the protocol, thereby introducing bias and unnecessary heterogeneities; and staff not measuring all relevant and required outcomes, especially adverse events. Again, improved training of participant investigators and support staff regarding research, along with more experience doing research, can reduce these problems, just as they have been reduced in high income countries.

In international studies, data management and methods centres should take a more active and facilitative role than they do in high income countries, although there is room for improvement there as well. In particular, regularly reporting back to investigators on the quantity and quality of data can help identify, manage and reduce the element of chance and bias during the running of the trial. Automated monthly reports can identify all patients who are overdue in receiving data submissions, providing direct assistance to local teams for tracking cases and troubleshooting local processes. In trials where there are no official site coordinators or programme managers, this is a tremendous help. Visual displays of data by patient include forecasting upcoming visits and assessments or tests. With modern software, these reports are relatively easy to generate,

automate and interpret in the international context (i.e. less text or language). Reports, along with conference calls and emails, sustain communications between the fairly infrequent face to face research meetings of investigators, steering committees, data personnel and trial consultants. Full meetings are difficult to organize and fund where trials are truly multicentre and international. Because local investigators are busy with clinical duties and their support staff may turn over several times during a trial, strong coordination between an active data management and methods centre and the investigators in LMICs is very important.

Many trial sample sizes are based on relatively small numerical differences in outcome measures or infrequent rates of events. This is a testimony to past successes in developing safe and effective treatments, but it is a challenge to obtain a high level of statistical power. In suboptimal trial activities by local teams, undermeasurement of events and side effects combined with significant losses to follow-up can cut the ability to detect a difference between treatment arms or to establish non-inferiority. These difficulties are evident in many published trials, even those from high income countries, but the risks of operational failure that undermine statistical power are greater in LMICs. Periodic, systematic screening of cases that have remote follow-up (checking their charts, calling contacts by phone, screening at national vital registries) should be conducted explicitly at least twice a year, to recontact patients or obtain documentation of more recent health care visits or deaths. Local help, hired for purposes of the trial, can call and visit patients to obtain some vital data.

### 24.2.3. Good impact

Research in radiation oncology must have an impact, although this is difficult to measure. 'Surrogate measures' for clinical impact include publications, citations of publications, uploading of data into meta-analyses and systematic reviews, secondary grants and analyses of data (e.g. further hypotheses generating analyses, economic modelling), and further studies of trial materials (e.g. new pathology investigations on banked tissues). These measures might be evidence of trial productivity, but they might be poor surrogates of clinical impact.

The absence of very good real time treatment and outcome registries severely limits the ability to determine patterns of practice. On the one hand, variety can suggest equipoise between options, which can be honed into a good research question and randomized trial [24.8]. On the other hand, too few registries make it difficult to evaluate temporal change in practice and clinical outcomes following dissemination of research results [24.9].

Another impact of trials should be improvements in quality indicators (e.g. completeness of data submissions, few data queries and little loss to

follow-up) from trial to trial. Participating in research can help investigators and data management and methods centres develop research footprints, conducting and reporting their own local and locoregional studies and trials. Tracking the research output and quality for investigators, and their departments and students, is increasingly possible.

## 24.3. THE ENTERPRISE OF RESEARCH

Research in radiation oncology is supported much less with investor monies than is pharmaceutical or drug research. Radiation is widely misunderstood to be a relatively simple, single modality which has been well investigated. Because the control of all cancers is not yet perfect, it is also widely believed that new agents must be developed to replace radiation, surgery, existing chemotherapies and even new targeted therapies. Great emphasis was placed on completing the genome project to make the twenty-first century the 'century of biology'. However, investment in new agents has slowed during the past decade [24.21], while radiotherapy remains the core of cancer treatment worldwide. Radiotherapy is, in fact, a complex modality with many subtleties. There may be many mechanisms at play, to various degrees, regarding radiobiological effects across the entire dose schedule range, and across dose encompassed tissues [24.22]. Gradients and transitions in mechanisms need to be further exploited for benefit, but finding funding for these may be problematic. In contrast, critical technological and engineering developments in the past few decades have been commercially viable. These have been in imaging (including electron density, map based volume planning) and computing (including higher resolution imaging, dose sculpting and strong beam collimator controls). Consequently, these have come to the fore in high income countries, revolutionizing radiation oncology in some centres. However, many regions and countries have few radiation facilities and continue to manage patients with relatively simple radiation methods [24.23]. Simple plans and equipment can certainly cure many patients of cancer, so the extent to which all centres in the world and all patients need to migrate towards complex planning and delivery systems is unclear, although we are far from a stopping point today.

The IAEA has a mandate — and expertise and wide experience — to help develop peaceful uses of the atom at the international level and in partnership with countries. It is absolutely necessary for supranational, not for profit agencies to expand research in radiation oncology at those levels. The IAEA is perhaps uniquely positioned to address radiation mechanisms and evaluate newer radiation technologies or options.

More local contributions to research are sorely needed. National economies are developing, centres are improving and increasing in number, and the number of newly trained clinical staff is growing. Unnecessary local barriers to research should be reduced and research should be accelerated by building infrastructure. Member States of the IAEA are undergoing demographic transitions and long term economic evolution, and they are beginning to acquire a real interest in meeting the challenge posed by the cancer epidemic. National cancer control strategies are important, but a shared vision in, and greater practical support from, countries for regional, continental and international research is also needed. It should not be that each country develops completely separate programmes of research; that would be inefficient and it would not leverage existing knowledge and resources. It would lead to unnecessary duplicate studies. Duplication (as distinct from replication) is not a luxury but a waste of resources. Collaborative networks [24.2, 24.9, 24.10] at the regional and higher levels are needed. These must be encouraged and supported by communities of countries and their representatives and associated agencies. In addition to providing more funding, countries could streamline ethics approvals. They should also make greater provision for some clinicians to become clinical investigators, with more time per case to comply with protocols, accrue more patients, produce quality results, help to disseminate results, and advocate on behalf of patients and based on research findings. Multicentre international trials need to be of as short a duration as possible, and with sufficient local support to avoid operational failure.

There has been a great propensity to conduct clinical studies in small geographical regions, as this is much easier than conducting such studies in large regions. However, important global questions cannot be ignored. Results from trials conducted in small regions are almost always intended, by sponsors and investigators, to have wide application. But wider application of geographically limited studies is inconsistent, and it is open to challenge [24.6, 24.24]. It makes more sense to develop methods and conduct comprehensive trials with greater participation over good geographical and socio-demographic ranges, to explore heterogeneity and to expedite knowledge transfer and uptake of research findings. One can only conclude that existing methods of investigator collaboration are insufficient. Greater interactive social and collaborative networks of investigators, data managers, statisticians and methodologists are possible [24.25]. Furthermore, present educational methods for teaching students and frontline clinicians about research and statistics are not producing junior staff capable of conducting or participating collaboratively in solid local, regional or international research, and of continuing to do so throughout their careers. Learning in-context methods for acquiring knowledge, skills and experience, and having these within networks, may be a solution to this chronic problem [24.26]. This may be true for all countries, regardless of income level.

Another requirement for improving research in radiation oncology is to build a more robust data management system. Methods for data management are well established [24.27] in major trials groups in Europe and North America, but management units remain isolated and have insufficient sharing and little standardization of methods [24.28]. It is pointless to globally train investigators for research without also growing a global capacity for good and efficient data management at the regional, continental and international levels. A network of data management and methods centres could be an innovative way to support studies, registries and trials in radiation oncology. For organizational agility, such centres can act as hubs for studies, training and research about research. Later they can be portals for emergent studies testing new gene, protein and nanomaterial agents at a time when venture capital will find a need to support research in radiation oncology.

## 24.4. SUMMARY

Research is an essential component of modern oncology. It represents the best of enlightenment ideals as expressed in the natural sciences and applied to clinical care and cancer survivorship. Radiation oncology has advanced steadily by careful scientific and clinical research, with important commercial pressure mediated by technology and engineering. Disruptive technologies have now entered the market. The field of radiation medicine has become dynamic at a time when radiation treatments will be more widely needed. Age, co-morbidities and concurrent agents necessitate that radiation be optimized for safety and efficacy, using all available tools and technologies. Good research questions, answered with good methods, can have a great impact in this second century of radiotherapy. A larger global strategy for more research in radiation oncology is possible. It needs to include in-context research training; a supportive and engaged network of data management and methods centres; greater standardization and efficiencies in training and data management; more assistance from institutions, organizations and countries; and collaborative networking. Prospective studies, clinical and outcome registries, and randomized controlled trials are required to meet the challenge of the cancer epidemic by providing focused, definitive evidence in support of making wise clinical and politico–economic decisions about patient care and cancer control.

## 24.5. KEY POINTS

— Clinical research is a systematic approach to collecting evidence through careful observation and measurement to enable propositional knowledge claims.
— Clinical research requires access to patients and excellent patient care.
— Clinical decisions should be influenced, and in some cases may be determined, by all available evidence.
— Two of the best ways to explore homogeneity–heterogeneity are to establish real time prospective cancer outcome registries for health service and epidemiology research, and to conduct international multicentre randomized clinical trials.
— Clearly, therapeutic radiation as a modality has not been exhausted; instead it has entered another period of discovery. Radiotherapy will remain one of the most important modalities to treat cancer for another generation.
— Studies need to optimize new radiotherapy strategies into solid platforms so that radiotherapy can be safely combined with emergent technologies.
— The difficulty with research in radiation oncology today is not finding enough good questions but having sufficient available infrastructure to get answers.
— Research in radiation oncology is urgent because it takes time to acquire mature findings.
— International collaboration is easier with today's global electronic integration.
— A good research question must be relevant, ethical and motivating.
— A good treatment question must specify the target population, the contrasting treatment options and the clinical outcome measure.
— Priorities must favour core issues where answers can make real differences in the lives of patients.
— Not all questions require large and expensive randomized controlled trial designs.
— Lower levels of evidence than randomized trials may be sufficient to answer some research questions.
— The optimal study design and excellent methods and measures should be selected to address a research question.
— International trials have greater startup problems, including delays arising from peculiarities in regulations and approval mechanisms.
— Research in radiation oncology must have an impact. This is challenging to measure.
— Research in radiation oncology is far less supported with investor monies than is pharmaceutical or drug research.

— Radiotherapy is widely misunderstood to be a relatively simple, single modality which has been well investigated.
— It is necessary for supranational, not for profit agencies to expand research in radiation oncology. The IAEA is perhaps uniquely situated to address radiotherapy mechanisms and evaluate newer radiotherapy technologies or options.
— Collaborative networks at the regional and higher levels are needed. Another requirement is to build a more robust data management system. A network of data management and methods centres could be an innovative way to support studies, registries and trials in radiation oncology.

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# Part VII

# RADIOTHERAPY AROUND THE WORLD

# Chapter 25

# STATUS OF RADIOTHERAPY AROUND THE WORLD

## 25.1. THE MIDDLE EAST — A. Al Mousa, J. Imad, M. Rasmi

The population in the Middle East region was approximately 300 248 000 in 2010 [25.1, 25.2], ranging from 1.12 million in Cyprus to 75.6 million in the Islamic Republic of Iran. More than 50% of the population is under 25 years of age, while only 1−5% is above 60 years of age. The incidence of cancer is lower than in more developed regions, varying from 50 to 190 cases per 100 000 population [25.3]. To date, there has not been a formal and systematic survey of radiotherapy resources in the region, although the IAEA's Directory of Radiotherapy Centres (DIRAC) suggests that there is a significant variation in the availability of radiotherapy resources in this region [25.4].

Data from the GLOBOCAN 2012 database show that 368 226 new cancer cases were estimated in the Middle East in 2012 [25.3]. Given that approximately 50% of patients need radiotherapy and 25% may need additional treatment (re-treatment), around 184 000–203 000 patients per year are estimated to need radiotherapy treatment for cancer in the region [25.5−25.9].

Regarding the megavoltage (MV) unit load, and taking into consideration treatment complexity, the IAEA suggested in 2010 that the ideal ratio would be between 400 and 500 patients per machine per year [25.10]. European service planning benchmarks suggested 450 patients per machine per year [25.11]. In Australia and Turkey, the target was set at 400 patients per machine per year [25.12, 25.13]. The suitable goal for the region could be 450 patients per machine per year, and this is the benchmark used here for our calculations of teletherapy machine needs (Table 25.1).

For radiotherapy personnel planning, the following international benchmarks were used: one radiation oncologist per 250 newly diagnosed patients; one medical physicist per 400 newly diagnosed patients; and two radiotherapists (RTTs) per MV unit for up to every 25 patients treated daily, or four RTTs per MV unit for up to every 50 patients treated daily. In addition, two RTTs per MV unit for every 500 patients simulated annually, one mould room technician for every 600 patients treated annually, and one supervisor per centre are suggested [25.14−25.16].

The data for radiotherapy resources in the Middle East were taken from the IAEA's DIRAC database (accessed in February 2017) [25.4]. Population statistics were derived from the United Nations [25.2], and the gross national

TABLE 25.1. DISTRIBUTION OF RADIOTHERAPY EQUIPMENT IN THE MIDDLE EAST

| | Population (million) | Gross national income per capita (US $) | No. of new cancer cases/ year[a] | Estimated demand for megavoltage (MV) machines[b] | Existing radiotherapy centres | Existing MV machines | Existing MV machines/ million | Existing MV machines/1000 new cases/year |
|---|---|---|---|---|---|---|---|---|
| Bahrain | 1.359 | 18 730 | 900 | 1.1 | 1 | 2 | 1.5 | 2.2 |
| Cyprus | 1.129 | 29 430 | 3 400 | 4 | 1 | 3 | 2.6 | 0.88 |
| Iran, Islamic Rep. of | 75.6 | 4 520 | 84 800 | 103 | 37 | 66 | 0.87 | 0.77 |
| Iraq | 33.7 | 2 340 | 25 700 | 31 | 8 | 13 | 0.38 | 0.5 |
| Israel | 7.695 | 27 170 | 29 200 | 35 | 9 | 35 | 4.5 | 1.19 |
| Jordan | 6.457 | 4 342 | 6 400 | 8 | 5 | 11 | 1.7 | 1.7 |
| Kuwait | 2.892 | 46 612 | 1 700 | 2 | 1 | 4 | 1.38 | 2.3 |
| Lebanon | 4.292 | 8 880 | 9 100 | 11 | 11 | 19 | 4.42 | 2.0 |
| Oman | 2.904 | 21 681 | 1 500 | 2 | 1 | 2 | 0.68 | 1.3 |
| Qatar | 1.939 | 97 967 | 1 000 | 1.2 | 1 | 3 | 1.54 | 3.0 |
| Saudi Arabia | 28.705 | 19 890 | 17 500 | 21 | 13 | 35 | 1.21 | 2.0 |

TABLE 25.1. DISTRIBUTION OF RADIOTHERAPY EQUIPMENT IN THE MIDDLE EAST (cont.)

| | Population (million) | Gross national income per capita (US $) | No. of new cancer cases/ year[a] | Estimated demand for megavoltage (MV) machines[b] | Existing radiotherapy centres | Existing MV machines | Existing MV machines/ million | Existing MV machines/1000 new cases/year |
|---|---|---|---|---|---|---|---|---|
| Syrian Arab Rep. | 21.118 | 2 750 | 21 800 | 26 | 3 | 8 | 0.37 | 0.36 |
| Turkey | 74.509 | 9 890 | 148 000 | 181 | 92 | 209 | 2.8 | 1.41 |
| UAE | 8.106 | 41 930 | 2 900 | 3.5 | 3 | 7 | 0.86 | 2.4 |
| Yemen | 25.569 | 1 460 | 11 400 | 15 | 1 | 2 | 0.07 | 0.17 |
| Palestine | 4.271 | 1 230 | 2 900 | 3.5 | 1 | 2 | 0.46 | 0.68 |
| Total | 300.248 | 14 310 (median) | 368 226 | 448 | 188 | 421 | 1.4 | 1.14 |

[a] Based on data from GLOBOCAN 2012.

[b] The radiotherapy utilization rate has been calculated assuming that 55% of cancer patients will need radiotherapy. The re-treatment rate is not considered here and the calculated rate should be taken as a minimum.

income (GNI) per capita data are from the International Monetary Fund [25.1]. Data on Bahrain and Palestine were obtained through personal communications.

The number of radiotherapy departments and MV teletherapy machines (cobalt-60 units plus medical linear accelerators (linacs)) in 2017 are shown in Table 25.1. The data were used to determine the number of installed MV machines and to estimate the demand for MV units, taking into consideration the population as well as the number of new cancer cases per year as per Globocan 2012 [25.3].

In Table 25.1, the radiotherapy utilization (RTU) rate has been calculated assuming that 55% of cancer patients will need radiotherapy. This assumption is based on the results of Australian studies: 52.3% for Australia in 2005 [25.6] and a 55% estimate for cancers in Africa [25.5]. In addition, up to 25% might receive a second course of radiotherapy in developed countries, but this proportion for developing countries is not known. Therefore, the re-treatment rate is not considered here and the calculated rate should be taken as a minimum.

The teletherapy machine throughput (the number of new treatment courses per machine per year) has been estimated at 400 or 500 in India and Belgium. The average for Europe in the ESTRO-QUARTS Project [25.11] was 450, and this was the benchmark used here.

Large differences were seen across the region, with the number of MV machines per million population (the MV index) ranging from 0.07 in Yemen to 4.5 in Israel, with an average of 1.4 for the region as a whole. The Islamic Republic of Iran, Iraq, Oman, the Syrian Arab Republic, the United Arab Emirates and Yemen have less than 1 MV machine per million population. Palestine is in a similar situation. Bahrain, Cyprus, Israel, Jordan, Lebanon, Qatar and Turkey exceed the region's average. The variation in the number of teletherapy machines per 1000 cancer cases per year ranged from 0.17 in Yemen to 3.0 in Qatar when standardized by cancer incidences. Bahrain, Kuwait, Lebanon, Qatar, Saudi Arabia and the United Arab Emirates have 2 or more machines per 1000 cancer cases.

The total number of radiotherapy departments identified in the region as of February 2017 was 188, with 421 MV machines installed. There were 38 brachytherapy units, 85% of them being iridium-192 high dose rate (HDR) machines. A total of 176 simulation imaging devices were also available, and 209 treatment planning systems were recorded.

There are two proton beam facilities under construction using cyclotrons. These are located in Saudi Arabia (planned to be operational in 2017) and in Abu Dhabi (planned to be operational in 2018).

The number of recorded radiation oncologists was 807, which represents 2.2 radiation oncologists per 1000 newly diagnosed cancer patients per year and 4 radiation oncologists per 1000 'radiotherapy patients' per year (55% of the total

cancer patients) for the whole region. If the RTU rate is between 50 and 60% of cancer patients, then 184 000–220 000 patients may need radiotherapy per year. If, ideally, one radiation oncologist is available for every 250 new patients, then between 736 and 880 radiation oncologists are needed. The existing number falls in this range.

The number of radiation medical physicists reported was 513, with the ideal level being between 460 and 550. Currently, there are approximately 1370 RTTs. This indicates a ratio of 6−7 RTTs per 1000 radiotherapy patients per year.

The ideal number of MV teletherapy machines in the region is 448; however, the current number is 421, which is 94% of the ideal. This translates into a shortage of 27 machines for the entire region. The undersupply or deficit was most noticeable in Yemen, the Syrian Arab Republic and Iraq, with a deficit of 87%, 69% and 58% of their calculated needs, respectively. An adequate number was found in Bahrain, Cyprus, Israel, Oman and Turkey, where the supply of MV equipment approaches the estimated demand. Palestine is in a similar situation. Jordan, Kuwait, Lebanon, Saudi Arabia and the United Arab Emirates showed an oversupply relative to the calculated demand. The level of teletherapy supply was correlated with the population, crude cancer incidence and GNI/capita, while undersupply was more correlated with economic and political status.

The current level of MV units per 1000 cancer patients/year in the Middle East is about 1.14. When compared with 33 European countries, these have 1.12 MV units per 1000 cancer patients/year [25.17]. When compared with countries in the Asia–Pacific region, only Japan, Australia, New Zealand and Singapore, out of 17 countries, showed a higher ratio [25.18].

With regard to personnel, the ratio of 2.2 radiation oncologists per 1000 cancer patients found in the region is only observed in Mongolia (2.0), probably owing to the smaller population, whereas this rate is 1.2 in Japan, 2.8 in Australia [25.19], 1.7 in North America, 4.0 in western Europe and 0.89 in Singapore.

## 25.2. NORTH AFRICA — L. Kochbati

### 25.2.1. Introduction

Over the last few years, the situation with regard to the availability of radiotherapy equipment has evolved steadily in almost all North African countries, specifically: Algeria, Egypt, Libya, Morocco and Tunisia. As a result, there is no recent publication that accurately presents the current status of radiotherapy resources and/or the needs of this region.

### 25.2.2. Demographic and epidemiological aspects

The North African countries are quite comparable in their demographic, economic and sociocultural background [25.20]. They also share almost the same cancer risk and cancer protection factors, i.e. level of industrialization, control of infectious diseases, Mediterranean diet, and sexual and reproductive behaviour. Hence, it is not surprising to observe large similarities in cancer epidemiology patterns across these five countries [25.20]. The overall cancer incidence rate ranges from 86.3 (age standardized rate (ASR)) in Setif, Algeria, to 156.1 in Gharbia, Egypt, among men, and from 80.3 (Setif, Algeria) to 164 (Algiers, Algeria) in women. Data published by nine cancer registries in the region are summarized in Table 25.2. These incidences represent one third to one half of those observed in Europe. The most frequent cancers are the same in all North African countries, namely lung, breast, colorectal, bladder and prostate cancer.

TABLE 25.2. CANCER INCIDENCE (PER 100 000 AGE STANDARDIZED ACCORDING TO THE WORLD POPULATION) IN NORTH AFRICA (ALL SITES EXCEPT NON-MELANOMA SKIN CANCER)

| | Morocco | Algeria | Tunisia | Libya | Egypt |
|---|---|---|---|---|---|
| Men | 100.3–128.6 | 86.3–143 | 123.7–146.1 | 126.8 | 156.1 |
| Women | 104.2–109.3 | 80.3–164 | 89.1–101.4 | 102.4 | 119.3 |

### 25.2.3. Radiotherapy resources in North Africa as of 2012

A total of 145 MV machines in 85 centres have been recorded in North Africa. Cobalt-60 units represent 31% (45 units) of the total. Linear accelerators account for 69% (100 machines). There are 36 conventional simulators and 26 computed tomography (CT) scanners with 63 treatment planning systems (TPSs), and 26 brachytherapy afterloading devices in the region. Table 25.3 summarizes the distribution of machines and staff per country. In terms of technical level, most centres are in transition from two dimensional (2-D) to three dimensional (3-D) conformal radiotherapy planning and delivery.

### 25.2.4. Population served by machines: Present situation and needs

The population served by a single MV machine in North Africa varies from one country to another, as shown in Table 25.4. Currently, it varies from 0.54 MV machines per million in Algeria to 1.36 in Tunisia.

To estimate the need for radiotherapy units in the region, we refer to the calculation method adopted by Barton et al. [25.5]. The proportion of patients with cancer in low and middle income countries (LMICs) with an indication of radiotherapy is probably higher than in regions of high income because of the types of cancers and the stages at which these tumours are diagnosed. We estimate that at least 60% of all cancer patients should receive radiotherapy during their life span. On the other hand, it is estimated that the capability of the treatment machines ranges from 400 to 500 patients per year [25.21]. The estimated demand for radiation units in Tunisia, for example, becomes:

> 12 189 (number of new radiotherapy cases per year) × 60% (the proportion of cancer patients in which radiotherapy is indicated) divided by 450 (number of patients treated per machine per year) = 16.3.

It is obvious that the estimated demand for MV machines is at least 1.3 to 2 times the number currently available. It is worth noting that these estimates do not apply to Libya, because many of the existing machines there are not working or are being replaced.

### 25.2.5. Education in radiation oncology and medical physics in North Africa

The number of radiation oncologists and medical physicists is shown in Table 25.3; there are 340 radiation oncologists and more than 140 medical physicists. Academic education in radiation oncology is available in all five North African countries. Residents in radiation oncology are mostly trained in their respective countries, even if some of them receive part of their training abroad. Medical physics education programmes are available in all of these countries except Libya.

To estimate the needs of radiation oncologists, we considered that a senior radiation oncologist could handle the complete care of at least 250 radiotherapy patients per year (this number could vary depending on the complexity of treatment, whether the facility is a teaching hospital, etc.) [25.22]. Taking into account the number of new cancer patients per year in each country, it is clear that present staffing levels do not meet the actual demand, and there is scope to double the number of radiation oncologists per country (Table 25.4).

TABLE 25.3. CURRENT STATUS OF FACILITIES AND STAFFING IN NORTH AFRICA

| | Centres | Linac | Cobalt-60 | Simulator (+/– CT) | TPS | LDR | HDR | Radiation oncologists | Medical physicists |
|---|---|---|---|---|---|---|---|---|---|
| Algeria | 8 | 9 | 10 | 9 | 6 | 8 | 2 | 60 | 23 |
| Egypt | 48 | 57 | 17 | 31 | 30 | —[a] | 6 | 150 | 54 |
| Libya | 4 | 3 | 4 | 3 | 2 | 2 | 0 | 10 | —[a] |
| Morocco | 15 | 25 | 5 | 12 | 19 | 5 | 9 | 90 | 45 |
| Tunisia | 10 | 6 | 9 | 7 | 6 | 3 | 1 | 30 | 18 |
| Total | 85 | 100 | 45 | 62 | 63 | n.a. | 18 | 340 | n.a. |

**Note:** Linac — linear accelerator; CT — computed tomography; TPS — treatment planning system; LDR — low dose rate; HDR — high dose rate.
n.a. — not applicable.
Data collected from a survey undertaken among national coordinators of the five target countries attending the 6th AFROG meeting in Kampala, Uganda, in February 2012.

[a] —: data not available.

TABLE 25.4. POPULATION SERVED BY MACHINES AND ESTIMATED DEMAND

| | Population (millions) | Megavoltage (MV) machines | MV machines/ million population | New cancer cases 2012 | Estimated need of MV units | WHO recommendation 1999 (2–5/million population) | Estimated demand for radiation oncologists |
|---|---|---|---|---|---|---|---|
| Algeria | 35 | 19 | 0.54 | 37 908 | 51 | 70–175 | 91 |
| Egypt | 82 | 74 | 0.9 | 108 611 | 145 | 164–410 | 260 |
| Libya | 5.4 | 7 | 1.29 | 6 077 | 8 | 11–27 | 15 |
| Morocco | 33 | 30 | 0.9 | 35 018 | 47 | 66–165 | 84 |
| Tunisia | 11 | 15 | 1.36 | 12 189 | 16 | 22–55 | 29 |

### 25.2.6. Conclusion

The supply of radiotherapy infrastructure and staff does not meet the estimated needs in all of the North African countries even if there is a discernible trend towards better coverage when compared with the situation reported in 1999 by Levin et al. [25.23], or that reported by Barton et al. in 2006 [25.5]. To improve radiotherapy availability and to facilitate access to one of the most cost effective forms of cancer treatment, it is mandatory to plan ahead for the development of radiotherapy services, and to invest in equipment, education, and awareness of the public and decision makers about the role of radiotherapy in cancer treatment.

## 25.3. SUB-SAHARAN AFRICA — J.B. Kigula Mugambe, A. Kavuma

### 25.3.1. Introduction

Sub-Saharan Africa comprises 48 countries, with a total population of about 850 million [25.24]. The age standardized incidence rate for cancer in this region is 121.0 per 100 000 people [25.3], implying more than one million new cancer cases annually. It is expected that over 50% of cancer patients would benefit from radiotherapy, either alone or in combination with surgery and/or chemotherapy [25.25], meaning that about 500 000 patients per year would require radiotherapy in sub-Saharan Africa.

### 25.3.2. Facilities

To establish the status of radiotherapy in sub-Saharan Africa, a survey was conducted during the 6th African Radiation Oncology Group (AFROG) Conference in February 2012, in Kampala, Uganda, which brought together radiation oncologists and medical physicists from all over Africa. From the survey, as well as from the IAEA's DIRAC database and the 2011 WHO report, it was established that the following 27 countries, with a total population of 192 million (22.6% of sub-Saharan Africa) have no radiotherapy facilities at all: Benin, Burkina Faso, Burundi, Cabo Verde, Central African Republic, Chad, Comoros, Congo, Côte d'Ivoire, Djibouti, Eritrea, Guinea, Guinea Bissau, Lesotho, Liberia, Malawi, Mozambique, Niger, Réunion, Rwanda, Sao Tome and Principe, Seychelles, Sierra Leone, Somalia, South Sudan, Swaziland and Togo. Since then, Benin and Niger have begun actively developing their first radiotherapy centres. However, of the 48 countries in the region, only 21 have radiotherapy facilities. Table 25.5 summarizes the status of radiotherapy in sub-Saharan Africa where the service exists. The equipment includes both public

and private sector radiotherapy units (linacs, cobalt-60 units and brachytherapy units).

The number of teletherapy units per million population is very low, with the exception of South Africa and Mauritius. There are currently 132 teletherapy units in the region, giving a machine per million population (MMP) ratio of 0.16. Of these, 85 (64.4%) units are in South Africa alone, giving an MMP ratio of 1.70. Mauritius has the highest MMP ratio at 2.43, which is better than the global average of 1.80 owing to its very low population [25.4, 25.26]. The rest of the region has only 44 teletherapy units serving a population of over 600 million, with an average MMP ratio of 0.07. The MMP ratios in most sub-Saharan countries are much lower than those of North African countries, such as Egypt, Morocco and Tunisia, with values of 0.84, 0.94 and 1.36, respectively. This indicator compares unfavourably with Europe and North America, whose MMP ratios are 6.0 and 14.4, respectively [25.26]. The IAEA suggests a minimum of one teletherapy machine for every 500 new cancer cases per year [25.27], which means that for sub-Saharan Africa, with an expected 500 000 cancer cases per year that would benefit from radiotherapy, 1000 units would be required.

It was established that most centres in this region are still using 2-D planning radiotherapy and more than 70% of the treatments are palliative, with only a few centres in the process of migrating to 3-D conformal radiotherapy. A number of centres in South Africa have started implementing intensity modulated radiation therapy (IMRT), though none are using more sophisticated techniques, such as image guided radiation therapy (IGRT), modulated arc therapy, or stereotactic body radiotherapy.

### 25.3.3. Staffing

The basic staffing of a radiotherapy unit includes radiation oncologists, medical physicists and RTTs. The AFROG survey revealed that there are about 260 radiation oncologists, 180 medical physicists and 700 RTTs practising in sub-Saharan Africa. Of these, more than 50% of the staff are in South Africa. The rest of the region, with about 450 000 cancer cases (which could benefit from radiotherapy), has a severe shortage of all these cadres. The IAEA suggests that a basic radiotherapy clinic with one MV unit have at least four to five radiation oncologists, three to four medical physicists and seven RTTs [25.27]. Many of the centres in this region fall far below this requirement. The IAEA also recommends one radiation oncologist for every 200–250 new patients treated annually and one medical physicist for every 400 new patients. The cancer incidence in sub-Saharan Africa requires at least 2000 radiation oncologists and 1250 medical physicists, which is almost tenfold what is currently available. Unfortunately, the

TABLE 25.5. STATUS OF RADIOTHERAPY IN SUB-SAHARAN AFRICA
*(data from a survey during the 6th AFROG Conference in 2011)*

| | Population[a] (million) | Equipment | | | Machines[b]/ million population | Staffing | | | Most common cancers | | | Training ability | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cobalt-60 units | Linacs | Brachy-therapy units | | RO | MP | RTT | 1st | 2nd | 3rd | RO | MP | RTT |
| Angola | 19.1 | 0 | 1 | 0 | 0.05 | —[c] | —[c] | —[c] | Cervix | Breast | Liver | X | X | X |
| Botswana | 2.0 | 1 | 0 | 1 | 0.50 | 1 | 2 | 4 | Cervix | Breast | Colon | X | X | X |
| Cameroon | 19.6 | 2 | 0 | 2 | 0.10 | 3 | 2 | 4 | Cervix | Breast | Prostate | ✓ | X | ✓ |
| Dem. Rep. of Congo | 71.7 | 0 | 1 | 0 | 0.01 | 1 | —[c] | —[c] | —[c] | —[c] | —[c] | X | X | X |
| Ethiopia | 83.0 | 2 | 0 | 0 | 0.02 | 4 | 2 | 4 | Cervix | Breast | Head and neck | X | X | X |
| Gabon | 1.5 | 1 | 0 | 0 | 0.67 | —[c] | —[c] | —[c] | —[c] | —[c] | —[c] | X | X | X |
| Ghana | 24.4 | 2 | 1 | 1 | 0.12 | 6 | 10 | 16 | Breast | Prostate | Cervix | ✓ | ✓ | ✓ |
| Kenya | 40.5 | 2 | 4 | 3 | 0.15 | 11 | 8 | 19 | Breast | Cervix | Oesophagus | X | X | ✓ |
| Madagascar | 20.7 | 1 | 0 | 1 | 0.05 | 2 | 4 | 5 | Breast | Cervix | Head and neck | X | X | X |
| Mali | 15.4 | 0 | 1 | 0 | 0.07 | 2 | 0 | 2 | Cervix | Breast | Oesophagus | X | X | X |

TABLE 25.5. STATUS OF RADIOTHERAPY IN SUB-SAHARAN AFRICA
*(data from a survey during the 6th AFROG Conference in 2011)* (cont.)

| | Population[a] (million) | Equipment | | | Machines[b]/ million population | Staffing | | | Most common cancers | | | Training ability | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cobalt-60 units | Linacs | Brachy-therapy units | | RO | MP | RTT | 1st | 2nd | 3rd | RO | MP | RTT |
| Mauritania | 3.5 | 0 | 1 | 1 | 0.73 | 1 | 2 | 2 | Cervix | Breast | Colon | X | X | ✓ |
| Mauritius | 1.3 | 2 | 1 | 1 | 2.43 | 7 | 4 | 12 | Breast | Colon | Cervix | X | X | X |
| Namibia | 2.3 | 1 | 0 | 2 | 0.44 | 2 | 1 | 2 | Cervix | Breast | Colon | X | X | X |
| Nigeria | 158.4 | 2 | 3 | 3 | 0.03 | 18 | 8 | 18 | Cervix | Breast | Head and neck | ✓ | ✓ | ✓ |
| Senegal | 12.4 | 1 | 0 | 0 | 0.08 | 2 | 2 | 3 | Cervix | Breast | Liver | X | X | X |
| South Africa | 50.0 | 8 | 77 | 25 | 1.70 | 150 | 100 | 500 | Cervix | Breast | Lung | ✓ | ✓ | ✓ |
| Sudan | 30.9 | 5 | 5 | 2 | 0.32 | 23 | 18 | 57 | Breast | Prostate | Cervix | ✓ | ✓ | ✓ |
| United Rep. of Tanzania | 44.8 | 2 | 0 | 2 | 0.04 | 5 | 2 | 12 | Cervix | Kaposi's sarcoma | Breast | ✓ | X | ✓ |

TABLE 25.5. STATUS OF RADIOTHERAPY IN SUB-SAHARAN AFRICA
*(data from a survey during the 6th AFROG Conference in 2011)* (cont.)

| | Population[a] (million) | Equipment | | | Machines[b]/ million population | Staffing | | | Most common cancers | | | Training ability | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cobalt-60 units | Linacs | Brachy-therapy units | | RO | MP | RTT | 1st | 2nd | 3rd | RO | MP | RTT |
| Uganda | 33.4 | 1 | 0 | 1 | 0.03 | 5 | 5 | 9 | Cervix | Breast | Head and neck | X | X | ✓ |
| Zambia | 12.9 | 1 | 1 | 1 | 0.15 | 5 | 3 | 5 | Cervix | Breast | Head and neck | X | X | ✓ |
| Zimbabwe | 12.6 | 0 | 2 | 1 | 0.16 | 8 | 5 | 20 | Cervix | Breast | Head and neck | ✓ | X | ✓ |
| Total | 660.4 | 34 | 98 | 47 | Average = 0.37 | 256 | 178 | 694 | | | | | | |

**Note:** RO — radiation oncologist; MP — medical physicist; RTT — radiotherapist.

[a] Population figures based on World Bank statistics [25.24].

[b] Refer to teletherapy units only.

[c] —: data not available.

AFROG survey indicates that only a few countries have training programmes for these three professions.

### 25.3.4. Common cancers

As indicated in Table 25.5, the most common cancers in sub-Saharan Africa are: cervical, breast, head and neck, prostate, colorectal, liver and oesophageal cancers, which is in agreement with the Globocan 2012 data. With the exception of cancer of the liver, patients with all of these cancers would benefit from radiotherapy. The high incidence of cervical cancer necessitates many brachytherapy units. Unfortunately, many countries either have no brachytherapy units or have just one unit. For example, Uganda's only radiotherapy centre treats more than 500 new cervical cancer cases per year, but has only one low dose rate brachytherapy unit.

### 25.3.5. The way forward

Sub-Saharan Africa is faced with numerous socioeconomic and political challenges. These significantly influence the delivery of health services, including radiotherapy. The availability of radiotherapy service in a country does not necessarily mean that its population can access that service. Financial constraints, lack of awareness and poor road infrastructure influence accessibility. For example, the Democratic Republic of the Congo is a vast country with only one centre in Kinshasa, and it is very difficult for people in the eastern part of the country to access it. Late presentation of patients for cancer management is another formidable challenge, aggravated by the issues mentioned above. The countries in this region have to address the problem of increasing cancer burden and the increasingly important role of radiotherapy in cancer management. There is an urgent need for the establishment of radiotherapy centres that are distributed widely across the region, accompanied by the training of more personnel. On the positive side, several countries in this region, e.g. Eritrea, Malawi and Niger, are in the process of establishing radiotherapy facilities in cooperation with the IAEA. Others, such as Ghana, Nigeria and the United Republic of Tanzania, are in the process of expanding the existing services. The countries in this region should address the late presentation problem by increasing awareness and establishing effective prevention and early detection programmes as part of their national cancer control strategies. They should also develop appropriate cancer policies with the continued support of international organizations such as the IAEA and the World Health Organization (WHO).

## 25.4. SOUTHEAST ASIA — S. Gondhowiardjo, M.J. Calaguas, G.B. Prajogi

### 25.4.1. Introduction

Southeast Asia is a diverse region that consists of 11 countries sharing a large number of social and cultural similarities. Based on World Bank and International Monetary Fund data [25.28, 25.29], with the exception of Singapore, most of the countries in this region are classified as LMICs. In 2010, the gross domestic product (GDP) per capita in these countries ranged from US $543 in Timor-Leste to US $37 789 in Singapore.

The South East Asian Radiation Oncology Group (SEAROG) is a community of radiation oncology associations in five countries in the Southeast Asia region. It was founded on 12 May 2007 in Singapore. The five original member countries gathered with the common objectives of working together to find solutions for shared problems regarding disease patterns and resources, to advance the knowledge and practice of radiation oncology, to improve the standards in education in this field, and to improve outcomes of cancer treatment. SEAROG today includes Indonesia (Indonesian Radiation Oncology Society), Malaysia (Malaysian Oncological Society), the Philippines (Philippines Radiation Oncology Society), Singapore (Singapore Radiological Society) and Thailand (Thai Society of Therapeutic Radiology and Oncology). This section was prepared with the contribution of SEAROG member countries to describe current radiotherapy capacities in the Southeast Asia region.

### 25.4.2. Cancer incidence and radiotherapy utilization rate

The proportion of cases of the predominant types of cancer treated with radiotherapy reveals the utilization pattern. This is influenced by the difference in the distribution of cancer cases, the socio-demographic characteristics of the countries as well as the maturity of the national cancer control programme in each country. The Globocan 2012 project [25.3] reported 786 448 new cancer cases (excluding non-melanoma skin cancers) annually in the Southeast Asia region. The estimated incidence for the ten most common cancers is provided in Table 25.6.

Female malignancies, such as breast and cervical cancer, dominate the list of cancer incidence and, based on a short survey conducted in 2010 among SEAROG member countries (Table 25.7), these types of cancer were treated most effectively by radiotherapy technology in Southeast Asia.

Lung cancer and breast cancer are estimated to be the most common cancers in this region as well as in other parts of the world. However, in contrast to other more developed regions, the radiotherapy utilization rate for lung cancer is rela-

tively low in Southeast Asia. It ranked third as the predominant indication for radiotherapy in the Philippines and Singapore, but it is not as commonly seen in other countries where late and metastatic stages of lung cancer predominate, such as in Indonesia. On the other hand, the moderate endemicity of nasopharyngeal cancer makes it a very common indication for radiotherapy in the Southeast Asia region.

TABLE 25.6. ESTIMATED INCIDENCE OF THE TEN MOST COMMON CANCERS IN SOUTHEAST ASIA [25.3]

| Cancer | Estimated numbers | Crude rate | Age standardized rate (W) |
|---|---|---|---|
| Breast | 107 545 | 35.3 | 34.8 |
| Lung | 105 018 | 17.3 | 19.2 |
| Liver | 79 953 | 13.2 | 14.2 |
| Colorectum | 69 016 | 11.4 | 12.5 |
| Cervix uteri | 50 566 | 16.6 | 16.3 |
| Stomach | 33 572 | 5.5 | 6 |
| Non-Hodgkin's lymphoma | 26 610 | 4.4 | 4.7 |
| Prostate | 26 451 | 8.8 | 11.2 |
| Leukaemia | 25 805 | 4.3 | 4.4 |
| Nasopharynx | 25 596 | 4.2 | 4.3 |

TABLE 25.7. FIVE MOST COMMON INDICATIONS FOR RADIOTHERAPY IN SEAROG COUNTRIES

| | Indonesia | Malaysia | Philippines | Singapore | Thailand |
|---|---|---|---|---|---|
| 1 | Cervix | Breast | Cervix | Breast | Cervix |
| 2 | Breast | Nasopharynx | Breast | Head and neck | Head and neck |
| 3 | Nasopharynx | Cervix | Lung | Lung | Breast |
| 4 | Brain tumours | Rectum | Head and neck | Gynaecological | Lung |
| 5 | Rectum | Lung | Rectum | Prostate | Rectum |

### 25.4.3. Human resources

The total number of practising radiation oncologists in the five SEAROG member countries is currently over 300. In addition, the number of practising radiation oncologists in Viet Nam, Myanmar and Cambodia is 110, 23 and 3, respectively (Table 25.8). There are no data currently available for Brunei Darussalam, the Lao People's Democratic Republic and Timor-Leste, where radiation oncology services have not yet been initiated.

TABLE 25.8. RADIOTHERAPY HUMAN RESOURCES IN SOUTHEAST ASIA

| | Radiation oncologists | Medical physicists | RTTs |
|---|---|---|---|
| Brunei Darussalam | —[a] | —[a] | —[a] |
| Cambodia | 3 | 3 | 11 |
| Indonesia | 54 | 47 | 157 |
| Lao People's Democratic Rep. | —[a] | —[a] | —[a] |
| Malaysia | 60 | 76 | 297 |
| Myanmar | 23 | 4 | 13 |
| Philippines | 50 | 25 | 100 |
| Singapore | 30 | 20 | 94 |
| Thailand | 116 | 79 | 215 |
| Viet Nam | 110 | 58 | 98 |
| Timor-Leste | —[a] | —[a] | —[a] |
| Southeast Asia region | 446 | 312 | 985 |

[a] —: data not available.

Even for the Southeast Asian countries with relatively more mature national radiation oncology services, the number of practising radiation oncologists per member country relative to the number of newly diagnosed cancer cases per year is far from adequate. Most countries have less than a 2:1 ratio of radiation oncologists per MV unit, indicating the shortage of trained human resources in the region. This is also true for medical physicists, whose numbers are even lower than those of

radiation oncologists. It should also be remembered that in some countries medical physicists also perform additional tasks, including treatment planning and radiation protection, representing a very heavy workload for existing medical physicists.

### 25.4.4. Radiotherapy centres, equipment and facilities

In 2004, the results from the ESTRO-QUARTS project entitled Radiation Therapy for Cancer: Quantification of Radiation Therapy Infrastructure and Staffing were reported, providing an evidence based estimate of radiotherapy needs in Europe [25.30]. The model that was developed — adjusted for modern technological complexities, case mix and fractionation schedules — can be applied in other countries and regions outside Europe to provide a more accurate estimate of the need for radiotherapy, provided the crude incidence of various cancer types is known. With the use of GLOBOCAN data and evidence based estimates of appropriate rates of radiotherapy utilization for dominant cancer sites as reported by the CCORE project [25.6], the actual need for radiotherapy in the region can be estimated allowing for a re-treatment factor of 1.25 and optimum annual machine workload of 450 treatment courses. According to these data, a substantial gap still exists between the need for and availability of radiotherapy, with most of the countries having an actual capacity far below levels recommended by estimates based on the QUARTS model benchmark.

Indeed, for most countries in the region, reaching the conservative recommendation of one to two MV units per million population amounts to a challenging undertaking. For Indonesia alone, for example, this would mean a total of 227 teletherapy machines, when the current number is 39. The number of centres with existing radiotherapy services ranges from 1 to 32, with maximum capacities less than 10% of the estimated national needs in most countries. What is worse, there are still three countries in this region where radiotherapy services cannot be provided.

Taking into account each country's population, the ratio of MV units per million population ranges from 0 in Brunei Darussalam, the Lao People's Democratic Republic and Timor-Leste to 3.15 in Singapore (Fig. 25.1). To some extent, a linear trend which exists between the ratio of MV units per million population and GDP per capita seems similar to what has been observed in Latin American countries in 2004 and in LMICs in 2006 [25.31, 25.5].


*FIG. 25.1. Megavoltage units per million population in Southeast Asia.*

Despite having the smallest number of radiotherapy centres among SEAROG member countries, Singapore is currently the best served country in this region, with approximately 3.15 MV units per million population. Its population also has the best access to radiotherapy among the Southeast Asian countries, with approximately 1 radiotherapy centre per 142 $km^2$ (Table 25.9). However, even for Singapore, machine availability is still low compared with estimated needs (Fig. 25.2).

In most of Southeast Asia, radiotherapy centres are located in major cities or on major islands, making the interpretation of these numbers a rough estimate at best. Cancer patients in major cities might have access to several radiotherapy centres close to their homes, while for those from rural or remote areas, access to radiotherapy services is extremely limited. This is particularly true for countries consisting of multiple islands such as Indonesia and the Philippines, each having inhabited islands numbering in the hundreds or thousands.

TABLE 25.9. AVAILABILITY AND ACCESSIBILITY OF RADIOTHERAPY IN SOUTHEAST ASIA (JULY 2013)

| | Radiotherapy centres | Linacs | Cobalt-60 units | Area ($km^2$) | Population (2010) | Megavoltage units/million population | $km^2$/centre |
|---|---|---|---|---|---|---|---|
| Brunei Darussalam[a] | —[b] | —[b] | —[b] | 5 770 | 398 920 | —[b] | —[b] |
| Cambodia[a] | 1 | —[b] | 1 | 181 040 | 14 138 255 | 0.071 | 181 040 |
| Indonesia[c] | 22 | 19 | 17 | 1 904 570 | 239 870 937 | 0.163 | 73 252 |
| Lao People's Dem. Rep.[c] | —[b] | —[b] | —[b] | 236 800 | 6 200 894 | —[b] | —[b] |
| Malaysia[c] | 26 | 40 | —[b] | 330 800 | 28 401 017 | 1.408 | 12 723 |
| Myanmar[c] | 3 | —[b] | 7 | 676 590 | 47 963 012 | 0.104 | 135 318 |
| Singapore[c] | 5 | 16 | —[b] | 710 | 5 076 700 | 3.152 | 142 |
| Thailand[c] | 32 | 59 | 16 | 513 120 | 69 122 234 | 1.085 | 16 035 |
| Viet Nam[c] | 18 | 15 | 18 | 331 050 | 86 936 464 | 0.472 | 13 242 |
| Timor-Leste[c] | —[b] | —[b] | —[b] | 14 870 | 1 124 355 | —[b] | —[b] |
| Southeast Asia region | 144 | 191 | 58 | 4 495 320 | 592 493 586 | 0.420 | 31 217 |

[a] As of July 2013.
[b] —: data not available.
[c] As of December 2013.

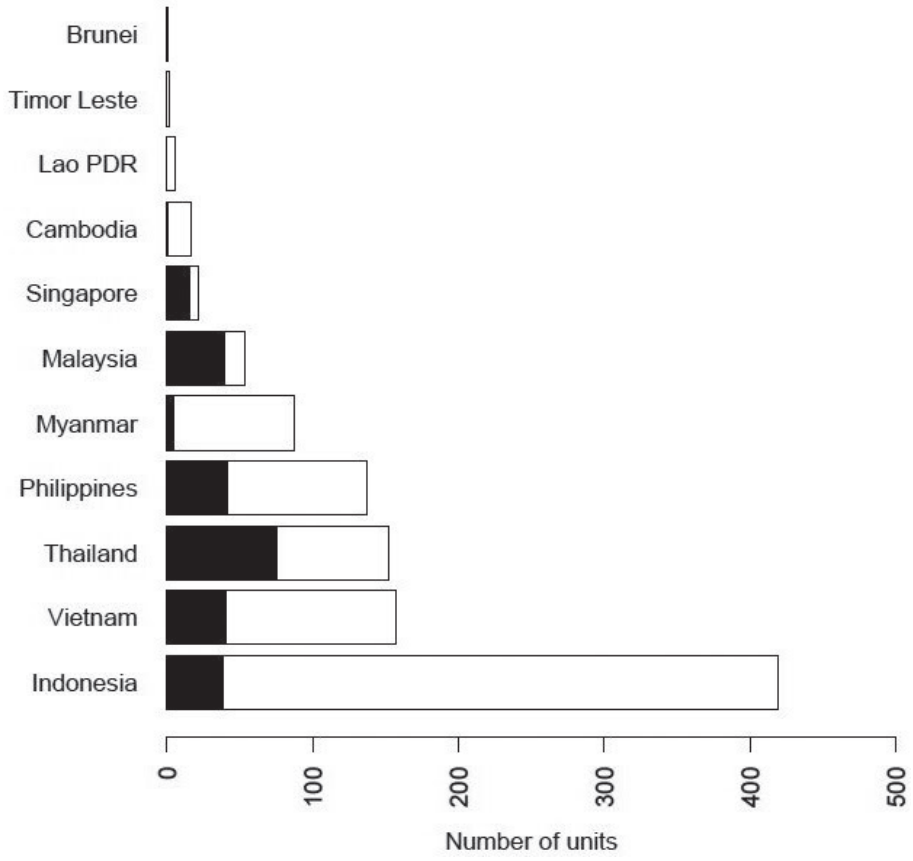


*FIG. 25.2. Required number of MV units compared with actual availability.*

### 25.4.5. Role of public and private sectors

In most of Southeast Asia, radiotherapy services are provided mainly by government owned health care facilities (Fig. 25.3). However, Malaysia, the Philippines and Singapore are notable exceptions. These countries exhibit a more balanced distribution of MV units among private and State owned health care facilities. The participation of the private sector seems to be a reasonable approach in countries where public health care funding is scarce, and this approach has been demonstrated in the Philippines, where the number of private radiotherapy centres exceeds that of public centres. However, whether the same model will be equally effective in other countries with better radiotherapy treatment access is still not clearly known, especially since in most countries, out of pocket funding (direct outlay by households) for health care still predominates

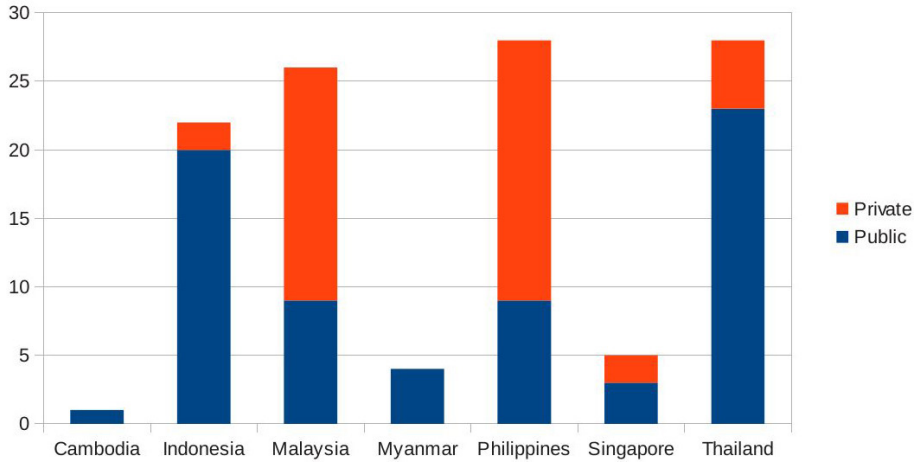


*FIG. 25.3. Ownership/source of funding for radiotherapy centres in Southeast Asia as of July 2013.*

over external sources such as private insurance, government insurance or social security schemes (Table 25.10).

### 25.4.6. Conclusion

Southeast Asia is a diverse region, not only in terms of geographical characteristics and culture, but also of development status, resource availability and maturity of national cancer control programmes. However, the countries in this region share a similar challenge: there is a wide gap between the required radiotherapy infrastructure and its actual availability. The need for and availability of resources differ greatly between countries. Each country must develop and continuously revise its national cancer control plan addressing its radiotherapy needs. Regarding the published evidence based estimates of the optimal radiation utilization rate, the older standard of one to two MV units per million population is conservative at best, but it can still be considered as a milestone in the long term plan for national cancer control programmes in countries with large populations and limited access to radiotherapy services.

### 25.4.7. Acknowledgements

The authors wish to thank the SEAROG executive committee members for their contribution to the collection of national data for this article. In particular, the authors wish to thank N. Asavametha and T. Phungrassami of the Thai Society

TABLE 25.10. HEALTH CARE FUNDING IN SOUTHEAST ASIA [25.28]

| | Total health expenditure per capita (US $) | Total health expenditure (% of GDP) | Out of pocket health expenditure (% of total health expenditure) | Public health expenditure (% of government expenditure) |
|---|---|---|---|---|
| Brunei Darussalam | 790.7 | 3.00% | 0.09% | 7.0% |
| Cambodia | 42.1 | 5.94% | 61.55% | 9.3% |
| Indonesia | 55.4 | 2.36% | 35.25% | 6.9% |
| Lao People's Dem. Rep. | 35.8 | 4.06% | 61.30% | 3.7% |
| Malaysia | 336.4 | 4.81% | 40.47% | 7.2% |
| Myanmar | 12.5 | 2.02% | 86.21% | 0.8% |
| Philippines | 66.9 | 3.82% | 53.95% | 6.1% |
| Singapore | 1 501.3 | 3.91% | 55.42% | 9.8% |
| Thailand | 167.7 | 4.31% | 16.45% | 14.0% |
| Viet Nam | 79.7 | 7.21% | 55.34% | 8.9% |
| Timor-Leste | 73.2 | 1.23% | 7.42% | 9.8% |

of Therapeutic Radiology and Oncology; G. Lim, I. Wahid and A. Bustam of the Malaysian Oncological Society; Wong Fuh Yong of the Singapore Radiological Society; and N.J. Cupino of the Philippines Radiation Oncology Society.

## 25.5. RADIOTHERAPY IN SOUTH ASIA — R.R. Prasad

### 25.5.1. Background

The South Asia region, according to the World Bank's classification, includes eight countries [25.32]. The region has a wide variety of landscapes and features extensive ethnic diversity. It accounts for approximately 16.5% of the world's and 34% of Asia's population [25.33]. Within the region, the environment, dietary practices and socioeconomic status differ markedly. For example, there are differences between urban and rural lifestyles, and in indicators of health and well-being. More than 500 million people live on less than US $1.25 a day in this region [25.34]. Moreover, the challenges related to development in South Asia are enormous due to persistent poverty, complex social stratification, and inadequate infrastructure.

The life expectancy at birth ranges from 45.5 to 73.1 in South Asia. It is lowest in Afghanistan and highest in Sri Lanka [25.35]. According to the United Nations Development Programme's Human Development Index (HDI), Sri Lanka, Maldives, India and Bhutan belong to the 'medium human development' group, while the rest of the countries of the region are in the 'low human development' category. Health expenditure, as a percentage of GDP ranges from 2.2 to 7.6%. It is highest and lowest in Afghanistan and Pakistan, respectively. Table 25.11 shows the different indices related to South Asian countries [25.3, 25.35–25.39].

### 25.5.2. Cancer burden

South Asia is experiencing a shift in disease burden from mainly infectious diseases to an increasing incidence of non-communicable diseases, including cancer. Against 1 348 819 new cancer cases (excluding non-melanoma skin cancers) seen in 2012, an estimated 2 125 665 new cases will occur by 2030 [25.3]. There are marked variations in cancer incidence, mortality, patterns of care, availability of infrastructure and treatment facilities, and trained staff strength involved in cancer care in the region.

The following facts emerge from the region based on Globocan 2012 data. The five most common cancers (for both sexes) are cancers of the cervix, breast, lip and oral cavity, lung and stomach. Afghanistan has the highest age

TABLE 25.11. SOUTH ASIA: SELECTED DATA

| | Population[a] | GDP (US $)[a] | Life expectancy (at birth, both sexes)[b] | Human Development Index[c] | Health expenditure (% of GDP)[d] | Age standardized rate (W) of incidence/mortality (per 100 000 persons per year, all cancers excluding non-melanoma skin cancer, both sexes)[e] |
|---|---|---|---|---|---|---|
| Afghanistan | 35 320 445 | 20 038 215 159 | 45.5 | 0.398 | 7.6 | 115.2/97.7 |
| Bangladesh | 150 493 658 | 172 886 567 164 | 66.2 | 0.500 | 3.5 | 104.4/80.8 |
| India | 1 241 491 960 | 2 048 517 438 874 | 66.7 | 0.547 | 4.1 | 94.0/64.5 |
| Nepal | 30 485 798 | 19 769 642 123 | 65.9 | 0.458 | 5.5 | 85.2/67.7 |
| Pakistan | 176 745 364 | 243 631 917 866 | 67.2 | 0.509 | 2.2 | 111.8/79.6 |
| Sri Lanka | 20 869 000 | 78 823 610 057 | 73.1 | 0.691 | 2.9 | 94.8/54.6 |
| Bhutan | 738 267 | 1 958 803 867 | 67.6 | 0.522 | 5.2 | 79.2/67.3 |
| Maldives | 320 081 | 3 061 829 145 | 70.4 | 0.661 | 6.3 | 88.9/53.7 |

[a] Source: Ref. [25.36].
[b] Source: Ref. [25.35].
[c] Source: Ref. [25.37].
[d] Source: Ref. [25.38].
[e] Source: Ref. [25.3].

standardized rate (ASR) of incidence for cancer (for both sexes), followed by Pakistan, Bangladesh, Sri Lanka, India, Maldives, Nepal and Bhutan. The ASR of mortality is highest for Afghanistan, followed by Bangladesh, Pakistan, Nepal, Bhutan, India and Sri Lanka, and is lowest in Maldives.

For men, lung cancer is the most common cancer in Bangladesh, India and Nepal, while lip and oral cavity cancer is most common in Maldives, Pakistan and Sri Lanka. The highest ASR of incidence for lung cancer in males has been reported in Bangladesh, where it contributes 14.4% of new cancer cases. Bhutan has the lowest ASR of incidence for lung cancer in the region. Gastric cancer is more common among men from Afghanistan and Bhutan compared with men from the other countries of the region.

Among women, breast cancer is the most common cancer in Afghanistan, Bangladesh, India, Maldives, Pakistan and Sri Lanka. The highest ASR of incidence for breast cancer is seen in Pakistan, and the lowest in Bhutan. In Pakistan, breast cancer constitutes 40% of the cancer load. Cervical cancer is most common in Nepal, followed by Bhutan. Twenty per cent of the total cancer load in Nepal is due to cervical cancer, while Afghanistan has the lowest incidence of this disease in the region.

The highest incidence of lip and oral cavity cancer (for both sexes) in the region has been reported for Maldives. This is followed by Sri Lanka, Pakistan, Bangladesh, India, Afghanistan and Nepal. It is lowest in Bhutan, where it constitutes only 3.2% of the total cancer load.

The incidence of cancer of the oesophagus is the highest in Bangladesh, while it is lowest in Nepal. The incidence of colorectal and prostate cancers is highest in Maldives. Bhutan has shown the highest rates of incidence for stomach, nasopharynx and liver cancers. The incidence of cancer of the gall bladder is the highest in Nepal. In Afghanistan, the age adjusted incidence rates of cancer of the urinary bladder, kidney, colorectum and brain are highest among the various countries in South Asia. Leukaemia is most common in Sri Lanka. The five most common cancers seen in different countries of South Asia are shown in Table 25.12.

### 25.5.3. Risk factors

No matter how effective cancer treatment may become, prevention comes first. Vaccination against human papillomavirus (HPV) and hepatitis B virus, and organized screening for cervical cancer are urgently needed in the region but are difficult to achieve. Exposure to tobacco and its byproducts is by far the best known and most frequent cause of cancer in adults, causing an estimated 40% of all deaths from cancer. Consumption of tobacco in all its forms is the single

TABLE 25.12. FIVE MOST COMMON CANCERS IN SOUTH ASIA FOR BOTH SEXES

| Afghanistan | Bangladesh | India | Nepal | Pakistan | Sri Lanka | Bhutan | Maldives | South Asia |
|---|---|---|---|---|---|---|---|---|
| Breast | Breast | Breast | Cervix | Breast | Lip, oral cavity | Stomach | Breast | Breast |
| Stomach | Cervix | Cervix | Breast | Lip, oral cavity | Breast | Cervix | Cervix | Cervix |
| Oesophagus | Oesophagus | Lip, oral cavity | Lung | Cervix | Other pharynx | Lung | Lip, oral cavity | Lip, oral cavity |
| Cervix | Lung | Lung | Ovary | Lung | Stomach | Oesophagus | Lung | Lung |
| Corpus uteri | Lip, oral cavity | Colorectum | Stomach | Ovary | Oesophagus | Ovary | Ovary | Stomach |

**Note:** Data from Globocan 2012, http://www.globocan.iarc.fr/.

largest preventable cause of cancer. The most common tobacco related cancers in the region are those of the lung, head and neck, and oesophagus.

South Asia is the largest region in the world for the production and consumption of tobacco products. In addition to cigarettes, tobacco is used in this region in various forms, such as 'bidis', 'kreteks' and 'cheroots', as well as in smokeless forms for chewing. An open market and more disposable income make South Asian countries attractive markets for such products as tobacco and alcohol. Bangladesh has the highest rate of tobacco smoking, followed by Maldives, Pakistan, Nepal, India and Sri Lanka. Similar data from Afghanistan and Bhutan are not available. Smoking rates are much higher for men than for women, except in Nepal where it is high for both sexes. Tobacco use among young people is also becoming a problem in this region. The Global Youth Tobacco Survey involving countries of the region shows that one in ten students (13–15 years old) smoke [25.40]. Higher taxation of cigarettes has been found globally to be the single most effective intervention to decrease smoking. Tobacco taxes and consumption have a strong inverse relation worldwide: in comparison to high income countries, an increase in taxes in LMICs will have double the effect [25.41].

Another important risk factor is alcohol. Annual per capita consumption of alcohol has increased in countries like India and Nepal [25.42]. The tendency to obesity is a growing problem in every country of the region [25.43]. Other factors include the increase in the population of this region, especially the increase in the ageing population (when the incidence of many cancers becomes most noticeable). This will be a major reason for the increase in the cancer burden in LMICs worldwide [25.44].

### 25.5.4. National cancer control programmes and cancer registries

While some countries such as Bangladesh, India, Pakistan and Sri Lanka have national cancer control programmes, other countries of the region lack an organized cancer control strategy [25.45–25.48]. Realizing the importance of NCDs, all countries of the region except Afghanistan have opened a unit, branch or department in their Ministry of Health to address this problem [25.49]. Population based cancer registries, albeit with limited coverage, are operational in India, Pakistan and Sri Lanka [25.50–25.52].

### 25.5.5. Radiotherapy

Radiotherapy plays a fundamental role in the continuum of cancer care and its key role in the management of cancer is likely to continue for several years to come. The recognition of the need for radiotherapy is higher in this region,

as shown by the advanced stage of presentation and different profiles of cancer cases. However, it is necessary to improve and expand radiotherapy services, ideally within the framework of national cancer control strategies.

It is possible to provide effective radiotherapy services for most cancer cases at a moderate cost, even without recourse to sophisticated technology. External beam radiotherapy can be accurately and safely delivered with cobalt-60 units or medical linacs.

There are some common problems related to radiotherapy within the region. For example, the lack of timely accessibility of radiotherapy prevents the achievement of optimal results. However, availability alone does not determine access to radiotherapy. Geographical or spatial accessibility and the ability patients and their family members to cover the direct and the indirect costs of treatment are major barriers preventing access to radiotherapy services. The majority of radiotherapy centres are concentrated in major cities, leaving large geographical gaps.

Lack of awareness of indications of radiotherapy and its availability among primary physicians is another important reason for suboptimal utilization of radiotherapy services. Many radiotherapy centres are under-resourced, with an inadequate number of machines and limited staff. There commonly are long waiting periods for patients referred for radiotherapy. Many centres lack vital equipment such as simulators, shielding blocks and mould room facilities. Often they have inadequate equipment maintenance or access to spare parts, or even basic dosimetry equipment for calibration and quality assurance. Some centres even carry out treatment using decayed cobalt-60 sources, a practice considered to be radiobiologically ineffective. Adequate documentation of vital facts related to various aspects of radiotherapy is lacking in many centres. The necessary radiation protection infrastructure for monitoring and regulatory control is not adequate or available in some of these countries.

Out of eight countries of the region, only five have operational radiotherapy services [25.4] (Table 25.13). This means that a total of more than 36 million people from Afghanistan, Bhutan and Maldives have to depend on other countries for access to radiotherapy facilities. Radiotherapy services are available in Bangladesh, India, Nepal, Pakistan and Sri Lanka. There are 414 radiotherapy centres in the region, ranging from 5 in Nepal to 357 in India.

In the South Asia region, there are approximately 613 MV units: 330 linacs and 283 cobalt-60 units, representing 0.37 MV units per million population. Bangladesh, India, Nepal, Pakistan and Sri Lanka have 0.16, 0.41, 0.19, 0.28 and 0.6 MV units per million population, respectively.

The number of linacs is growing faster than that of cobalt-60 units, the traditional workhorse. Bangladesh and India have more linacs than cobalt-60 units; Nepal has an equal number of linacs and cobalt-60 units; and there are

TABLE 25.13. RADIOTHERAPY RESOURCES IN SOUTH ASIA

| | Radiotherapy centres | Number of megavoltage units | Linacs | Cobalt-60 units | Megavoltage units per million population | Radiation oncologists | Medical physicists |
|---|---|---|---|---|---|---|---|
| Afghanistan | None | None | None | None | None | None | None |
| Bangladesh | 16 | 25 | 13 | 12 | 0.16 | 128 | 28 |
| India | 357 | 518 | 287 | 231 | 0.41 | 1138 | 778 |
| Nepal | 5 | 6 | 3 | 3 | 0.19 | 16 | 9 |
| Pakistan | 29 | 51 | 25 | 26 | 0.28 | 113 | 92 |
| Sri Lanka | 7 | 13 | 2 | 11 | 0.6 | 20 | 15 |
| Bhutan | None | None | None | None | None | None | None |
| Maldives | None | None | None | None | None | None | None |
| South Asia region | 414 | 613 | 330 | 283 | 0.37 | 1415 | 922 |

**Note:** Data collated from the following sources: IAEA Directory of Radiotherapy Centres (DIRAC) [25.4], national representatives participating in an IAEA project, and personal communications.

Although great care has been taken to maintain the accuracy of the information in Tables 25.13 and 25.14, much of which has been received from multiple sources, the possibility of discrepancies due to difficulties in the verification of the information and possible variations in the time period of reporting cannot be excluded. As such, the IAEA does not take responsibility for any consequences which may arise from its use.

more cobalt-60 units than linacs in Pakistan and Sri Lanka. The ratio of cobalt-60 units to linacs is 0.9:1, 0.8:1, 1:1, 1.04:1 and 5.5:1 for Bangladesh, India, Nepal, Pakistan and Sri Lanka, respectively. Brachytherapy services are required in the region, as cervical cancer is the most common cancer in South Asia. At present, there are over 250 brachytherapy units in the region. These are mainly high dose rate units. There are nine gamma knife systems in the region: one in Pakistan and eight in India. Three helical tomotherapy units, four robotic radiotherapy machines and two intraoperative radiotherapy (IORT) facilities are all available exclusively in India.

Based on the estimate of new cancer cases by 2030, South Asia will require 2338 MV units (Table 25.14). For most countries of the region, reaching the conservative recommendation of one to two MV units per million population is thus a daunting task. There are currently 1415 radiation oncologists and 922 medical physicists in the region. The estimated numbers of radiation oncologists and medical physicists required by 2030, based on IAEA recommendations, are shown in Table 25.14 [25.27]. In Bangladesh, India, Nepal, Pakistan and Sri Lanka, the ratio of radiation oncologists to medical physicists is 4.5:1, 1.5:1, 1.7:1, 1.2:1 and 1.3:1, respectively. Pakistan has the highest number of medical physicists relative to radiation oncologists. Though large numbers of cancer patients continue to be treated in the public sector, the contribution of the private sector is growing. Newer and more sophisticated radiotherapy technologies are being offered mostly in the private sector. This has increased the cost of cancer care in South Asia quite dramatically. Despite the high cost of treatment, a 92% increase in the number of cancer patients seeking treatment in the private sector has been observed in Pakistan [25.53].

Most radiation oncologists practice as ‘clinical oncologists’ (i.e. medical and radiation oncology) because of their training and the relative lack of medical oncologists in the region. Some have limited themselves to the exclusive practice of medical oncology due to the unavailability of radiotherapy machines. This shortage of radiation oncologists, medical physicists and other technical staff is expected to increase.

Radiotherapy has an important role to play in palliative cancer care in the region, considering the advanced stage of presentation in many patients. Palliative care must be an integral part of a national cancer control strategy. To ensure that there is an adequate level of pain relief, the availability of oral morphine is critical. This may require changes in laws and regulations in some countries.

The IAEA, through its technical cooperation projects, the Programme of Action for Cancer Therapy (PACT) and its human health programme, and in collaboration with WHO and other partners, has been actively involved in the development and upgrading of radiotherapy facilities in the South Asia region.

TABLE 25.14. DEMAND FOR MV UNITS, RADIATION ONCOLOGISTS AND MEDICAL PHYSICISTS IN SOUTH ASIA BY 2030

| | Estimated no. of new cases in 2030 (Globocan 2012 data) | Estimated no. of new cases requiring radiotherapy | No. of MV units available (2012–2013) | Estimated no. of MV units required in 2030 | Estimated no. of radiation oncologists required in 2030 | Estimated no. of medical physicists required in 2030 |
|---|---|---|---|---|---|---|
| Afghanistan | 32 882 | 18 085 | None | 36 | 72 | 45 |
| Bangladesh | 217 954 | 119 875 | 25 | 240 | 479 | 300 |
| India | 1 569 196 | 863 058 | 518 | 1 726 | 3 452 | 2 158 |
| Nepal | 29 206 | 16 063 | 6 | 32 | 64 | 40 |
| Pakistan | 241 124 | 132 618 | 51 | 265 | 530 | 331 |
| Sri Lanka | 34 057 | 18 731 | 13 | 37 | 74 | 47 |
| Bhutan | 804 | 442 | None | 1 | 2 | 2 |
| Maldives | 442 | 243 | None | 1 | 1 | 1 |
| South Asia | 2 125 665 | 1 169 116 | 613 | 2 338 | 4 676 | 2 924 |

**Note:** Assuming 55% of new cancer cases will require radiotherapy and 500 patients will be treated per MV unit in one shift per day. To calculate the number of radiation oncologists and medical physicists, it is assumed that annually 250 patients will be treated by one radiation oncologist and that one physicist will be required for every 400 patients receiving radiotherapy in a year. More radiation oncologists and physicists per programme will be required depending on the number of programmes and the complexity of treatment undertaken; this has not been included in the calculation.

Although great care has been taken to maintain the accuracy of the information in Tables 25.13 and 25.14, much of which has been received from multiple sources, the possibility of discrepancies due to difficulties in the verification of the information and possible variations in the time period of reporting cannot be excluded. As such, the IAEA does not take responsibility for any consequences which may arise from its use.

Currently, projects are continuing in Afghanistan, Bangladesh, Pakistan and Nepal. A number of integrated missions of PACT (imPACT) reviews have visited Bangladesh, Nepal, Pakistan and Sri Lanka. During these missions, a team of experts undertakes a comprehensive assessment of the country's cancer control planning, its cancer information collection, as well as its existing prevention measures and measures to ensure early detection and provide diagnosis, treatment and palliative care. The team also evaluates the country's training capabilities and the role of civil society. The assessment includes a review of the existing regulatory requirements and national radiation safety infrastructure using as a basis the IAEA's International Basic Safety Standards [25.54].

Additionally, the IAEA offers a wide spectrum of activities in support of education, training, human resource development and capacity building, as well as publications that describe best international practices which can be utilized by Member States in South Asia.

### 25.5.6. Summary

Cancer in South Asia is currently a public health problem of increasing magnitude. Increasing longevity of the population, rising public awareness of early symptoms, improved diagnostic facilities and adoption of a different lifestyle and diet have led to a significant rise in the incidence of cancer in the region. South Asian countries face a major challenge in all four key components of cancer control: prevention, early detection, diagnosis, and treatment and palliation.

Even without access to sophisticated technology, it is possible to provide effective radiotherapy care for most of the cancer cases at moderate costs without compromising the outcome. This requires the use of evidence based, resource sparing clinical protocols. Closing the gaps in the availability of radiotherapy facilities and building human resource capacity are the other major challenges.

The fight against cancer is a long term endeavour, and success hinges largely on strong government commitment. Regional cooperation can complement national efforts. Involvement and mutual cooperation among governments, various international organizations, academic and research institutions and non-governmental organizations are also very important.

### 25.5.7. Acknowledgements

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## 25.6. RADIOTHERAPY IN CHINA — Ci Zhu, Wei Bo Yin, Bo Chen, Chun Li Zhang, Hong Zhi Zhang, Ye Xiong Li

### 25.6.1. Background

China is the world's most populous country, with more than 1.393 billion inhabitants, accounting for over a fifth of the world's population [25.55]. Its GDP per capita has increased sixfold in two decades, making it the world's second largest economy in terms of nominal GDP [25.56]. China was classified by the World Bank in 2012 as an upper middle income country. Over this period of accelerated economic growth, China has also witnessed an increase in the incidence of cancer.

Every minute, six people in China are diagnosed with cancer, and one in five may fall victim to the disease by the time they reach the age of 75. There are approximately 2.7 million cancer deaths per year in China according to the 2012 Annual Report of the China National Central Cancer Registry. The lifetime risk of cancer for Chinese is 22%. Cancer incidence by age shows that among 100 000 people, 87 adults aged between 35 and 39 will get cancer, and 154 adults aged between 40 and 44 will develop some form of malignancy. The incidence of cancer among the over-50 population accounts for nearly 80% of the overall cancer cases in China. Lung cancer still remains the top killer among Chinese, with the highest mortality rate, followed by liver cancer, gastric cancer, oesophageal cancer and colorectal cancer [25.57]. In 2012, the estimated incidence of cancer was 3 065 400 new cases [25.3]. Tables 25.15 and 25.16 present the 2012 data for the incidence of cancer in China.

Radiotherapy is the most cost effective cancer treatment modality. According to a report from the Royal College of Radiologists and a study carried out by the Swedish Council on Technology Assessment in Health Care, for patients with malignancies, after evaluating the contributions of different modalities in curing cancer, it was found that of those cured, 49% were cured by surgery, 40% by radiotherapy alone or in conjunction with other modalities, and 11% by chemotherapy alone or together with other modalities [25.58, 25.59].

TABLE 25.15. INCIDENCE OF CANCER IN CHINA: SELECTED NATIONAL INDICATORS [25.57]

| | Male | Female | Both genders |
|---|---|---|---|
| Population (thousands) | 706 481 | 654 883.0 | 1 361 364.0 |
| Number of new cancer cases (thousands) | 1822.8 | 1242.7 | 3065.4 |
| Age standardized rate (W) | 211.2 | 139.9 | 174.0 |
| Risk of getting cancer before age 75 (%) | 20.2 | 13.3 | 16.8 |
| Number of cancer deaths (thousands) | 1429.5 | 776.5 | 2205.9 |
| Age standardized rate (W) | 164.6 | 82.6 | 122.2 |
| Risk of dying from cancer before age 75 (%) | 15.2 | 7.6 | 11.5 |
| Five most frequent cancers (ranking defined by total number of cases) | Lung | Lung | Lung |
| | Liver | Breast | Stomach |
| | Stomach | Stomach | Liver |
| | Oesophagus | Colorectum | Colorectum |
| | Colorectum | Liver | Oesophagus |

### 25.6.2. History of Chinese radiotherapy services

China's experience of using radiotherapy to treat cancer began with the installation of the first superficial X ray machine at Peking Union Medical College Hospital in early 1920, followed by the first 200 kV deep X ray machine installed at the French Hospital in Shanghai in 1923, and the first Chinese radiotherapy department established at the Affiliated Hospital of Peking University in 1932. However, the field of radiotherapy in China was still in its infancy between the 1930s and 1960s, as all operating machines were imported from foreign countries, making radiotherapy very difficult to access for cancer patients (Fig. 25.4). Progress was slow until the mid-1970s, when the first batch of megavoltage machines (cobalt-60 machines and linacs) was produced by Chinese manufacturers. Owing to the efforts of radiotherapy pioneers such as Wu Huanxing, Gu Xianzhi, Liu Taifu, and Yin Weibo, who brought radiotherapy to China and shaped how Chinese patients would be treated today, radiotherapy was installed as one of the mainstream modalities of cancer treatment. In 1986,

TABLE 25.16. ESTIMATED INCIDENCE, MORTALITY AND FIVE YEAR PREVALENCE OF THE FIVE MOST FREQUENT CANCERS AMONG MEN AND WOMEN IN CHINA PER YEAR
(GLOBOCAN 2012 — all cancers excluding non-melanoma skin cancer [25.3])

| Cancer | Five most frequent cancers among Chinese men | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Incidence | | | Mortality | | | Five year prevalence | | |
| | Number | (%) | ASR (W) | Number | (%) | ASR (W) | Number | (%) | Prop. |
| Lung | 459 495 | 25.2 | 52.8 | 421 695 | 29.5 | 48.3 | 430 987 | 17.3 | 76.0 |
| Liver | 293 318 | 16.1 | 33.7 | 281 802 | 19.7 | 32.3 | 220 108 | 8.8 | 38.8 |
| Stomach | 283 487 | 15.6 | 32.8 | 221 478 | 15.5 | 25.5 | 418 634 | 16.8 | 73.8 |
| Oesophagus | 160 436 | 8.8 | 18.6 | 140 329 | 9.8 | 16.2 | 161 578 | 6.5 | 28.5 |
| Colorectum | 146 528 | 8.0 | 16.9 | 79 074 | 5.5 | 8.9 | 337 911 | 13.5 | 59.6 |
| All cancers excluding non-melanoma skin cancers | 1 822 769 | 100.0 | 211.2 | 1 429 461 | 100.0 | 164.6 | 2 495 611 | 100.0 | 440.1 |

TABLE 25.16. ESTIMATED INCIDENCE, MORTALITY AND FIVE YEAR PREVALENCE OF THE FIVE MOST FREQUENT CANCERS AMONG MEN AND WOMEN IN CHINA PER YEAR
(GLOBOCAN 2012 — all cancers excluding non-melanoma skin cancer [25.3]) (cont.)

| Cancer | Five most frequent cancers among Chinese women | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Incidence | | | Mortality | | | Five year prevalence | | |
| | Number | (%) | ASR (W) | Number | (%) | ASR (W) | Number | (%) | Prop. |
| Stomach | 121 509 | 9.8 | 13.1 | 103 688 | 13.4 | 10.7 | 175 325 | 6.9 | 32.5 |
| Colorectum | 106 899 | 8.6 | 11.6 | 60 342 | 7.8 | 6.1 | 245 143 | 9.6 | 45.4 |
| Liver | 101 452 | 8.2 | 10.9 | 101 401 | 13.1 | 10.7 | 70 802 | 2.8 | 13.1 |
| All cancers excluding non-melanoma skin cancer | 1 242 669 | 100.0 | 139.9 | 776 485 | 100.0 | 82.6 | 2 549 427 | 100.0 | 472.6 |

**Note:** ASR — age standardized rate; Prop. — proportion per 100 000 persons.

*FIG. 25.4. The first 800 Marie cobalt-60 machine developed and produced by the Xinhua medical equipment factory in Shandong Province, China, in 1969, breaking the foreign monopoly [25.62].*

the China Society for Radiation Oncology (CSTRO) was founded, indicating that a network advancing radiation oncology practice in China was taking shape. One year later, the first issue of the Chinese Journal of Radiation Oncology was published, offering a platform for the timely exchange and sharing of laboratory and clinical research outcomes among radiation oncology professions across the country.

During the past two decades, with the introduction of the gamma knife and stereotactic radiotherapy, 3-D conformal radiotherapy, IMRT, IGRT and other advanced techniques, China experienced not only a big jump in its radiotherapy equipment and facilities, but also a dramatic growth in the excellence of radiation oncology specialist staff nationwide (Table 25.17).

### 25.6.3. Structure of radiation oncology in mainland China from 1986 to 2011

The provision of high quality radiation oncology services has been universally acknowledged as one of the significant cornerstones of modern modalities in cancer treatment. Due to China's large population, timely, equitable and affordable access to radiation oncology services remains a difficult goal in the development of Chinese radiation oncology.

From 1986 to 2011, CSTRO conducted a series of national surveys on the structure of radiation oncology facilities, the equipment and the associated supporting staff in mainland China. These surveys aimed to identify the basic structural characteristics of radiation oncology. This included making comparisons of the growth of relevant infrastructure and personnel, measuring

TABLE 25.17. MAJOR MILESTONES IN THE HISTORY OF CHINESE RADIATION ONCOLOGY, 1969–2009 [25.60–25.62]

| Time | Milestone |
|---|---|
| 1920 | First superficial X ray machine installed at Peking Union Medical College Hospital. |
| 1923 | 200 kV machine installed at the French Hospital, Shanghai. |
| 1932 | First radiotherapy department established at the Affiliated Hospital of Peking University. |
| 1969 | First Chinese-made 800 Marie cobalt-60 machine (source to skin distance: 60 cm) developed and produced at the Xinhua medical equipment factory in Shandong Province, China. It broke the foreign monopoly on cobalt machines (see Fig. 25.4). |
| 1970 | Dongfang Hong medical equipment factory begins to batch manufacture 250 kV deep therapy X ray machines in Beijing. |
| 1972 | Nuclear medical instrument factory in Shanghai successfully develops and produces the 3000 Marie cobalt-60 machine with rotation function (source to skin distance: 80 cm). |
| 1970s | Computed tomography (CT) largely being used in diagnostic imaging. |
| 1986 | CSTRO founded. |
| 1987 | First issue of Chinese Journal of Radiation Oncology published. |
| 1990s | Three dimensional conformal radiotherapy and stereotactic radiotherapy used in China. |
| 2000 | Advanced development and application of intensity modulated radiation therapy. |
| 2004 | Adoption of positron emission tomography and CT in radiotherapy to target tumours precisely. |
| 2006 | Image guided radiation therapy being used in many Chinese radiation centres. |
| 2008 | Sino-American Network for Therapeutic Radiology and Oncology (SANTRO) established to foster communication among radiation oncologists from China and the United States of America for promoting excellence in patient care. |
| 2009 | First volumetric arc radiotherapy machine installed at Beijing Cancer Hospital. |

a facility's capability to deliver radiotherapy, and planning new radiotherapy facilities in accordance with future needs. The methods used to conduct surveys have been described by Yin Weibo et al. [25.63–25.65]. The latest survey showed that there were 1162 radiation oncology departments/centres delivering MV radiotherapy in 2011, in contrast to 1986, when there were only 264 radiotherapy departments able to perform radiotherapy, as shown in Table 25.18 [25.65]. The number of in-patient beds in radiotherapy centres has also grown rapidly, as has the number of patients treated by them (Table 25.19).

The radiotherapy work force has been constantly expanding in size. The number of registered radiation oncologists in 2011 was 9895, up from 1715 in 1986. The number of medical physicists has also risen since 1986, reaching 1887 in 2011. According to the Sixth Nationwide Survey on Radiation Oncology of Continent Prefecture of China in 2011, there were 8000 medical physicists who took the certification examinations administered by the National Public Health Ministry, with 5000 medical physicists gaining the certification by 2010 [25.65]. There were still no medical physicists in 38 radiation oncology departments out of 385 departments conducting IMRT in 2011.

Since 1986, data on linacs, CT simulators, treatment planning systems and dosimeters have been accumulating. The number of brachytherapy afterloaders has increased (Table 25.20). The table also shows a transition from conventional simulators to CT simulators from 2006 to 2011. The situation with regard to the ratio of linacs to cobalt 60 machines per million population has improved as well (Table 25.21).

During the past decade, a large range of radiotherapy techniques aimed at enhancing precision in dose delivery have been established in China, in part due to dramatic advancements in medical imaging. In addition, China is speeding up its pace in adopting the new radiation technologies. Table 25.22 shows the number of radiation departments/centres conducting radiotherapy with new technologies between 2001 and 2011.

TABLE 25.18. NUMBER OF RADIATION ONCOLOGY DEPARTMENTS/CENTRES AND PERSONNEL IN CHINA: TRENDS FROM 1986 TO 2011 [25.65]

| Year | No. of radiation oncology departments/ centres | No. of radiation oncologists | No. of medical physicists | Ratio of radiation oncologists/medical physicists | No. of radiation oncology nurses | No. of radiotherapists | No. of supporting engineers | Total no. of radiation oncology staff |
|---|---|---|---|---|---|---|---|---|
| 1986 | 264 | 1 715 | 180 | 10:1 | 1 062 | 1 410 | 312 | 4 679 |
| 1994 | 369 | 2 764 | —[a] | | 2 361 | 2 212 | —[a] | 7 337 |
| 1997 | 453 | 3 440 | 423 | 8:1 | 3 094 | 2 245 | 730 | 9 932 |
| 2001 | 715 | 5 113 | 619 | 8:1 | 5 002 | 3 465 | 932 | 15 131 |
| 2006 | 952 | 5 247 | 1 181 | 4:1 | 6 864 | 4 559 | 1 141 | 18 992 |
| 2011 | 1 162 | 9 895 | 1 887 | 5:1 | 11 689 | 6 103 | 1 411 | 30 985 |

[a] —: data not available.

TABLE 25.19. IN-PATIENT BEDS AND NEW PATIENTS IN RADIOTHERAPY FACILITIES BETWEEN 2001 AND 2011 [25.65]

| | 2001 | 2006 | 2011 |
|---|---|---|---|
| In-patient beds in radiation oncology facilities | 23 571 | 35 503 | 56 847 |
| New patients per day | 32 989 | 42 109 | 58 069 |
| New patients per year | 282 937 | 409 440 | 569 056 |

### 25.6.4. Geographical distribution of radiotherapy resources in China

The poorly balanced geographical distribution of radiotherapy resources explains the most significant characteristic of Chinese radiotherapy — the most cutting edge radiotherapy resources are centralized in fast growing metropolitan areas (such as Beijing, Shanghai and Guangzhou). Less developed areas are struggling to allocate their rapidly increasing number of cancer patients to the insufficient number of radiotherapy facilities. Geographical proximity plays an important role in a patient's access to radiation oncology care, in conjunction with other factors such as a patient's insurance coverage and willingness to seek radiotherapy treatments. Lack of radiotherapy facilities and services within an appropriate distance makes the opportunities to be cured and released from pain even less accessible in the eyes of cancer patients in rural areas. Table 25.23 shows that only in Shandong and Beijing provinces does the number of linacs and cobalt-60 machines per million population exceed two.

### 25.6.5. Discussion and conclusions

From being totally dependent on imported radiotherapy machines to being a major linac and cobalt-60 machine producer and exporter worldwide, from having 264 radiation oncology departments with 4679 radiation oncology staff in the whole country in 1986 to having 1162 radiation oncology departments with a team of 30 985 radiation oncology staff in 2011, China's capabilities in the field of radiation oncology have increased significantly. However, this progress only scratches the surface of meeting the increase in demand for radiotherapy. Even though the number of linacs reached 0.97 teletherapy machines per million population in 2011, there still remains a lot of ground to cover to meet the IAEA recommended one to two teletherapy machines per million [25.10, 25.65]. Following the report by Delaney et al. [25.6] that approximately half of cancer patients need radiotherapy treatment, 1 875 255 patients in China should receive

TABLE 25.20. RADIOTHERAPY EQUIPMENT PATTERN IN CHINA FROM 1986 TO 2011 [25.65]

| Year | Linac | Cobalt-60 machine | Deep X ray machine | Afterloader | Dosimeter | Conventional simulator | CT simulator | TPS | Stereotactic radiotherapy | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Gamma knife | | |
| | | | | | | | | | X knife | For head | For body |
| 1986 | 71 | 224 | 239 | 78 | 180 | 100 | 0 | 45 | 0 | 0 | 0 |
| 1994 | 164 | 304 | 194 | 217 | 215 | 170 | 0 | 75 | 0 | 0 | 0 |
| 1997 | 286 | 381 | 179 | 282 | 302 | 332 | 0 | 177 | 0 | 0 | 0 |
| 2001 | 542 | 454 | 171 | 379 | 517 | 577 | 0 | 381 | 244 | 33 | 34 |
| 2006 | 918 | 472 | 146 | 400 | 796 | 827 | 214 | 851 | 467 | 74 | 75 |
| 2011 | 1296 | 286 | 81 | 317 | 1041 | 376 | 376 | 410 | 410 | 122 | 108 |

**Note**: A number of gamma knife machines are used, not only for cranial targets but also for the body. CT — computed tomography; TPS — treatment planning system.

TABLE 25.21. CHANGES IN THE DISTRIBUTION OF LINACS AND/OR COBALT-60 MACHINES PER MILLION POPULATION IN CHINA BETWEEN 2001 AND 2011

| Year | Population (millions) | Linacs | Linacs (per million population) | Cobalt-60 machines | Linacs + cobalt-60 machines | Linacs + cobalt-60 machines (per million population) |
|---|---|---|---|---|---|---|
| 2001 | 1265.83 | 542 | 0.43 | 454 | 996 | 0.79 |
| 2006 | 1306.28 | 918 | 0.70 | 472 | 1390 | 1.06 |
| 2011 | 1339.72 | 1296 | 0.97 | 286 | 1582 | 1.18 |

TABLE 25.22. NUMBER OF RADIATION DEPARTMENTS/CENTRES PERFORMING RADIOTHERAPY WITH NEW TECHNIQUES AND THE PERCENTAGE OF FACILITIES USING SPECIFIED EQUIPMENT CLINICALLY DURING 2001–2011

| Year | No. of radiation centres | Stereotactic radiotherapy | | Stereotactic radiotherapy (gamma knife) | | 3-D conformal radiotherapy | | Intensity modulated radiation therapy | |
|---|---|---|---|---|---|---|---|---|---|
| | | No. of centres | Ratio (%) | No. of centres | Ratio (%) | No. of centres | Ratio (%) | No. of centres | Ratio (%) |
| 2001 | 715 | 202 | 28.3 | 24 | 3.4 | 195 | 27.3 | 44 | 6.2 |
| 2006 | 952 | 408 | 42.9 | 78 | 8.2 | 579 | 60.8 | 115 | 12.1 |
| 2011 | 1162 | 381 | 32.8 | 130 | 11.2 | 862 | 74.2 | 385 | 33.1 |

TABLE 25.23. GEOGRAPHICAL DISTRIBUTION OF LINACS AND COBALT-60 MACHINES PER MILLION, IN DIFFERENT PROVINCES, CITIES OR AUTONOMOUS REGIONS OF CHINA IN 2011 (BY PER CAPITA MACHINES) [25.65]

| Province (including municipalities) | Population (in millions) | Linacs | Cobalt-60 machines | Linacs + cobalt-60 machines | Linacs (per million population) | Linacs + cobalt-60 machines (per million population) |
|---|---|---|---|---|---|---|
| Beijing | 19.61 | 48 | 7 | 55 | 2.45 | 2.80 |
| Shandong | 95.79 | 173 | 22 | 195 | 1.81 | 2.04 |
| Shanghai | 23.02 | 44 | 0 | 44 | 1.91 | 1.91 |
| Shanxi | 35.71 | 40 | 21 | 61 | 1.12 | 1.71 |
| Hebei | 71.85 | 71 | 46 | 117 | 0.99 | 1.63 |
| Jiangsu | 78.66 | 99 | 26 | 125 | 1.26 | 1.59 |
| Tianjin | 12.94 | 17 | 2 | 19 | 1.31 | 1.47 |
| Henan | 94.02 | 112 | 22 | 134 | 1.19 | 1.43 |
| Hubei | 57.24 | 60 | 9 | 69 | 1.05 | 1.21 |
| Fujian | 36.89 | 30 | 14 | 44 | 0.81 | 1.19 |
| Inner Mongolia | 24.71 | 25 | 4 | 29 | 1.01 | 1.17 |

TABLE 25.23. GEOGRAPHICAL DISTRIBUTION OF LINACS AND COBALT-60 MACHINES PER MILLION, IN DIFFERENT PROVINCES, CITIES OR AUTONOMOUS REGIONS OF CHINA IN 2011 (BY PER CAPITA MACHINES) [25.65] (cont.)

| Province (including municipalities) | Population (in millions) | Linacs | Cobalt-60 machines | Linacs + cobalt-60 machines | Linacs (per million population) | Linacs + cobalt-60 machines (per million population) |
|---|---|---|---|---|---|---|
| Guangxi | 46.03 | 42 | 12 | 54 | 0.91 | 1.17 |
| Shanxi | 37.33 | 36 | 7 | 43 | 0.96 | 1.15 |
| Liaoning | 43.75 | 47 | 3 | 50 | 1.07 | 1.14 |
| Anhui | 59.50 | 51 | 14 | 65 | 0.86 | 1.09 |
| Heilongjiang | 38.31 | 38 | 2 | 40 | 0.99 | 1.04 |
| Jilin | 27.46 | 22 | 5 | 27 | 0.80 | 0.98 |
| Zhejiang | 54.43 | 51 | 2 | 53 | 0.94 | 0.97 |
| Xinjiang | 21.81 | 20 | 1 | 21 | 0.92 | 0.96 |
| Jiangxi | 44.57 | 36 | 7 | 43 | 0.81 | 0.96 |
| Sichuan | 80.42 | 46 | 26 | 72 | 0.57 | 0.90 |
| Chongqing | 28.85 | 21 | 4 | 25 | 0.73 | 0.87 |

TABLE 25.23. GEOGRAPHICAL DISTRIBUTION OF LINACS AND COBALT-60 MACHINES PER MILLION, IN DIFFERENT PROVINCES, CITIES OR AUTONOMOUS REGIONS OF CHINA IN 2011 (BY PER CAPITA MACHINES) [25.65] (cont.)

| Province (including municipalities) | Population (in millions) | Linacs | Cobalt-60 machines | Linacs + cobalt-60 machines | Linacs (per million population) | Linacs + cobalt-60 machines (per million population) |
|---|---|---|---|---|---|---|
| Hunan | 65.68 | 47 | 8 | 55 | 0.72 | 0.84 |
| Hainan | 8.67 | 7 | 0 | 7 | 0.81 | 0.81 |
| Guangdong | 104.30 | 69 | 14 | 83 | 0.66 | 0.80 |
| Gansu | 25.58 | 15 | 3 | 18 | 0.59 | 0.70 |
| Qinghai | 5.63 | 2 | 1 | 3 | 0.36 | 0.53 |
| Ningxia | 6.30 | 3 | 0 | 3 | 0.48 | 0.48 |
| Guizhou | 34.75 | 10 | 4 | 14 | 0.29 | 0.40 |
| Yunnan | 45.97 | 14 | 0 | 14 | 0.30 | 0.30 |
| Tibet | 3.00 | 0 | 0 | 0 | 0.00 | 0.00 |

this form of treatment every year. However, the actual number of patients receiving treatment is 569 056 per year [25.65].

Lack of awareness on the part of primary and secondary care doctors referring patients for radiotherapy treatment, patients' misconceptions of the side effects of radiotherapy together with low reimbursement rates prevent a large number of cancer patients from receiving the benefits of radiotherapy treatment in China. In order to remove misunderstandings, appropriate and timely radiation oncology education should be made available to patients, doctors and the general public.

In addition to large discrepancies in radiotherapy facilities and human resources between less developed areas and faster developing parts of the country, China is also facing serious challenges from a growing ageing population, indicating a future increase in the incidence of cancer. Despite impressive developments over the past 25 years in the area of radiation oncology human resources, there is still a deficiency in the number of medical physicists. Estimates based on the recommendation of the IAEA indicate that there should have been 2400–3200 medical physicists in mainland China by 2011. However, the reality is that there are only 1887 medical physicists involved in clinical practice. Therefore, well structured medical physics graduate and residency programmes as well as academic accreditation systems are needed. To tackle the challenges facing radiation oncology services in China will require not only further investment in equipment and staffing but also innovative methods of managing workload to shorten the patient pathway through the process of radiotherapy planning and treatment.

## 25.7. LATIN AMERICA — E. Rosenblatt, E. Zubizarreta, L.A. Linares

### 25.7.1. Background

The Latin American region comprises a total of 28 countries (including dependencies) and an estimated total population of 576 million. The predominant languages spoken are Spanish and Portuguese. English, French and Dutch are also spoken in the Caribbean and there are many indigenous languages spoken across the region. The majority of countries in Latin America are classified as LMICs. However, the following are considered upper middle income countries as per the World Bank's classification: Argentina, Costa Rica, Mexico and Panama. Chile and Uruguay are high income countries as of March 2017.

### 25.7.2. Cancer epidemiology

In 2012, there were a total of 1 096 056 new cancer cases, and the overall risk of getting cancer before the age of 75 was 16.8% [25.3]. There were 603 359 cancer deaths (55% of the incidence), and the risk of dying of cancer before the age of 75 was 10%. The five most frequent cancer types as defined by their crude incidence were prostate, breast, cervix uteri, colorectum, and lung cancer. Breast cancer (ASR (W) = 47.2) and cancer of the uterine cervix (ASR (W) = 21.2) are the most common in women, while prostate (ASR (W) = 54.2) and lung (ASR (W) = 18.7) cancer are the most common in men [25.3].

### 25.7.3. Radiotherapy resources

Zubizarreta et al. [25.31] reported the level of radiotherapy resources available in Latin American countries in 2003. A survey was conducted among 19 countries participating in an IAEA/ARCAL regional project. The authors reported the existence of 470 radiotherapy centres in the 19 target countries, with 710 teletherapy machines, of which 314 (44%) were linacs and 396 (56%) were cobalt-60 units. A classification of radiotherapy centres according to their level of development was used as follows: level 0 — has a stand-alone cobalt-60 machine; level 1 — offers teletherapy and brachytherapy, a treatment planning system, immobilization, a radiation oncologist and the services of a medical physicist at least part time; level 2 — offers simulator imaging, has the ability to make field specific blocks and offers the services of a full time medical physicist; and level 3 — has IMRT, stereotactic radiotherapy or IORT. Of the 470 centres, 85 (18%) were stand-alone teletherapy machines (level 0), of which five were not in use awaiting refurbishment; 51% were of level 1 standard; and 25% were of level 2. Fourteen centres (3%) were level 3, with nine specialized units devoted to stereotactic radiotherapy.

Since then, no systematic attempts have been made to update the radiotherapy infrastructure data in the region. DIRAC [25.4] contains information on infrastructure and staffing. The resources in the Latin American region are summarized in Table 25.24. The information is based on DIRAC, as of March 2013.

Figure 25.5 shows the situation with regard to radiotherapy centres, teletherapy machines, ancillary equipment and brachytherapy systems in the Latin American region between 2002 and 2012. The data have been gathered from three points in time as follows: data in 2002 are from the Zubizarreta et al. survey [25.31]; data in 2007 are from an update of that survey; and data in 2012 are from the DIRAC database. Based on these data, the teletherapy machine per

TABLE 25.24. SUMMARY OF RADIOTHERAPY RESOURCE ESTIMATES ACCORDING TO THE DIRAC DATABASE (AS OF 23 MARCH 2013)

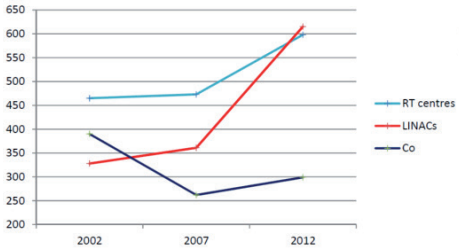
| | No. of countries | No. of radiotherapy centres | Linacs | Cobalt-60 units | Teletherapy machines (linacs and cobalt-60 units) | Teletherapy machines/million | Brachytherapy systems |
|---|---|---|---|---|---|---|---|
| Latin America | 28 | 598 | 615 | 299 | 914 | 1.6 | 239 |

million rate for Latin America is 1.6. This compares with 14.4 for North America, 6.0 for Western Europe, 2.0 for Eastern Europe, 0.2 for Africa, 0.3 for Southeast Asia, 4.4 for Australia, and 7.0 for Japan.

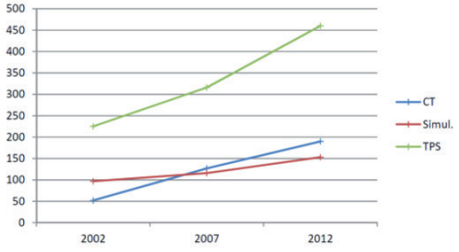
Assuming that 60% of cancer patients in LMICs will require radiotherapy, this means that in 2012, 657 633 patients required this treatment modality. If a standard teletherapy machine can, on average, treat 500 patients per year, then the total need in terms of teletherapy machines in 2012 (the reference year of Globocan epidemiological data) would be 1315 machines. Today, there are approximately 914 machines. This indicates a relative deficit of 401 machines in the whole region. This calculation is based on a number of assumptions, and does not take into account the case mix, fractionations used or the complexity of techniques for the teletherapy machine throughput.

### 25.7.4. Quality and access

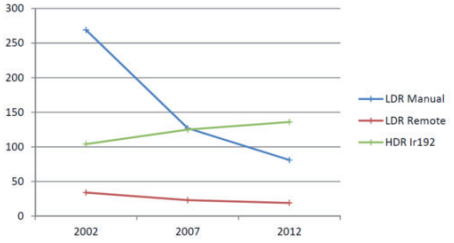
A notable characteristic of radiotherapy services across this region is the heterogeneity in terms of quality of the service. In particular, in the larger countries such as Brazil, Mexico and Argentina, well equipped and well staffed state of the art facilities — usually private centres — coexist with a majority of centres, which have to struggle with limited resources [25.66].




*Radiotherapy centres and teletherapy machines in Latin America (2002–2012). Note the crossing of the graphs for Co-60 and linacs.*




*CT units, simulators and treatment planning systems in Latin America (2002–2012). Note the increase in availability of all modalities.*




*Brachytherapy systems in Latin America (2002–2012). Note the predominance of HDR over LDR systems in 2012.*

*FIG. 25.5. Trends in radiotherapy infrastructure in Latin America between 2002 and 2012.*

Access to radiotherapy services is at best unequal. In most countries, a minority of cancer patients can access the private radiotherapy centres or seek treatment abroad, usually in the United States of America. Middle class patients are treated in the public system, in centres run by Ministries of Health or the social security network. Finally, poorer patients may get access to foundation hospitals or public hospitals which provide services free of charge or for a minimal fee, or in many cases may not have access to radiotherapy treatments at all. Countries and territories that do not offer any radiotherapy service at this time include Antigua, Belize, French Guiana, Grenada and Haiti.

In Ecuador, a cancer foundation takes almost exclusive action and provides services in the field of cancer and radiotherapy, with the Government relying solely on this organization. Currently, Ecuador is revising this structure and a new modernization plan for oncology and radiotherapy services is being discussed.

Venezuela has taken significant steps towards updating its radiotherapy infrastructure in a short period of time. Since training of human resources takes time, there has been a gap between technology acquisition and human resource development and placement, which the country is gradually addressing.

The regional professional society for radiation oncology (Latin American Association for Radiation Oncology (ALATRO)) established a regional school in 2010 through which it organizes and implements four regional courses every year. In this educational effort, ALATRO is supported by other national and international organizations such as SEOR (Sociedad Española de Oncología Radioterápica), ESTRO and the IAEA.

Many governments in the region have become aware of the important role of radiotherapy and other radiation medicine techniques in the context of cancer control and are investing accordingly. In addition, the region is witnessing significant developments in the private sector. New radiotherapy equipment is being purchased and installed, including linacs and HDR brachytherapy machines, and many centres have moved to modern treatment approaches such as 3-D conformal radiotherapy and IMRT. Thus, it can be said that over the last decade the region has experienced progress in terms of provision of services with better equipment. However, the development of human resources to operate this equipment has not followed suit. There is still a need for the training of professionals, and many radiotherapy departments are seriously understaffed, which is a safety risk. The problem is particularly acute in the case of medical physicists and RTTs.

While there are training programmes for radiation oncologists, many countries lack such programmes in medical physics and radiotherapy technology. The education programmes for RTTs are the most heterogeneous in Latin America, ranging from a five year academic programme in Chile to one year on the job training in Nicaragua.

The IAEA has been assisting its Member States in the implementation of technical cooperation projects in radiotherapy. Typical projects in the Latin American region in recent years have included: the establishment of an HDR brachytherapy unit in El Salvador; the initiation of an IMRT service in Bogota, Colombia; a new radiotherapy unit in Cuenca, Ecuador; stereotactic radiotherapy in Brazil; and training and education programmes in other countries (see Chapter 28, Success Stories in Radiotherapy Development Projects).

The region has clearly entered the path of introducing the new technologies and modernization of radiotherapy services, but the process is slow and variable, with some countries still lagging behind what is considered standard quality radiotherapy.

## 25.8. AUSTRALIA, NEW ZEALAND AND PAPUA NEW GUINEA — Eng-Siew Koh, T.P. Hanna, M.B. Barton

### 25.8.1. Introduction

Australia has a population of over 22 million and New Zealand 4 million people [25.67]. Both are classified as high income countries. In 2007, there were over 100 000 new cases of cancer diagnosed in Australia (excluding basal and squamous cell carcinoma of the skin), with the most commonly diagnosed cancers being prostate, bowel, breast, melanoma of the skin and lung cancer [25.68]. The incidence profiles are similar in New Zealand. In both countries, lung cancer accounted for the most cancer deaths in 2008 (19%), followed by colorectal, prostate and breast cancers [25.69]. In Australia, the age standardized death rate per 100 000 population due to cancer is 140.8 for men and 92.9 for women. The relative survival rate for cancer patients in Australia is among the best in an international comparison of six developed nations [25.70].

Radiotherapy services across Australia and New Zealand are predominantly outpatient based and provided in public sector specialist cancer care facilities. According to the IAEA's DIRAC database [25.4], there are currently 69 radiotherapy centres in Australia and eight in New Zealand. Megavoltage linacs for standard 3-D external beam radiotherapy, brachytherapy, as well as stereotactic radiotherapy for both cranial and extracranial applications are available in selected large metropolitan based centres. Across Australia and New Zealand, a wide range of current imaging technologies, including CT, magnetic resonance imaging (MRI), and positron emission tomography, are available for incorporation into radiation treatment planning. IMRT was first introduced around 2001 for head and neck cancers and is now available in most radiotherapy centres for selected tumour sites and clinical indications.

Other emerging technologies, including IGRT, volumetric modulated arc therapy and tomotherapy, are currently being evaluated for their clinical utility by relevant governmental and professional bodies and integrated into practice at selected treatment centres. A research MRI-linac located in Sydney will be one of four such facilities worldwide and will address the integration of cutting edge MRI technology into radiotherapy planning and treatment delivery. There are active clinical trials, including those trials undertaken by the cooperative Trans-Tasman Radiation Oncology Group.

### 25.8.2. Workforce

There have been several reports addressing radiation oncology, radiotherapy and radiation oncology medical physics (ROMP) workforce models and recommendations for workforce profiles. Currently, there remains a shortage in the ROMP workforce across Australia and New Zealand.

### 25.8.3. Radiotherapy utilization rate

The evidence based estimation of an optimal RTU rate (the proportion of notifiable cancers for which radiotherapy is the treatment of choice) is 52.3% [25.6]. In addition, 25% of cancer patients require re-treatment after having had a previous course of radiotherapy [25.71]. Palliative radiotherapy is optimally recommended as the first course of radiotherapy in 14% of all newly diagnosed cancers.

Despite this, there remains a gap between optimal and actual RTU rates. Radiotherapy utilization rates in New South Wales, the most populous Australian state, remained at 38% for the period between 1999 and 2008 because investment in new facilities only just kept pace with the increase in the number of new cases of cancer with an indication for radiotherapy [25.72].

### 25.8.4. Inequalities in access and disparities in cancer outcomes in select groups

Despite the high income status of Australia and New Zealand, certain patient groups such as indigenous Australians and the Maori in New Zealand [25.73] have a very different pattern of cancer incidence and survival [25.74]. These groups continue to experience disparities in cancer care, in addition to being distant from needed services, leading to poorer access to screening and treatment. They also face lifestyle and occupational factors which lead to increased cancer risk compared with urban counterparts, accounting in part for inferior clinical outcomes [25.74].

Considerable investments in radiotherapy facilities and workforce have been made by commonwealth and state governments in Australia to reduce underutilization of radiotherapy and disparities of access to radiotherapy services. These have included the development of regional cancer centres, as well as single machine units. These initiatives have met with some success in improving RTU rates and minimizing disparities in access [25.72].

### 25.8.5. Papua New Guinea

Papua New Guinea, classified in the low and middle income group, has a current population of over 6.8 million people dispersed over 600 islands. Registrations at the National Cancer Registry do not document the true burden of cancer in Papua New Guinea. It is estimated that there are over 16 000 new cancer cases annually, and conservatively at least 12 750 deaths per year due to cancer [25.75], giving Papua New Guinea one of the world's highest per capita cancer rates. Cancers account for about 8% of all deaths. The age standardized death rate per 100 000 due to cancer is 151.8 for men and 106.9 for women [25.67]. The four cancers with the highest incidence are oral cavity, cervix, liver and breast, the burden of which disproportionately affects women. However, three of these cancers are potentially preventable. Relevant prevention strategies include tobacco and betel nut control, hepatitis B virus vaccination and HPV vaccination, together with cervical cancer screening.

Although cancer in Papua New Guinea has been recognized in the National Health Plan, a comprehensive approach to cancer control is lacking, with cancer treatment services currently ineffective, limited or non-existent due to gaps in workforce, skills, radiation facilities and drug supply [25.75]. Reflecting these issues, Papua New Guinea has only one radiotherapy centre, located in Lae, where (as of 2013) one old cobalt-60 machine and two LDR brachytherapy afteroaders remain in use [25.4, 25.67]. Adequate local staffing and professional training remain significant issues. Strategies to strengthen the workforce include an ongoing Australasian College of Physical Scientists and Engineers in Medicine (ACPSEM) initiative which supports a volunteer medical physicist from Australia to help staff the Lae Cancer Unit. A 2001 report entitled The Hidden Burden: Cancer in Papua New Guinea [25.75] offered detailed recommendations on all aspects of cancer control, including the significant challenge of developing longer term sustainable radiotherapy services.

## 25.9. STATES OF THE FORMER SOVIET UNION: EASTERN EUROPE AND CENTRAL ASIA — E. Fidarova, V. Sinaika

### 25.9.1. Background

After the collapse of the former Soviet Union, the States in Eastern Europe and Central Asia that gained independence shared common challenges related to massive economic and social changes. The viability and functioning of health care systems were also affected [25.76].

While there were technological advances in radiotherapy, including the introduction of cross-sectional imaging into treatment planning and the development of 3-D conformal radiotherapy, during the late 1980s and early 1990s, the countries of the former Soviet Union faced major economic difficulties. In general, access to modern radiotherapy facilities was limited in the majority of these States [25.77]. Additionally, radiotherapy specialists were still relatively isolated, with insufficient access to the latest professional publications, and lacked acceptance of the evidence based approach in medicine [25.76].

Differences in socioeconomic development, culture and political preferences resulted in various degrees and directions of reforms of health care systems. Countries began to diverge from each other, and gaps in the status of different medical services increased. The dynamics of health expenditure per capita can be used as an indirect indicator of this trend (Fig. 25.6).

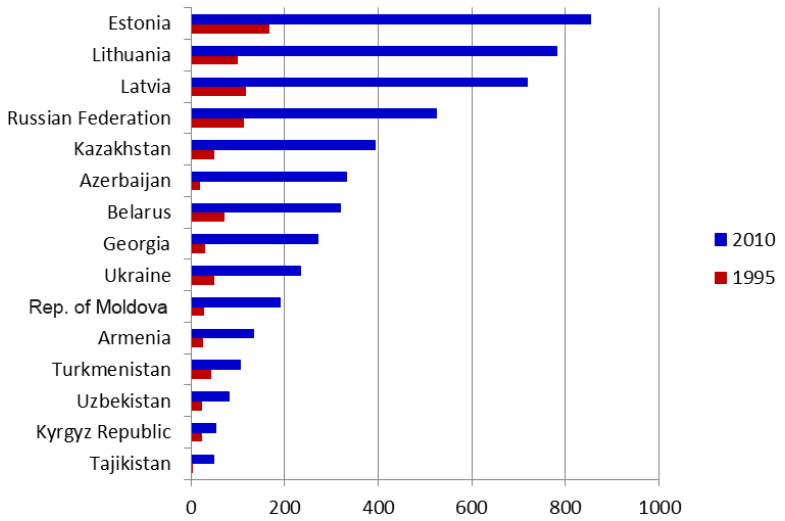



*FIG. 25.6. Dynamics of health expenditure per capita in Eastern Europe and Central Asia (current US $): 1995 versus 2010.*

After joining the European Union (EU) in 2004, the Baltic States (Estonia, Latvia and Lithuania) continued efforts towards harmonization of their radiotherapy practice according to EU standards. The situation in those countries is quite different from that in the rest of the region and will not be covered in this section.

According to World Bank data, the majority of countries in the region belong to the middle income group (five in the lower middle income group and four in the upper middle income group), whereas Kyrgyzstan and Tajikistan are classified as low income countries. The Russian Federation is the only country in the region which is in the high income group (Table 25.25).

TABLE 25.25. SELECTED INDICATORS IN COUNTRIES OF EASTERN EUROPE AND CENTRAL ASIA

| | Population (thousands) | Cancer incidence (thousands) | GNI per capita 2012 (US $) | Income group |
|---|---|---|---|---|
| Armenia | 3 108 | 10.9 | 3 720 | LMI |
| Azerbaijan | 9 421 | 13.9 | 6 220 | UMI |
| Belarus | 9 527 | 32.4 | 6 530 | UMI |
| Georgia | 4 304 | 12.4 | 3 210 | LMI |
| Kazakhstan | 16 381 | 40.4 | 9 710 | UMI |
| Kyrgyzstan | 5 448 | 5.8 | 990 | LI |
| Rep. of Moldova | 3 519 | 9.9 | 2 070 | LMI |
| Russian Federation | 142 703 | 458.4 | 12 700 | HI |
| Tajikistan | 7 078 | 5.5 | 860 | LI |
| Turkmenistan | 5 169 | 6.0 | 5 410 | UMI |
| Ukraine | 44 940 | 141.0 | 3 500 | LMI |
| Uzbekistan | 28 077 | 22.6 | 1 720 | LMI |

**Note:** HI — High income; LMI — lower middle income; UMI — upper middle income; LI — low income.

### 25.9.2. Cancer epidemiology

Cancer is the second most common cause of mortality in the region. More than 50% of all cancer cases are diagnosed at advanced stages (III and IV). The distribution of the most common malignancies is given in Table 25.26 [25.3]. Among the risk factors it is worth mentioning tobacco smoking, rates for which remain among the highest in the world. Smoking rates among men are reported to be above 50% in Belarus, Georgia, Kyrgyzstan and Ukraine, and 60% or more in Armenia, Kazakhstan and the Russian Federation [25.78].

### 25.9.3. Radiotherapy resources

In general, the status of radiotherapy equipment in centres in this region is less than optimal. The number of MV machines per million population ranges between 0 and 3.1. However, this indicator exceeds 2 MV machines per million only in Belarus, Kazakhstan, the Russian Federation and Ukraine (Table 25.5). For comparison, in Western Europe the number of MV machines per million population is around 5.5 [25.27]. Additionally, the number of machines itself does not reveal the true situation, as most equipment is outdated and often non-operational. For example, in Ukraine, only 15% of existing radiotherapy equipment is less than ten years old. The rest was manufactured between 1976 and 2000 (23% before 1980, 35% between 1980 and 1989, and 27% between 1990 and 2000) [25.79]. In the Russian Federation, in more than 75% of radiotherapy departments 90% of the equipment is outdated and does not meet modern quality and safety requirements. Often, the difference between planned and delivered dose reaches 30% [25.80, 25.81]. In Central Asian countries the situation is even more dramatic, as access to radiotherapy either does not exist, as in Turkmenistan, or is very limited, as in Kyrgyzstan, Tajikistan and Uzbekistan. In Tajikistan, less than one third of patients who require radiotherapy receive it. The main reasons are not only the insufficient number of treatment units and qualified staff, but also geographical and economic constraints, insufficient referral to radiotherapy as a result of miscommunication between health professionals, lack of awareness by referring physicians, and inadequate indications for radiotherapy from radiation oncologists.

The technical capabilities of the radiotherapy centres in the region are quite variable, with some institutions being better equipped than others. However, the situation with regard to human resources is quite similar. Table 25.28 shows the staffing levels in radiotherapy. There is a shortage of all radiotherapy professionals, especially medical physicists and RTTs.

The problems these countries are facing can be illustrated by the case of the Russian Federation. Currently, radiotherapy there is lagging substantially when

TABLE 25.26. MOST COMMON MALIGNANCIES IN COUNTRIES OF EASTERN EUROPE AND CENTRAL ASIA [25.3]

| | Most common cancers | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| Armenia | Breast | Lung | Colorectum | Stomach | Corpus uteri |
| Azerbaijan | Breast | Stomach | Lung | Colorectum | Brain, nervous system |
| Belarus | Lung | Colorectum | Breast | Stomach | Prostate |
| Georgia | Breast | Lung | Stomach | Brain, nervous system | Colorectum |
| Kazakhstan | Breast | Lung | Colorectum | Stomach | Cervix uteri |
| Kyrgyzstan | Stomach | Breast | Cervix uteri | Lung | Colorectum |
| Republic of Moldova | Colorectum | Lung | Breast | Stomach | Cervix uteri |
| Russian Federation | Colorectum | Breast | Lung | Stomach | Prostate |
| Tajikistan | Stomach | Oesophagus | Breast | Corpus uteri | Lung |
| Turkmenistan | Oesophagus | Stomach | Breast | Lung | Colorectum |
| Ukraine | Colorectum | Lung | Breast | Stomach | Corpus uteri |
| Uzbekistan | Breast | Stomach | Cervix uteri | Lung | Oesophagus |

TABLE 25.27. EXISTING RADIOTHERAPY EQUIPMENT IN COUNTRIES OF EASTERN EUROPE AND CENTRAL ASIA [25.17]

| | No. of radiotherapy centres | No. of linacs operational/total | No. of Co-60 units operational/total | No. of brachytherapy systems operational/total | No. of operational MV machines per million population |
|---|---|---|---|---|---|
| Armenia[a] | 2 | 1/2 | 3/3 | 2/3 | 1.3 |
| Azerbaijan[a] | 3 | 4/4 | 3/3 | 1/1 | 0.7 |
| Belarus | 13 | 11/11 | 18/18 | 18/18 | 3.1 |
| Georgia[a] | 4 | 2/2 | 1/4 | 2/2 | 0.7 |
| Kazakhstan[a] | 17 | 7/7 | 27/27 | 17/17 | 2.1 |
| Kyrgyzstan[a] | 1 | 0 | 1/2 | 0/1 | 0.2 |
| Rep. of Moldova[a] | 1 | 1/1 | 2/2 | 1/1 | 0.9 |
| Russian Federation[a,b] | 141 | 139 | 234 | 94 | 2.6 |
| Tajikistan[a] | 1 | 0 | 1/1 | 1 | 0.1 |
| Turkmenistan | 0 | 0 | 0 | 0 | 0 |

TABLE 25.27. EXISTING RADIOTHERAPY EQUIPMENT IN COUNTRIES OF EASTERN EUROPE AND CENTRAL ASIA [25.17] (cont.)

| | No. of radiotherapy centres | No. of linacs operational/total | No. of Co-60 units operational/total | No. of brachytherapy systems operational/total | No. of operational MV machines per million population |
|---|---|---|---|---|---|
| Ukraine[a] | 54 | 19/21 | 85/86 | 35/46 | 2.3 |
| Uzbekistan | 13 | 1 | 17 | —[c] | 0.6 |

[a] Personal communication (see acknowledgements).
[b] Only the total number is available.
[c] —: data not available.

compared with modern standards [25.82]. The regulatory and legal framework is outdated and is not applicable to modern radiotherapy departments, which are characterized by increased complexity of treatment procedures. There is also a generation gap among radiotherapy professionals. Education and training programmes for these individuals either are not in accordance with international standards (for radiation oncologists) or do not exist (for medical physicists and RTTs) [25.4]. Mechanisms for professional accreditation, certification and continuing medical education are not developed.

TABLE 25.28. HUMAN RESOURCES IN RADIOTHERAPY [25.82]

| | Radiation oncologists | Medical physicists | RTT (working as such) |
|---|---|---|---|
| Armenia[a] | 15 | 3 | 8 |
| Azerbaijan[a] | 24 | 6 | 18 |
| Belarus[a] | 137 | 70 | 108 |
| Georgia[a] | 18 | 9 | 23 |
| Kazakhstan[a] | 102 | 33 | ~100 |
| Kyrgyzstan[a] | 15 | 3 | 5 |
| Rep. of Moldova[a] | 20 | 4 | 12 |
| Russian Federation[a] | 1854 | 310 | 1800 |
| Tajikistan[a] | 5 | 2 | 4 |
| Turkmenistan | 0 | 0 | 0 |
| Ukraine[a] | 461 | 183 | 57 |
| Uzbekistan | —[b] | —[b] | —[b] |

[a] Personal communication (see acknowledgements).
[b] —: data not available.

In the Russian Federation, the profession of medical physicist was officially recognized only in 2009, while in other countries in the region it does not yet exist. The profession of RTT is not recognized in any of these countries. The usual responsibilities of RTTs, such as operating a treatment unit and patient positioning and immobilization, are carried out mostly by nurses who have received additional brief on the job training. In general, as a result of the lack of specialized education, the quality of the workflow is below the minimum European standard (e.g. one RTT at the treatment unit per shift, inadequate positioning of patients and minimal use of immobilization devices).

Modernization and strengthening of radiotherapy is an ongoing process in all countries of the former Soviet Union. Taking into account the existence of a common working language (Russian) and pre-existing links between countries and institutions, it could be beneficial to have a subregional approach in addressing common problems and sharing experience. The IAEA can facilitate the process of gaining better understanding of the current practices, infrastructure and education in these countries, which in turn will help to improve communication and inform these States of the way that the IAEA and other international organizations can assist their radiotherapy centres.

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# Part VIII

# INTERNATIONAL INITIATIVES

# Chapter 26

# THE ROLE OF THE INTERNATIONAL ATOMIC ENERGY AGENCY

**E. Rosenblatt, E. Zubizarreta, R.K. Chhem**

The IAEA is an independent, intergovernmental science and technology based organization within the United Nations system that serves as the global focal point for nuclear cooperation. Article II of the IAEA Statute states: "The Agency shall seek to accelerate and enlarge the contribution of atomic energy to peace, *health* and prosperity throughout the world" (emphasis added) [26.1]. With regard to radiotherapy, the IAEA has as its objective to enhance Member State capabilities to establish sound policies for radiotherapy and cancer treatment, and to ensure the effective, efficient and safe utilization of current and future radiotherapy technologies.

Epidemiological projections indicate that if current trends continue, the global cancer burden will increase from 12.6 million new cases per year in 2008 to 16.9 million per year by 2020 [26.2]. Seventy per cent of these cases will be in the developing world, where the number will grow from 5.2 million per year to 8.8 million per year by 2020 [26.3]. The IAEA's Directory of Radiotherapy Centres (DIRAC) [26.4] contains data on centres providing radiotherapy services worldwide. This database includes data on equipment (teletherapy and brachytherapy), on imaging and dosimetry, and on staffing and the number of patients treated annually. According to DIRAC, as of January 2017 there are 13 856 teletherapy machines operational worldwide, not counting particle therapy or circular accelerators. Of those, 27 are in low income countries, 1123 are in lower middle income countries, 3822 are in upper middle income countries and 8884 are in high income countries. These figures provide a snapshot as of the date of writing. They are dynamic and constantly changing. This disparity points to the fact that, according to current projections, the largest increase in the incidence of cancer will occur in countries and regions of the world that are poorly prepared to cope with it, even at current levels.

## 26.1. THE IAEA'S TECHNICAL COOPERATION PROGRAMME

The technical cooperation (TC) programme is the main mechanism through which the IAEA delivers services to its Member States. Through this programme, the IAEA assists Member States in building, strengthening and maintaining capacities in the safe, peaceful and secure use of nuclear technology in support of sustainable socioeconomic development. TC projects provide expertise in fields where nuclear techniques offer advantages over other approaches, or where nuclear techniques can usefully supplement conventional means. All IAEA Member States are eligible for support, although in practice technical cooperation activities tend to focus on the needs and priorities of less developed countries.

The TC programme focuses on applying nuclear technology to improve human health, support agriculture and rural development, advance water resource management, address environmental challenges and promote sustainable energy development, including the use of nuclear power for electricity. The programme also seeks to strengthen nuclear safety and security.

The TC programme operates in four geographical regions: Africa, Asia and the Pacific, Europe, and Latin America and the Caribbean. Following guidelines contained in its 'Country Programme Framework', the IAEA helps Member States within each region to address their specific needs, taking into consideration existing capacities and different conditions. The programme aims to leverage the differences among Member States in the same region by facilitating cooperation between them. For example, the capacities of technically advanced countries can be used to address the needs of less advanced countries.

IAEA TC projects in radiotherapy include the establishment or upgrading of radiotherapy facilities, the installation of high dose rate (HDR) brachytherapy units, quality assurance (QA) and training support for 3-D conformal radiotherapy or intensity modulated radiation therapy (IMRT) projects, training radiotherapists (RTTs) or establishing radiation oncology programmes, among others. In all these projects, the IAEA provides technical advice on radiotherapy issues, equipment and training required to bring the project to successful completion. Between 1980 and 2012, the IAEA provided US $263 million in cancer related assistance to developing countries (Fig. 26.1).


*FIG. 26.1. IAEA expenditures on cancer related TC projects between 1980 and 2007.*

## 26.2. EXAMPLES OF IAEA SUPPORT FOR RADIOTHERAPY SERVICES[1]

In Kenya, three RTTs and two course coordinators were trained in Cape Town, South Africa, under a project entitled Expanding Radiotherapy Services and Establishing a Training Programme for Radiation Therapy Technologists. The team subsequently started Kenya's first training programme for RTTs, which covers diagnostic imaging, nuclear medicine, radiotherapy and ultrasound. Fourteen students are currently enrolled in the programme.

[1] The examples in this section are taken from the IAEA Technical Cooperation Report for 2011, Report by the Director General, GC(56)/INF/4, IAEA, Vienna (2012).

In Zimbabwe, a single energy linear accelerator (linac) was procured under a project aimed at strengthening existing training programmes for radiation oncologists, medical physicists and RTTs. The Government of Zimbabwe provided US $1 million in extrabudgetary funds. The equipment will benefit patients at the Department of Radiology in the Parirenyatwa Group of Hospitals in Harare. The IAEA also supported a training programme in radiation oncology through improved teaching facilities and training for scientists and professionals.

Zambia's Cancer Diseases Hospital in Lusaka has state of the art equipment, including a linac, an HDR brachytherapy unit, and a cobalt-60 machine (see Chapter 28, Success Stories in Radiotherapy Development Projects). A project aimed at improving the quality of cancer treatment contributed to improving the quality of newly trained staff in medical physics and oncology, as well as training nursing staff in oncology. Through the project, an overall improvement has been achieved in the quality of services provided and the number of patients treated by the Radiotherapy Oncology Centre, Lusaka.

Several years of IAEA assistance resulted in important upgrades to the radiotherapy facilities in Mongolia. Qualified RTTs and medical physicists are now available, and a QA system was established and implemented in 2011. TC projects, with technical support provided through the IAEA's human health programme, have made an important contribution to increasing the knowledge and skills of radiation oncologists, medical physicists and RTTs.

A radiotherapy centre was established in the Oncological Dispensary in Ganja, Azerbaijan, under a project entitled Upgrading Radiation Oncology in the National Oncology Centre, with the Government sharing the cost of major equipment items.

Two radiation oncologists, a medical physicist and an RTT have received extensive training, both in the National Oncology Centre and in hospitals, in the Czech Republic. A modern cobalt-60 radiotherapy unit was provided and the quality of radiotherapy treatment was also improved with a modern treatment planning system (TPS) and the introduction of new radiotherapy protocols and a QA/quality control (QC) programme.

Seven fellowships and two Quality Assurance Team for Radiation Oncology (QUATRO) audits were carried out in Slovakia under a project entitled Upgrading Radiotherapy Services. These have improved the ability of the National Cancer Institute to offer training to other radiotherapy provider services in Slovakia who intend to move from classic radiotherapy to modern image guided radiation therapy and IMRT techniques. Counterparts were supplied with additional tools for clinical QA.

## 26.3. COORDINATING RESEARCH FOR AND IN MEMBER STATES

Article III of the IAEA Statute authorizes the IAEA to "encourage and assist research on, and development and practical application of, atomic energy for peaceful uses throughout the world" and to foster the exchange of scientific and technical information, as well as the "exchange of training of scientists and experts in the field of peaceful uses of atomic energy" [26.1]. The IAEA's coordinated research activities stimulate and coordinate research in selected nuclear fields by scientists in IAEA Member States.

The IAEA's coordinated research projects (CRPs) bring together research institutes in both developing and developed Member States to collaborate on topics of common interest. Research, technical and doctoral contracts are awarded to institutes in Member States for their completion of research work under these CRPs. The IAEA may also respond to proposals from institutes for participation in research activities under individual research contracts not related to a CRP. A small portion of available funds is used to finance individual projects which deal with topics covered by the IAEA's scientific programme.

The IAEA is currently conducting 12 CRPs in radiotherapy/radiobiology. The majority — nine — are clinical radiation oncology research projects of relevance to the radiation oncology community at large and of particular applicability in countries with limited resources exploring less resource intensive strategies.

In IAEA clinical trials, the accrual, treatment and follow-up of patients take place in selected radiotherapy centres around the world. Data are managed centrally by a data management and statistics centre, and the results are analysed by a professional team that includes IAEA staff. The CRP methodology adheres to the principles of the Declaration of Helsinki and good clinical practice guidelines for clinical research. Three of the 12 CRPs currently deal with radiation biology topics: stem cell research (aiming to decrease radiation induced normal tissue damage), radiation sterilization for tissue banking and biological dosimetry. The results of IAEA CRPs and expert meetings are presented in IAEA publications that are freely available to Member States [26.5–26.7], as well as in scientific peer reviewed journals [26.8–26.14].

## 26.4. SCIENTIFIC AND TECHNICAL PUBLICATIONS, TRAINING AND COMMUNICATION

The IAEA is a leading publisher in the nuclear field. Its scientific and technical publications include international safety standards, technical guides, conference proceedings and scientific reports.

### 26.4.1. Training and education of professionals

The importance of training and education in the radiation medicine disciplines cannot be overemphasized. The lack of radiation medicine professionals — in numbers and training — is one of the main obstacles for the successful implementation of national radiotherapy strategies in countries and regions.

The problem is addressed at various levels:

— Producing educational materials.
— Making existing materials available to centres with limited resources, in their local language.
— Organizing and conducting training events such as courses and workshops.
— Planning long term training and education on a national or regional scale. A particularly successful output has been the IAEA's 'Applied Sciences of Oncology' distance learning course, which had more than 2000 downloads in three years [26.14].

The IAEA has published a full series of syllabi for the education and training of radiotherapy professionals. The series includes a syllabus for radiation oncologists (endorsed by the European Society for Radiotherapy and Oncology (ESTRO) and the American Society for Radiation Oncology (ASTRO)), medical physicists, RTTs, radiation oncology nurses and radiation biologists. In these and other publications, careful attention is given to modern concepts in education and educational QA, working with educationalists who are IAEA staff members.

Recently, a 'Human Health Campus' web site was launched aimed at radiation medicine professionals (Fig. 26.2). The Human Health Campus (http://humanhealth.iaea.org) is an educational and resource web site for health professionals in radiation medicine (nuclear medicine, diagnostic imaging, radiation oncology and medical radiation physics) and nutrition. The IAEA seeks to foster a collaborative learning environment. Because medical and scientific knowledge evolves rapidly, this web site is updated regularly to ensure the quality of the IAEA's teaching and learning materials. Didactic materials have been designed to integrate the entire curriculum in radiation medicine, with expert advice and support from physicians, physicists, nutritionists and educationalists.


*FIG. 26.2. The IAEA Human Health Campus web site.*

The main goal of the Human Health Campus is to provide radiation medicine professionals with information for strengthening and improving their clinical practices and quality management through the use of up to date educational materials created by experts in the field. The web site is divided into six areas: Nuclear Medicine, Radiopharmacy, Radiation Oncology, Medical Physics, Technologists and Nutrition. Additional sections dedicated to teaching and diagnostic radiology are under construction. The establishment of these learning resources is founded on sound educational principles using a student centred approach, with active learning achieved through the use of lectures, interactive case studies, webinars and videos containing questions and answers, which are essential educational tools for a self-directed learning process.

The IAEA supports the education and training of professionals by funding and offering fellowships abroad when training is not possible within the country. The duration of fellowships varies from a few weeks or months to full professional training requiring years.

The IAEA has long recognized the high quality of ESTRO teaching courses. Since 1997, the IAEA has sponsored the participation in ESTRO courses of more than 1600 participants, mainly from central and eastern Europe and the Commonwealth of Independent States region. Since 2008, ESTRO and the IAEA have been conducting the ‘Best Practice in Radiation Oncology’, a process to train the trainers for RTTs.

### 26.4.2. Directory of Radiotherapy Centres

Since 1959, the IAEA has maintained a registry of radiotherapy hospitals and clinical institutions having radionuclide and high energy teletherapy machines for medical use — DIRAC. This registry was first published in book form in 1968. The present web based version of DIRAC is updated continuously, based on replies to questionnaires circulated by the IAEA among its Member States. It includes data not only on teletherapy machines, but also on sources and devices used in brachytherapy, and on equipment for dosimetry, patient dose calculation and QA. Information on staff strength at the installations (radiation oncologists, medical physicists, RTTs) is included as well. DIRAC is the only centralized database that describes current worldwide capacity for the delivery of radiotherapy. This unique quality of DIRAC allows extraction of the information necessary for analysis of the status of radiotherapy and estimation of the need for facilities in various countries or regions, or around the world.

### 26.4.3. Auditing beams

The IAEA/World Health Organization (WHO) thermoluminescent dosimetry (TLD) postal audit service has been used for over 8000 radiotherapy beams throughout the world over four decades. Analysis of these data has yielded much valuable information. In the early years, the TLD service recorded approximately 50% of audited beams having adequate calibration. This percentage of acceptable results has now increased to 96%. Clearly, regular participation in dosimetry audits leads to an improvement in dosimetry practices in radiotherapy in many hospitals worldwide. Another dosimetry audit programme for treatment planning (TPS audit) in external beam radiotherapy developed by the IAEA assesses the radiotherapy workflow for conformal techniques, from patient data acquisition and computerized treatment planning to dose delivery. The IAEA supports national and subregional TPS audit activities to improve the quality and safety of dose calculation in radiotherapy.

### 26.4.4. Comprehensive audits of radiotherapy centres

Another audit mechanism operated by the IAEA is QUATRO (Quality Assurance Team for Radiation Oncology), which delivers a comprehensive audit that reviews infrastructure, patient and equipment procedures, QA programmes, radiation protection, staffing levels and professional training of the local radiotherapy staff with the aim of improving quality. To date, more than 70 QUATRO audits and follow-up missions have been organized by the IAEA in radiation oncology centres in Africa, Asia, Europe and Latin America.

QUATRO audits identify and document areas for improvement in technology, human resources or procedures, and provide advice for further development of the audited centres. Overall, QUATRO audits have contributed to improvements at centres and have identified common issues to be addressed internationally. An example is the training of RTTs in central and eastern Europe now being implemented through the IAEA's cooperation with ESTRO.

### 26.4.5. Challenges of the introduction of new technologies

The actual or potential use of new, advanced radiotherapy technologies raises questions about their cost, efficacy and even ethics. The increased capital and operating costs and the burden of the increased QA are challenges. Some of the new technologies have the advantages of improved dose distributions and time savings, but require well qualified personnel and demanding QA/QC programmes. Advanced technology options in radiation oncology must be considered in the context of the needs and priorities of countries in terms of their essential infrastructure in order to allow for a smooth, incremental and safe progression.

An important theme echoed by experts is the shortage of skilled radiotherapy professionals in low and middle income countries (LMICs). While in the short term local solutions have been devised, there is still a need in many countries for long term workforce planning. Training must be adapted to both the working environment and the available technology; little benefit is derived by a country or institution when trainees are exposed to a technology not available locally. However, LMICs continue to follow the path of developing radiotherapy technology. The IAEA accompanies them on this path and provides guidance for a sound and effective transition.

As an example: the IAEA provides assistance to a group of 32 countries in central and eastern Europe, and States of the former Soviet Union. In some of these countries, governments are modernizing the radiotherapy infrastructure. Experience reveals heterogeneity in the level of radiotherapy development in these countries, which have different needs and priorities. Accordingly, a process of assessment of the current radiotherapy landscape has been undertaken to bridge gaps between countries in this region. The results of this process will be of value to the IAEA and other organizations in developing a framework for assistance and collaboration [26.15].

### 26.4.6. Programme of Action for Cancer Therapy

Cancer is a global problem and should be on the international health agenda because it affects millions in every country around the world. Tackling the

problem requires significant resources. The international community is aware of the need for better cooperation and coordinated efforts among all national and international stakeholders.

In response to the developing world's growing cancer crisis, the IAEA established the Programme of Action for Cancer Therapy (PACT) in 2004 to realize the public health impact obtained through technology transfer in radiotherapy and nuclear medicine. PACT was launched as an IAEA initiative, but its vision is for a global public–private partnership to confront the cancer crisis. Along these lines, in 2009 a joint programme for cancer control was established with WHO. This programme allows close collaboration with WHO and other key international health organizations, through a coordinated global response, in developing strategies and plans for working with LMICs in the design and implementation of comprehensive cancer control programmes.

PACT presents ambitious long term goals for the next 20 years. These goals are:

(a) To build a global public–private partnership of interested organizations committed to addressing the challenge of cancer in LMICs in all its aspects;
(b) To mobilize resources from charitable trusts, foundations, and others in the public and private sectors to assist LMICs in developing and implementing their radiation medicine capacities within a national cancer control programme;
(c) To ensure the effective and sustainable transfer of radiation medicine technologies or knowledge to all LMICs where unmet needs exist.

In the short term, the IAEA is working through PACT with WHO and other partners to raise cancer awareness on a global scale, assess needs in individual countries or regions and develop demonstration projects in selected countries that will attract donors to support these life saving initiatives to help sustain and replicate positive outcomes.

### 26.4.7. The AGaRT initiative to address a global radiotherapy shortage

Radiotherapy, diagnostic radiology, nuclear medicine and medical physics are essential for detecting, diagnosing, staging and treating cancer. Radiotherapy can, in many instances, save lives. Even in cases where the disease is too advanced to be cured, radiotherapy can provide palliation that allows patients to live out their lives as comfortably as possible. In high income countries, more than 50% of patients diagnosed with cancer will be administered radiotherapy at some point during their treatment. For many living in LMICs, radiotherapy remains an unattainable treatment option, with only 25% of patients for whom

radiotherapy is indicated in these countries having access to the radiotherapy treatment they need to increase their chances of survival.

Today, over 25 countries have no available radiotherapy units, leaving cancer patients living in those countries (or their governments) to spend enormous sums of money to be treated abroad or, more commonly, to go without treatment [26.16]. However, even when radiotherapy is available, it is often inadequately resourced for the number of cancer patients in need of care. Most high income countries have at least one radiotherapy machine available for every 250 000 people. In contrast, in nearly 20 LMICs, each unit must provide services for more than five million people and, in some cases, for 20 million or more people. But more than just greater availability of equipment is required to address the issue of global access to radiotherapy. In some countries, even if radiotherapy services are available, economic or geographical barriers can prevent treatment. In others, inadequate staffing, the acquisition of unsuitable equipment or poor equipment maintenance can leave cancer patients without proper access to treatment. Until LMICs can acquire the proper capacity for providing radiotherapy, millions of cancer patients throughout the world will continue to be deprived of an essential element of cancer treatment and palliation.

To address the shortfall of radiotherapy services in LMICs, the IAEA established the Advisory Group on Increasing Access to Radiotherapy Technology in Low and Middle Income Countries (AGaRT) in 2009 under PACT. AGaRT acts as a facilitator to bring together major radiotherapy equipment suppliers with users in LMICs to encourage a dialogue that will ensure that the unique radiotherapy service requirements of LMICs are met by the technology available. AGaRT provides a unique platform to:

(a) Assess current radiotherapy opportunities and capacities to increase access to radiotherapy technology;
(b) Identify gaps in the accessibility of radiotherapy services and the limitations in the delivery, operation and maintenance of radiotherapy equipment in LMICs;
(c) Review and recommend criteria for radiotherapy equipment that is affordable, effective and appropriate for the conditions of LMICs;
(d) Review and recommend minimum requirements to operate a radiotherapy facility safely and ensure its sustainability in LMICs.

It is envisioned that, through these activities, AGaRT will establish a mutual understanding among radiotherapy users and suppliers to address issues of cost, quality, availability, sustainability and complexity. AGaRT will encourage the selection of radiotherapy equipment that is affordable, sustainable and suitable for LMICs and, in so doing, increase access to radiotherapy.

To achieve universal access to radiotherapy services, a comprehensive strategy that can address all aspects of radiotherapy acquisition and use must be developed. Urgent solutions are needed as, by 2020, annual cancer cases in LMICs are expected to rise by 30%, to 10.3 million. AGaRT is working to drive down the cost of radiotherapy and to provide more sustainable and efficient equipment to treat patients by encouraging manufacturers to simplify their designs, while maintaining a consistently high level of safety and quality. However, AGaRT's efforts are only the first steps. International radiotherapy stakeholders need to continue to work together to ensure that AGaRT's outcomes are put to use as a complement to all other ongoing efforts, so that, eventually, radiotherapy will be accessible as an affordable, appropriate and sustainable technology for LMICs.

## 26.5. KEY POINTS

— The IAEA's technical cooperation programme is the main mechanism through which the IAEA delivers services to its Member States.
— Coordinated research projects bring together research institutes in both developing and developed Member States to collaborate on research topics of common interest.
— The IAEA is a leading publisher in the nuclear field. Its scientific and technical publications include international safety standards, technical guides, conference proceedings and scientific reports.
— The IAEA Human Health Campus is an educational and resource web site for health professionals in radiation medicine and nutrition.
— The IAEA's Directory of Radiotherapy Centres (DIRAC) is the only centralized database that describes current capacity for the delivery of radiotherapy worldwide.
— An audit modality operated by the IAEA within the framework of its Quality Assurance Team for Radiation Oncology (QUATRO) comprehensively reviews all aspects of work at radiotherapy departments.
— Advanced technology options in radiation oncology must be considered in the context of the needs and priorities of countries in terms of their essential infrastructure, in order to allow for a smooth, incremental and safe progression.
— Low and middle income countries (LMICs) follow the path of developing radiotherapy technology. The IAEA accompanies them on this path and provides guidance for a sound and effective transition.
— The Advisory Group on Increasing Access to Radiotherapy Technology in Low and Middle Income Countries (AGaRT) acts as a facilitator to bring together radiotherapy users in LMICs and major radiotherapy equipment

suppliers to encourage a dialogue that will ensure that the unique radiotherapy service requirements of LMICs are met by the technology available.

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# Chapter 27

# INTERNATIONAL ORGANIZATIONS INVOLVED IN CANCER RADIOTHERAPY

**A. Zietman, V. Valentini, P. Jimenez, S. Luciani, M. Gospodarowicz**

## 27.1. AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO)

The American Society for Radiation Oncology (ASTRO) was founded in 1958 with the goal of providing a unified voice for the emerging discipline of radiation oncology. Until the 1990s, its focus was primarily academic, organizing an annual scientific and educational meeting and providing research awards and recognition. In the 1990s, however, the important role of advocacy on behalf of the specialty in Washington, DC, became increasingly clear. As in the case of most other major specialty societies in the United States of America, this is now a major thrust of ASTRO's activities, focusing on such issues as regulation, reimbursement and safety. Along with this, the educational and research components have continued to expand. The research mission has been strengthened by the formation of the Radiation Oncology Institute, which is funded by members and vendors and which finances studies of critical importance to the specialty.

The annual meeting is now a major international event and has become the biggest radiation oncology meeting in the world, with over 12 000 attendees and 2000 presentations. Fifty per cent of the presentations now come from countries outside the USA. In addition, ASTRO leads or cosponsors nine other, smaller annual or biennial meetings, with the number of attendees ranging from 300 to 2000. These include: the multidisciplinary symposia on genitourinary, gastrointestinal and breast cancers sponsored by the American Society of Clinical Oncology; a cancer imaging meeting with the Radiological Society of North America; head and neck and thoracic meetings; and intensity modulated radiation therapy and stereotactic body radiotherapy practicals with the American Association of Physicists in Medicine.

ASTRO has a strong international mission reflecting its international membership. As well as welcoming international attendees to its educational meetings, the annual meeting has in recent years experimented with half-day courses in Chinese and Spanish, recognizing the heavy representation from Asia and Latin America. In addition, ASTRO has, for many years, worked with many different national specialty societies around the world to bring faculty

to their national meetings. Most continents have been represented, with recent meetings in Brazil, the Philippines and South Africa, to name just a few. Strong relationships have developed from these shared activities, with many young physicians subsequently coming to the United States of America for either observerships or fellowships. ASTRO's journal, the International Journal of Radiation Oncology·Biology·Physics, is one of the world's highest impact and most widely read journals in the discipline, and an expansion of its on-line activities will bring it to an even wider audience.

In the years ahead, ASTRO hopes to partner with other major international specialty societies (e.g. European Society for Radiotherapy and Oncology (ESTRO), Japanese Society for Radiation Oncology) and the IAEA to work in a coordinated manner to bring educational opportunities to other parts of the world. In addition, the hope is that through strong and collaborative guidelines developed with these organizations, the standards of those practising radiotherapy around the world can be raised.

## 27.2. EUROPEAN SOCIETY FOR RADIOTHERAPY AND ONCOLOGY (ESTRO)

ESTRO has recently articulated a primary vision that will shape and influence the direction of the society's activities in the coming years.

Thus, ESTRO will seek to ensure that every cancer patient in Europe will have access to state of the art radiotherapy as part of a multidisciplinary approach where treatment is individualized for the specific patient's cancer, taking account of the patient's personal circumstances.

In order to achieve this vision, ESTRO will support the following initiatives and model of clinical care as part of the future strategic development of the society:

(a) ESTRO will provide strategic leadership on the emerging and future approaches that will enable further improvements in the physical and biological optimization of radiotherapy.
(b) In support of the above, ESTRO will establish a forum where codes of practice, guidelines, education and professional development resources are easily accessible and tailored to the professional needs of the membership of the society.
(c) To enable improvements in clinical care, ESTRO will, through its congresses, special meetings, educational courses and journal(s), and new web based platforms, support the future development of radiation oncology.

(d) ESTRO will take all necessary measures to promote and advance multidisciplinary networking and 'oncopolicy' through a comprehensive, active and strategic partnership within the European Cancer Organisation.
(e) ESTRO will take a leadership role in advising the European Union, European Commission and European Economic Area on the future strategic development of all matters relating to the clinical discipline of radiation oncology within Europe.
(f) ESTRO will examine opportunities to liaise and develop collaborative partnerships with other European and international agencies and societies, in particular with those groups that directly work in or advise on the field of radiation oncology, including the European Union of Medical Specialists section of radiotherapy and the IAEA.
(g) ESTRO will take a similar leadership role, where appropriate, in advising the wide range of international health agencies, intergovernmental groups and non-governmental organizations on the future strategic development of radiation oncology at the global level.
(h) In recognition of the need to strengthen partnerships with industry, ESTRO will become a driving force in shaping and guiding collaborations between radiation oncology and industry, particularly with respect to product development pathways for equipment, as well as pharmaceutical and biotechnology sectors applicable to the field of radiation oncology.

## 27.3. UNION FOR INTERNATIONAL CANCER CONTROL (UICC)

Over 75 years ago, cancer researchers, recognizing the value of knowledge sharing and collaboration, created the Union for International Cancer Control (UICC). Currently, UICC brings together cancer professionals and volunteers in a unified mission to eliminate cancer as a life threatening disease for future generations.

The UICC membership includes over 700 organizations from more than 130 countries, all united by a mandate to control cancer. UICC aims to raise awareness about the global cancer problem, focusing on education, standard setting, support for global networks of influence and actions in support of the fight against cancer.

One of the oldest initiatives of UICC is its fellowships programme, which has been running successfully since 1962. Since it started, approximately 6000 grants have been awarded for fellowships and workshops. On average, 100 fellowships are awarded every year, and there are different schemes that answer different needs: the International Cancer Research Technology Transfer Programme one month fellowships, the Yamagiwa–Yoshida three month

fellowships and the one year American Cancer Society international fellowships for beginning investigators. In addition, UICC supports schemes such as the capacity building model in the Asia–Pacific region as well as joint fellowships with the International Agency for Research on Cancer (IARC). More than 600 expert volunteer reviewers ensure that the highest quality proposals are awarded fellowships. In the past five years, fellowships were awarded to grantees from 101 countries.

With their focus on advocacy for cancer control worldwide, UICC programmes address the most urgent and at the same time most achievable issues in cancer control in the world. These include programmes in childhood cancer, cervical cancer and pain relief. UICC is also supporting and collaborating with major cancer fighting organizations in bringing the issues of cancer to WHO and the United Nations. As a founding partner of the Non-Communicable Diseases (NCD) Alliance, UICC lobbies actively to place cancer control on the global agenda. The 2011 United Nations High Level Meeting on the Prevention and Control of Non-communicable Diseases provided a unique opportunity to put cancer on the global agenda. The follow-up actions to this meeting are continuing.

UICC activities include annual World Cancer Day celebrations on 4 February, and the annual World Cancer Leaders Summit that brings together key decision makers from around the world and encourages timely debate on emerging issues related to cancer. The summit provides an important forum to secure a coordinated, multilevel global response to address the spiralling cancer epidemic. It brings together global decision makers who can shape the way our generation addresses the task of eliminating cancer as a life threatening disease for future generations. Every two years, the UICC World Cancer Congress brings together over 3000 participants from across the world and represents a unique and ideal platform for the international cancer control community to meet, discuss, share, learn and connect in order to find solutions to reduce the impact of cancer on communities around the world.

The current UICC membership represents a wide variety of cancer organizations, from cancer institutes, national and international professional organizations, cancer control institutions, research organizations, and cancer advocacy organizations, to patient support organizations. With such comprehensive representation, UICC has a unique opportunity to speak for cancer control and, at the same time, a responsibility to connect various cancer fighting sectors to increase the effectiveness of their individual and collective efforts. The equity imperative we all face requires collaboration and partnerships in all aspects of cancer control to reduce the unnecessary deaths that are such a huge problem in the world today.

## 27.4. PAN AMERICAN HEALTH ORGANIZATION (PAHO)

Cancer is the second leading cause of death in the Americas, with an estimated 2.5 million people newly diagnosed and 1.2 million deaths per year. The most common cancers are lung, prostate and stomach cancer in men and breast, cervical and stomach cancer in women. This cancer burden is expected to nearly double in the next 10–15 years with the demographic changes in the region.

National cancer control programmes, including prevention, early detection, diagnosis, treatment and palliative care, have long been promoted by WHO and the Pan American Health Organization (PAHO) as the most efficient and effective way to manage this significant public health problem. Despite this, cancer control remains largely underappreciated within public health programmes in the region and is often left to be managed solely by tertiary level care providers. In many cases, these providers have limited capabilities to provide curative or palliative treatment to patients with advanced disease.

As a technical agency, PAHO plays a leading role in the Americas in assisting its Member States to plan for and manage public health matters, such as cancer. For over 60 years, PAHO has been working alongside health ministries and in collaboration with the IAEA to improve the quality and safety of and access to radiotherapy services. This has included providing radiotherapy evaluations, training radiotherapists and assessing needs. And with the initiation of PAHO's NCD programme in the mid-1990s, technical assistance for cancer has expanded to include cooperation across the continuum of cancer control. This has included efforts to: raise the political and financial support for a public health approach to cancer, assist health ministries to develop national cancer control plans, monitor cancer trends, assist with cervical cancer screening programmes and provide guidelines for the most prevalent cancer types.

Primary health care is an important part of health systems, especially for cancer prevention, screening and early detection, and for providing follow-up care for cancer patients who have been treated or those requiring end of life care. PAHO has been working with Member States to strengthen primary health care and, through integrated health service delivery networks (IHSDNs), to improve universal coverage and access, integrated and continuing care, and family and community orientation to better meet people's health needs. Thus, part of PAHO's comprehensive approach to cancer control has included developing and strengthening IHSDNs and integrating cancer care within primary health care to strengthen quality and patient outcomes for prevention, early detection and disease management.

Radiotherapy is used today for the treatment of numerous types of tumours and is frequently administered in combination with surgery, chemotherapy

or both. It is well recognized that radiotherapy will continue to be a critical component of cancer treatment in the coming decades. Its curative and palliative functions are particularly important for many common cancer types. Many factors influence the effectiveness and safety of radiotherapy treatments, such as accurate diagnosis, the disease stage and sound therapeutic decisions, the precise location of the tumour, and the planning and delivery of treatment. PAHO is assisting its Member States in the development of radiotherapy services, including referral systems and training of human resources to improve the effectiveness of treatments and to ensure patient safety by implementing comprehensive quality assurance programmes. PAHO also evaluates the provision of these services to ensure access and equity, as well as their proper integration in national cancer control plans.

There have been examples where equipment costing millions of dollars was never put into service or was underused, with significant financial and health costs. For this reason, PAHO also provides technical assistance to health authorities in introducing and placing these technologies in service more effectively. It is PAHO's policy to carry out comprehensive feasibility studies by experts prior to procuring and incorporating radiation medicine technology.

When issues of radiotherapy safety arise, PAHO Member States turn to the organization to provide a scientific and impartial evaluation of the situation, assessing the problem and suggesting how to improve practices and prevent future accidents, such as miscalibrated radiation devices.

Looking to the future and the expected significant increase in the incidence of cancer, PAHO is planning to increase its technical assistance to its Member States, especially: to increase primary prevention against tobacco use, human papillomavirus vaccination and promotion of health; to provide guidance on effective breast and cervical cancer screening; and to increase the availability and affordability of cancer drugs. The latter is achieved through its bulk procurement programme, the PAHO Strategic Fund. PAHO also recognizes that cancer control requires multistakeholder partnerships, with governments, civil society and the private sector working together to address cancer in a comprehensive manner. Thus, PAHO has expanded its partnership platform, bringing cancer stakeholders — including the IAEA — together to pool resources and coordinate efforts to prevent, cure and care for persons with cancer in the Americas (Fig. 27.1).

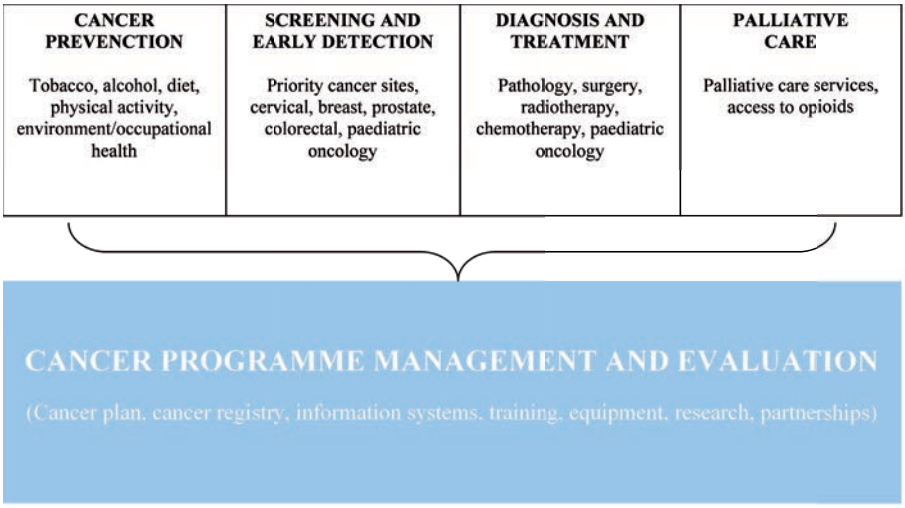


*FIG. 27.1. PAHO's comprehensive approach to cancer prevention and control.*

# Chapter 28

# SUCCESS STORIES IN RADIOTHERAPY DEVELOPMENT PROJECTS

## 28.1. INITIATING IMRT IN BOGOTA, COLOMBIA — E. Rosenblatt, R. Ospino Peña

In 2002, Colombia approached the IAEA with a request for assistance in establishing an intensity modulated radiation therapy (IMRT) programme at the National Cancer Institute (INC) in Bogota. The objective was to improve the accuracy of radiotherapy treatments, in particular for head and neck and pelvic cancers, thus improving patient outcomes and reducing toxicities.

An initial expert mission to the INC noted that there was not enough expertise in three dimensional conformal radiotherapy (3-D CRT) at that time to initiate an IMRT programme. In line with IAEA criteria, centres contemplating an IMRT programme should fill out a self-assessment questionnaire and, in general, must have at least two years of previous experience with 3-D CRT implementation [28.1]. Furthermore, it is desirable for centres to have an operational follow-up clinic where treated patients are followed for months and years after treatment in order to record and quantify their treatment outcomes in terms of tumour control and toxicity of therapy. This type of follow-up clinic did not exist in Colombia at that time.

The project was approached in two phases. In the first phase, between 2003 and 2005, the INC moved from two dimensional (2-D) to 3-D CRT with IAEA support and established a follow-up clinic. In the second phase, between 2005 and 2007, the INC initiated IMRT treatments. This phase required the upgrade of local space and facilities; the purchase and delivery of equipment and software; the training of staff, including radiation oncologists, medical physicists and technologists; and scientific visits of administrators to other centres already implementing IMRT programmes.

Two internationally recognized experts in medical physics and radiation oncology were present on-site during the first IMRT treatments, providing guidance and practical orientation to the local staff. As is usually the case in these projects, the IAEA organized a local course/workshop on the topic, bringing together external lecturers but also local experts. This served the purpose of facilitating dialogue and established the twinning partnership collaboration between centres with long standing experience in IMRT and the newly initiated programme.

As a result of the project, the INC, a large public hospital and the main teaching centre for oncology and radiotherapy in Colombia, joined the group of centres that practise this modern treatment modality in the country.

## 28.2. MODERN BRACHYTHERAPY IN EL SALVADOR — E. Rosenblatt, A. Molina Martinez

El Salvador, like other Central American countries, has among the highest incidences of cervical cancer in the world, with 18.7 cases per 100 000 population in 2008 (age standardized rate: 37.2). The Cancer Institute of El Salvador 'Dr. Narciso Díaz Bazán' is a private centre for public service financed by the Liga Nacional Contra el Cáncer de El Salvador, a non-profit foundation. The mission of the Institute is to provide radiotherapy services to 80% of the population of El Salvador, while the other 20% should be covered by the social security system, which has another treatment centre. Since this project was finalized, two new private radiotherapy centres have opened their doors in the city of San Salvador, providing modern external beam radiotherapy but not brachytherapy.

In El Salvador, $^{226}$Ra sources were used for gynaecological brachytherapy from the 1970s to 2005. In 2005, the use of $^{226}$Ra sources was stopped. Following the decommissioning of the radium sources for brachytherapy, the IAEA assisted the Institute in transitioning from the use of these sources to a modern HDR brachytherapy system. A series of national projects were initiated in 1997 by the Government with technical support from the IAEA. The projects included the building of a modern facility to house the unit, waiting rooms, an applicator insertion room and imaging facilities, and purchase and installation of equipment and training of staff.

Construction of the building was covered by Government funds. The IAEA helped deliver a high dose rate (HDR) three channel unit suitable for gynaecological applications as well as a contract to deliver $^{192}$Ir sources for a period of five years. In addition, the package included a treatment planning system (TPS) for brachytherapy, a ceiling mounted X ray machine for imaging, applicators and dosimetry instruments for QA and training.

A total of 8 fellowships, 2 scientific visits and 12 expert missions were organized and financed by the IAEA. The expert missions included radiation oncologists, medical physicists and technologists. A series of local events related to staff led to unforeseen delays in the actual initiation of brachytherapy treatments in the new unit.

To overcome the lack of previous experience in the use of HDR brachytherapy, the IAEA hired two experienced professionals (a radiation oncologist and a medical physicist) from a neighbouring country to assist the

local staff in the initial running of the unit. These two professionals remained in El Salvador for three months. During this period, they drafted a local treatment protocol with assistance from IAEA experts and initiated the actual treatment of a series of patients while simultaneously training local staff.

In this manner, the new HDR unit became fully operational in 2010 and is currently treating an average of 600–680 patients per year. The introduction of HDR brachytherapy resulted in a reduction of waiting lists, expedited treatment for patients and an improvement in the clinical outcomes in terms of toxicity and patient survival. The centre underwent a full IAEA quality audit in March 2010.

## 28.3. OPTIMIZING TOTAL BODY IRRADIATION FOR BONE MARROW TRANSPLANTS IN BULGARIA — E. Rosenblatt, L. Gocheva-Petkova

Each year, hundreds of cancer patients in Bulgaria receive bone marrow transplants as treatment for haematological malignancies such as leukaemia, lymphoma and multiple myeloma, or for solid tumours such as neuroblastoma, one of the more common cancers in infancy.

To undergo a bone marrow transplant, patients must first go through a preparatory process that conditions the body for the transplant. This involves a special radiotherapy technique called total body irradiation (TBI). TBI helps to make space for the transplanted marrow, destroys any malignant cells that may be left in the bone marrow after chemotherapy and suppresses the immune system to help prevent rejection of the transplant. To avoid complications, patients must also receive irradiated cellular blood components during the preparatory process.

The IAEA assisted medical professionals in Bulgaria in optimizing bone marrow transplants by providing the equipment and building the capabilities necessary to carry out TBI. The IAEA also offered very specialized radiotherapy training to the medical staff, including blood irradiation.

Under a technical cooperation project entitled Routine Application of Highly Specialized Total Body Irradiation Prior to Bone Marrow Transplantation, the IAEA provided technical support to hospitals in Bulgaria in essential areas of the pre-transplant conditioning regime that are key to improving cancer treatment in the country. These include optimizing TBI treatment and dose, and reducing the incidence and severity of a significant and usually fatal complication called a transfusion-associated graft-versus-host disease (TA-GVHD). TA-GVHD may occur in several clinical conditions, such as autologous bone marrow transplant or peripheral blood stem cell transplant. To avoid this complication, patients should receive irradiated cellular blood components throughout the period of their conditioning regime.

With the support of the technical cooperation project, a blood irradiator was purchased for the Queen Giovanna University Hospital (QGUH) in Sofia for irradiation of blood components to prevent the occurrence of TA-GVHD. A new linear accelerator (linac), which is an optimal tool to carry out TBI, was also provided through the project. The medical linac was installed at the QGUH in 2010, making its radiotherapy clinic the first and only one in the country capable of performing TBI.

A dedicated treatment table for TBI was also delivered under this project. This special table allows for the positioning of the patient in such a way that the radiation can be delivered more homogeneously to the whole body and the placement of adequate shields to protect the lungs.

Since November 2010, TBI has been performed on 21 adults and eight children. Over the same period, 3650 blood samples of patients with different kinds of leukaemia and lymphoma have been irradiated. Of these patients, 397 were children.

The routine application of the highly specialized therapeutic procedure of bone marrow transplant with TBI conditioning is now a reality in Bulgaria, and blood irradiation is used to support several areas of practice such as transfusion haematology, transplantation of organs, tissues and cells, and neonatology. These services are of special value for the children of Bulgaria.

## 28.4. ZAMBIA: THE CANCER DISEASES HOSPITAL — K. Lishimpi

Prior to 2005, Zambia had no radiotherapy services. The Ministry of Health engaged the IAEA in collaboration that led to the establishment of the first radiotherapy centre in the country. The project saw the establishment of the Cancer Diseases Hospital (CDH) at the end of 2005. The hospital was officially opened on 19 July 2007 and more than 7000 new cancer patients have since been cared for. This initial project assisted the Ministry of Health in identifying concrete milestones that needed to be put in place for the successful implementation of the project. The project developed a document that dealt with:

— Financing the construction of the facility and purchase of radiotherapy equipment;
— Training of the seminal core staff to run the centre once constructed;
— Identifying community mobilization issues.

The Government of Zambia agreed to co-finance the construction and equipping of the first radiotherapy centre in cooperation with the OPEC Fund for International Development (OFID). Construction was completed between

2003 and 2005, and in 2006 radiotherapy equipment was delivered, installed and commissioned. Through the year, planning for running costs was carried out and small equipment, treatment accessories and reference books were procured.

In 2003, the core staff were identified, made up of four medical doctors, seven radiotherapists, three medical physicists, five oncology nurses and two maintenance engineers. They were sent to South Africa to train at the University of the Witwatersrand and the University of Pretoria.

The hospital now has the following equipment:

(a) Treatment units:
- — One linac;
- — One $^{60}$Co unit;
- — One orthovoltage machine;
- — One HDR brachytherapy unit;
- — External beam and brachytherapy TPSs;
- — One conventional simulator;
- — Mould room and workshop.

(b) Diagnostic units:
- — One mammography unit;
- — One 4-D ultrasound unit;
- — One computed tomography (CT) simulator;
- — One magnetic resonance imaging (MRI) machine;
- — Laboratory equipment including microscopes and haematology and chemistry devices.

(c) Specialized clinics:
- — Unit I: gynaecological cancer, genitourinary cancer and Kaposi's sarcoma;
- — Unit II: breast cancer, haematological malignancies, skin cancer;
- — Unit III: head and neck cancer, central nervous system malignancies, gastrointestinal cancer and paediatric cancer;
- — Chemotherapy unit: for patients requiring chemotherapy;
- — Radiotherapy unit: for patients requiring radiotherapy, both external beam radiotherapy and brachytherapy facilities.

(d) Palliative care:
- — Pain unit: optimal pain management and palliative care service;
- — Imaging unit: MRI and CT scans, mammography and ultrasound.

Since 2006, the CDH has been implementing a national project supported by the IAEA to assist in the enhancement of national capacity and quality in the delivery of radiotherapy services in Zambia. The training provided to staff, the expert mission services and the equipment delivered have led to an overall

improvement in the quality and quantity (improved access for patients) of the services delivered by the hospital. In another project, the IAEA contributed to strengthening the delivery of radiotherapy services by helping to improve the skills of key personnel and to developing a local radiotherapist (RTT) training programme for sustainable local human resource development.

It was evident that local human resource development should be extended to other key personnel in radiation oncology, including radiation oncologists, oncology nurses, oncology pharmacists and medical physicists. These training programmes are earmarked to start during Phase II of the CDH project, which is to create a training centre and a 160 bed in-patient facility, among others. The second phase has also been co-financed by the Government of Zambia and OFID.

CDH hospital statistics indicate that the Muchinga, Northern, Northwestern and Western provinces in Zambia are facing challenges in referring cancer patients to CDH. No diagnostic, treatment and follow-up capacity for cancer management is available there. This problem has highlighted the need to start on phase III, which will make available radiotherapy services in these provinces. Phase III will complete the equipping of CDH with positron emission tomography (PET)/CT machines and a medical linac, and create five other radiotherapy facilities that will be attached to existing local general hospitals under the supervision of CDH.

CDH will need to attain higher levels of service in order to become a centre of excellence for Zambia. To achieve this, CDH will need well trained staff to roll out radiotherapy services to the other provinces. Benchmarks for attaining best practice and the highest standards of care will need to be set in order for CDH to achieve this end. It is anticipated that CDH will evolve into a national referral centre with four to five satellite centres and become the National Cancer Institute of Zambia.

The establishment of CDH, including a training programme for RTTs, is a model of successful tripartite collaboration among the Government of Zambia, OFID and the IAEA.

## 28.5. RADIOTHERAPY SERVICE IN MAURITANIA — E. Rosenblatt, E. Zubizarreta, A. Djeutie, A. Meghzifene, M.M. Mohamedou

Mauritania, a country of 3.4 million people, did not have any radiotherapy facility until 2009. As is usually the case in countries without radiotherapy services, cancer patients with a need for this treatment travelled to neighbouring countries (Morocco or Tunisia) or to Europe to receive it, or switched to alternative forms of care.

Cancer is a rising cause of death in Mauritania. According to WHO estimates, about 2200 people died of cancer in 2011, of whom 1400 were aged

below 70 years of age [28.2]. The number of patients sent abroad for treatment by the National Health Insurance Fund rose to 500 patients in 2007, causing a significant drain on the State budget. Cancer was the main cause of health related travel abroad. The average cost of such travel was two million ouguiya per patient (US $8000) [28.3].

Through a technical cooperation project initiated in 2009 between the Mauritanian Government and the IAEA, the latter assisted the country with the establishment and operation of its first radiotherapy facility. The National Oncology Centre, including a radiotherapy department, was built in Nouakchott in 2010 and began operation in early 2011 with a limited staff, all hired from abroad. Its equipment includes a modern medical linac with a multileaf collimator and portal imaging, a CT simulator, a 3-D CRT TPS and a remote afterloading HDR brachytherapy system. The centre was planned with an additional bunker, where a second accelerator can be installed in the future. Except for the training of the Department Head, the entire professional team has been trained through the IAEA's technical cooperation fellowship programme.

The centre treated a total of 250 patients in 2012 and treated 176 in the first half of 2013. Most patients undergo simulation and computerized radiotherapy treatment planning. The centre ensures the sustainability of the equipment through full maintenance contracts for the major radiation equipment and source replacements for the HDR brachytherapy unit.

More professional staff members are undergoing training in other Francophone African countries. The brachytherapy device has yet to become fully operational.

Between 1991 — the date of the first official evacuation of a Mauritanian cancer patient for treatment abroad — and 2008 — the date of the establishment of the cancer centre — there was no specific support policy for cancer patients in Mauritania. As a result, the creation of the oncology centre faced three main challenges:

(1) The total absence of basic infrastructure, including buildings and equipment;
(2) The total absence of trained human resources capable of taking care of cancer patients;
(3) Pressure from the families of hundreds of patients who had been sent abroad for treatment to rapidly establish the centre and repatriate their sick relatives.

Four years later, and despite these challenges, Mauritania had an operational radiotherapy unit (Figs 28.1 and 28.2) and a very well equipped national human

resource team consisting of three radiation oncologists, three medical physicists and six RTTs.

This project has been a positive achievement thanks to a combination of three factors:

(1) The presence of a strong political will, as evidenced by the direct involvement of the President of Mauritania, who regularly monitored the project and was personally involved in raising the funds necessary for its advancement;
(2) The choice of a strong partner in the IAEA, which supported the project through staff training and technical expertise;
(3) The formation of a small project management team that was committed and aware of the importance of the challenges.

The successful experience of Mauritania should be shared. The National Oncology Centre could become a training hub for the Francophone West African subregion in collaboration with the IAEA and regional universities. This would allow the education and training of competent radiotherapy professionals to support neighbouring countries facing similar challenges. In addition, the lessons learned from this project will contribute to the establishment of other cancer and radiotherapy centres in Mauritania and beyond.

The National Oncology Centre has hosted a regional training course for RTTs from Francophone African countries organized by the IAEA. In the future, the centre is expected to become sustainable with regard to RTTs trained locally before the incorporation of a second teletherapy machine.

## 28.6. UPGRADING RADIOTHERAPY SERVICES IN THE FORMER YUGOSLAV REPUBLIC OF MACEDONIA — I. Stojkovski

The former Yugoslav Republic of Macedonia has a population of 2.1 million and an annual per capita gross domestic product (GDP) of around US $4500, which positions it as a middle income country. According to data from the World Bank, and owing to the conflicts in the former Yugoslavia, a significant decrease in the GDP per capita was recorded in the region between 1991 and 2001, which predictably had a substantial impact on overall health care expenditure.

Radiotherapy is provided by the University Clinic of Radiotherapy and Oncology (formerly the Institute of Radiotherapy and Oncology), in Skopje, which is the only centre in the country. The institute treated patients from the whole southern part of the former Yugoslavia. The overall population served by

this clinic was roughly 5 million and approximately 4000 patients were treated annually with curative and palliative radiotherapy [28.4].

As mentioned above, owing to the economic devastation of the country, caused mainly by the wars in the former Yugoslavia and the transition of its economic system, investment in the health care sector, especially in radiotherapy, has been minimal or non-existent. In the mid-1990s, radiotherapy equipment consisted of treatment units manufactured in the 1960s and 1970s, e.g. an old $^{60}$Co machine (installed in 1962), a linac (installed in 1977), one $^{137}$Cs afterloader (1979) and two old orthovoltage machines from the 1960s. During that time, there were about 15 radiation oncologists practising in the institute, together with two physicists, ten RTTs, and several oncology nurses and other allied professionals. Despite the fact that the personnel at the centre were trained in modern European cancer centres, they were unable to practise modern radiation oncology owing to the lack of modern radiotherapy equipment.

Collaboration between the former Yugoslav Republic of Macedonia and the IAEA began in November 1995 with a technical cooperation project entitled Modernization of Brachytherapy involving the University Clinic of Radiotherapy and Oncology. In April 1996, an IAEA expert mission visited the Clinic and reported that the radiotherapy equipment was inadequate. However, the staff had very good clinical experience and potential for development. The experts suggested a significant expansion of the proposed project, and in the following year the Clinic was included in an IAEA regional project entitled Modernization and Improvement of Radiotherapy.

From 1997 to 2004, a total of 16 IAEA fellows (radiation oncologists, medical physicists and RTTs) from the former Yugoslav Republic of Macedonia were trained through the IAEA's fellowship programme. In addition, the Clinic's staff participated in numerous IAEA and European Society for Radiotherapy and Oncology (ESTRO) courses.

Through IAEA assistance, the Clinic received a 2-D TPS and basic dosimetry equipment in 1997, a new $^{60}$Co machine in 1999, a low dose rate brachytherapy afterloader in 2000, and a conventional simulator in 2002. Through two subsequent national projects implemented between 2003 and 2006 and between 2007 and 2009, the Clinic was equipped with modern HDR brachytherapy equipment and received additional assistance for the introduction of IMRT treatments. Following a request from the Clinic to national authorities for more modern radiotherapy equipment, further expansion was undertaken through IAEA projects with the addition of two modern linacs and a CT simulator [28.1]. The construction of a new building was completed in 2002, and new equipment purchased by the Government of the former Yugoslav Republic of Macedonia was installed in February 2004.


*FIG. 28.1. National Oncology Centre, Nouakchott, Mauritania.*

*FIG. 28.2. Modern medical linac for cancer treatment. (Photo courtesy of the National Oncology Centre, Nouakchott, Mauritania.)*

After ten difficult years, the University Clinic of Radiotherapy and Oncology took a significant step forward in a relatively short period of time and achieved the status of a 'centre of competence' for radiotherapy through a Quality Assurance Team for Radiation Oncology (QUATRO) audit performed by the IAEA in October 2005. The Clinic also became a leader in radiotherapy in the region, training fellows from neighbouring countries. It is involved in IAEA coordinated research activities in the area of cancer radiotherapy.

In summary, the assistance from the IAEA has been essential and has helped the University Clinic of Radiotherapy and Oncology to achieve its current level of competence in radiation oncology. Proper re-equipment of the Clinic and building of human resource capacity led to the successful implementation of three complex projects. In addition, the involvement of and support by the IAEA played a role in making the case for the importance of radiotherapy in the country's health care system, leading to a substantial investment by the Government in comprehensive cancer care.

The benefits of these achievements have reached all stakeholders. Medical professionals have become more motivated with the improvement in working conditions and are now able to provide the best possible care to their patients. Patients are also satisfied that they are receiving modern radiotherapy treatment in their home country. Finally, there will be a positive financial impact resulting from the substantial decrease in costs of patients' treatments made possible by building radiotherapy capacity in the country.

These are concrete and effective actions taken by an international organization in the fight against cancer, and represent the investment of significant resources that have resulted in improved infrastructure, an expanded workforce and increased access for patients to modern diagnosis and treatment.

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# Chapter 29

# LESSONS LEARNED FROM RADIOTHERAPY DEVELOPMENT PROJECTS

**E. Zubizarreta, D. Van Der Merwe**

## 29.1. INTRODUCTION

This chapter examines some problems found to be common in the process of setting up, running or expanding radiotherapy facilities. The establishment of radiotherapy services is essential to consolidate any national cancer control plan. In other words, such a plan cannot exist without radiotherapy. The IAEA guidance on setting up a radiotherapy programme covering the clinical, medical physics, radiation protection and safety aspects gives an estimate of one teletherapy machine needed per million population [29.1].

The IAEA's Directory of Radiotherapy Centres (DIRAC) shows that the number of megavoltage (MV) machines per million population varies from 8.2 in the United States of America to 5.5 in western Europe. There are still many countries without a single radiotherapy department, especially in Africa, and many others have very low coverage, e.g. up to one external beam radiotherapy machine to cover a population of 35 million, which is close to having no coverage. There are many possible reasons for this situation. In many low income countries, the combination of lower life expectancy, low income taxes, a small budget for public health, and unmet basic needs such as housing, prevention and/or treatment of infectious diseases (malaria, tuberculosis, human immunodeficiency virus (HIV), diarrhoea), drinkable water and sewerage makes the cancer control problem a lower priority. The indicators shown in Table 29.1 illustrate these points.

Establishing a radiotherapy programme requires careful planning, including the requirement for successive phases. Resources should be available for designing, building, purchasing, maintaining and replacing equipment, and for providing training in its use. In the case of a first radiotherapy facility with basic staffing levels, there is not likely to be enough expertise to guide and oversee the process in many or all of these areas.

TABLE 29.1. SELECTED INDICATORS FROM THE EUROPEAN UNION AND SUB-SAHARAN AFRICA[a]

| | European Union | Sub-Saharan Africa |
|---|---|---|
| Life expectancy | 80 years | 55 years |
| Percentage of population living on less than US $2 per day | 0% | 72% |
| Per capita public expenditure on health per year | US $3500 (Germany) | US $12 (Chad) |

[a] Source: The World Bank.

## 29.2. THE FIRST RADIOTHERAPY FACILITY

Manuals have been published by the IAEA to guide the process of setting up a first radiotherapy facility [29.1, 29.2]. The first step in the process should be to prepare a strategic master planning document that includes not only a detailed analysis of the needs and timelines, but also the medium and long term plans for future expansion of the services. The lack of such a master plan can result in important components of the process being inadvertently left out, an inadequate or unrealistic timeline, or unexpected costs when expanding the facility.

The architectural design is also very important, as the radiotherapy facility should not only have enough space to house treatment and diagnostic equipment, clinics and planning facilities, but there should also be a proper connection between them to ensure a smooth workflow. Future expansion should also be planned.

Proper selection of the equipment to be installed is essential. The easiest way to begin is to install a basic machine first and, when the staff members are confident, a second one that is more complex. A simple basic machine — a telecobalt or monoenergetic linear accelerator (linac) — will be cheaper to acquire and to maintain and easier to commission, and there will be less downtime. The investment required to install and run a multimodality linac is double the cost of a basic machine, or equal to the initial and running costs of two basic machines. Twice the number of patients can be treated with two basic machines, which is a strong argument when access to services needs to be prioritized. Appendix I to the IAEA publication Comprehensive Audits of Radiotherapy Practices: A Tool for Quality Improvement provides basic guidelines to start a radiotherapy clinic when resources are limited [29.3].

The documents for tender and equipment specifications should be carefully prepared. These documents frequently lack sufficient detail, especially on the conditions of the ongoing maintenance contract.

The timeline is critical and should include all preparatory work needed, including training of professional staff and construction of the building. Figure 29.1 presents a simplified timeline showing that training, especially of radiation oncologists, should begin at least two years before construction of the facility. There have been instances where a building was completed and the equipment installed, but the staff returned from training abroad only after many years, and it was necessary to hire foreign personnel to run the facility in the meantime. There have been other instances where the professional staff came back and the radiotherapy facility was not yet ready. It should also be emphasized that long term training abroad for professional staff is very costly, and recognition, registration and employment of personnel should therefore be planned in advance.

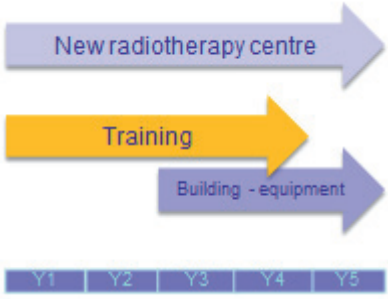


*FIG. 29.1. Simplified timeline including training, buildings and equipment.*

Governments should also have a retention policy in place to discourage the emigration of trained professional staff. This has been found to be a common problem in some regions.

## 29.3. SUSTAINABILITY

Governments should carefully monitor the operational or running costs. A rule of thumb is that equipment maintenance is approximately 10% of the purchase cost per year. Another 10% per year should be saved as amortization to replace the equipment in 10–15 years. The other components are salaries,

consumables, and building maintenance and amortization. Thus, the initial price of equipment should be multiplied by 2 in a ten year period to cover maintenance and amortization [29.2].

A programme to encourage development and continuous education of professional staff should be part of the retention policy mentioned above. This should be based on the establishment of training programmes at the national level [29.1, 29.2].

## 29.4. EXPANSION

Expansion of the first facility, or addition of new ones, should be addressed in the strategic master planning document. In many ways, the process will replicate everything that happened when establishing the first facility in terms of timeline, training, selection of equipment, buildings, etc. The experience in many projects has been that adequate expansion of the radiotherapy facility was not taken into account at the time of the initial design, making it very difficult to carry out expansion. Figure 29.2 shows that timelines for the first facility and for expansion of the facility are similar.

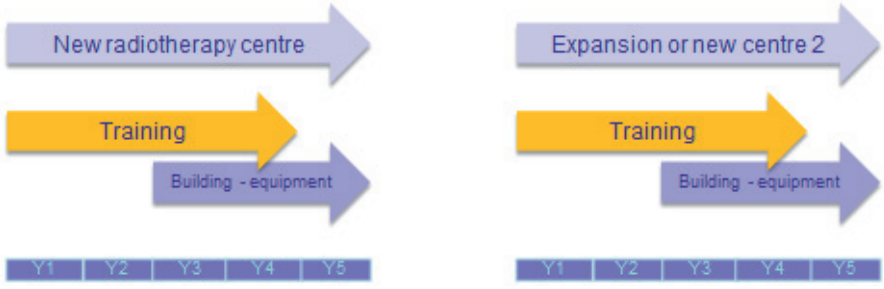


*FIG. 29.2. Timelines for the first facility and expansion.*

Everything mentioned about sustainability in Section 29.3 applies here as well. Costing concepts are outlined in Ref. [29.2]. More detailed costing analysis and examples are addressed in Chapter 18 on costing in radiotherapy.

## 29.5 KEY POINTS

— When establishing a radiotherapy clinic, careful planning is essential, and should include the various phases and a detailed budget (strategic master plan document).
— It is important to seek guidance from external experts and/or the IAEA.
— The planning should include budgeting ahead for operational running costs, equipment maintenance and amortization.
— Future expansion should also be planned.
— The architectural design is also very important, as the radiotherapy facility should not only have enough space to house treatment and diagnostic equipment, clinics and planning facilities, but there should also be a proper connection between them to ensure a smooth workflow.
— Proper selection of the radiotherapy equipment to be installed is essential. The documents for tender and equipment specifications should be carefully prepared.
— Staff training should be initiated about two years before construction of the buildings begins.
— A staff retention policy should be considered and implemented.
— When expanding, the process will replicate everything that happened when establishing the first facility in terms of timeline, training, selection of equipment and construction.

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# Part IX

# THE FUTURE

# Chapter 30

# A VISION OF THE FUTURE

**E. Rosenblatt, E. Zubizarreta, B. Vikram, D. Petereit**

Unforeseen developments and discoveries notwithstanding, a prediction regarding the future of radiotherapy must be based on a careful observation and analysis of current trends. In general terms, future developments in radiation oncology relate to two broad categories: developments in technology that will improve the accuracy of physical dose delivery, and developments in biology that will enhance the selectivity of cell kill by radiation, thus improving the therapeutic index. For health planners, international organizations or non-governmental organizations (NGOs) engaged in technical cooperation to strengthen radiotherapy services across the world, it is important to scan the scientific horizon and identify developments and trends that may impact radiation oncology in the future and be ready for them.

## 30.1. ESTIMATING INCREASE IN DEMAND

In 2012, the world population was 7.05 billion. GLOBOCAN 2012 reported a total of 14 067 900 notifiable cancer cases worldwide for that particular year [30.1]. The same source predicts a total of 17 113 588 cancer cases for 2020 and 21 645 658 for 2030. How many of these cancer patients will need radiotherapy? Recognizing the present situation in terms of cancer epidemiology, radiotherapy utilization (RTU) rate and current availability of radiotherapy resources worldwide, it is possible to attempt a tentative projection.

In Australia, the optimal RTU rate was reported to be 52.3% in 2005 [30.2], and in a subsequent review in 2012 it was reported to be 48% [30.3]; this can be rounded up to a RTU rate of 50% in developed countries.

Using the epidemiological evidence based approach, the mean RTU rate for all IAEA regions has been calculated to be 49% (see Table 3.2). When considering the "developing regions" only, the mean RTU rate is 52.3%. The difference is small, and is in agreement with the IAEA study finding of a 52% RTU rate for 9 middle income countries [30.4].

Since cancer under-reporting is common in developing countries and patients often present with more advanced stages of disease, these estimates of the RTU rate should be viewed as minima.

Prescribing a second course of radiotherapy to a patient who has already been treated is not a rare occurrence. The second radiotherapy course may be directed to the same previously irradiated volume (true re-irradiation), to a metastatic site or to a second primary tumour. The retreatment rate appears to be different for developed and developing countries. In Australia, it has been estimated to be 25% [30.5]. In developing countries, the retreatment rate tends to be lower since a higher proportion of patients present with advanced disease, reducing the number requiring retreatment for disease recurrence or a second primary tumour. Barton and Williams (Chapter 3) have estimated a 10% retreatment rate for LMICs. Rosenblatt et al. [30.4] found it to be 11% in 9 middle income countries studied.

The proportion of protracted radiotherapy courses versus short course treatments will affect the total number of fractions needed, which in combination with the complexity of the techniques used, will in turn determine the number of megavoltage machines needed.

Considering that the retreatment rate varies between 10% and 25% (and retreatment often uses hypofractionated regimens), it was not used to adjust the 50% worldwide RTU rate applied in Table 30.1. This table reveals that the current availability of megavoltage machines worldwide is below the number needed in 2015, and a significant increase will be necessary to cover future needs. For example, 3400 additional machines will be needed by 2020, and about 8000 additional machines to cover the projected need in 2030.

Since the crude cancer incidence in the world will increase, it is not risky to assume that the demand for all three mature cancer treatment modalities (surgery, radiotherapy and systemic therapies) will increase as well. If, in the more distant future, cancer is effectively managed through genetic manipulation, it is possible that locoregional modalities of treatment, such as surgery and radiotherapy, will be used less. Until this approach becomes a reality, the result of the above exercise is cause for concern because current capacity in radiotherapy services is not sufficient to cover the needs of low and middle income countries, making the future even grimmer if decisive action is not taken.

## 30.2. PATIENT CARE

In early cancers, where cure rates are already high, the focus will be on decreasing the adverse effects of radiotherapy. This may be accomplished by better selection of patients who may not need radiotherapy at all (such as those with early breast and prostate cancers), testing novel technology to decrease irradiation of the organs at risk (intensity modulated radiation therapy (IMRT), proton radiotherapy) and developing and testing new drugs that prevent or

TABLE 30.1. PROJECTIONS OF CANCER INCIDENCE, RADIOTHERAPY DEMAND AND MEGAVOLTAGE MACHINES

| | 2008 | 2015 | 2020 | 2030 | 2035 |
|---|---|---|---|---|---|
| Total cancer patients worldwide | 12 662 600 | 15 206 036 | 17 113 588 | 21 645 658 | 23 980 858 |
| Total number of cancer patients needing radiotherapy (50% of the total cancer patients, not adjusted for stage or retreatments) | 6 331 300 | 7 603 018 | 8 556 794 | 10 822 829 | 11 990 429 |
| Megavoltage machine throughput | 500 new patients/ year | 500 new patients/ year | 500 new patients/ year | 500 new patients/ year | 500 new patients/ year |
| Estimate number of megavoltage machines needed worldwide | 12 662 | 15 206 | 17 113 | 21 645 | 23 980 |
| Megavoltage machines available worldwide as of May 2017 (DIRAC) | | 13 653 | | | |

**Note:** The data sources used for this estimate do not reflect the operational status of the equipment reported.

mitigate the adverse effects of radiation without protecting the cancer (the lessons of erythropoietin should be taken into account) [30.6, 30.7]. Drugs developed as countermeasures against terrorism could prove valuable as radioprotectors for cancer patients undergoing radiotherapy.

For more advanced cancers treated with radiotherapy, with or without surgery and chemotherapy, the local control rates remain unsatisfactory. Dose escalation beyond 60–70 Gy has generally yielded disappointing results (e.g. glioblastoma, non-small cell lung cancer, oesophageal cancer), but the reasons for failure remain unclear. It is notable that the limiting factor in these examples was not excessive normal tissue toxicity but poor tumour control despite the higher doses. Accelerated radiotherapy has been somewhat more successful in a few sites such as the head and neck and lung [30.8–30.10]. Another approach to increasing the biological dose that is worth rigorously testing is the use of charged particles heavier than protons, e.g. carbon ions.

Overall, metastatic cancers are currently incurable. Irradiation of symptomatic metastases is usually employed for effective palliation. Occasionally, abscopal responses at remote sites are observed [30.11]. Research into the immunological response of cancers to irradiation has suggested novel ways of harnessing that response for suppressing local and distant tumour growth in some types of cancer [30.12].

## 30.3. DEVELOPMENTS IN TECHNOLOGY

### 30.3.1. External beam photon therapy

Cobalt-60 teletherapy units have been replaced almost completely by medical linacs in North America, Western Europe [30.13], Australia and Japan. However, in many developing countries, cobalt-60 units still represent the workhorse for the provision of radiotherapy due to their relative sturdiness, and their simpler servicing and maintenance needs. The replacement of a cobalt-60 source, which must ideally be done every five years, has become an insurmountable obstacle for many limited resource centres. Security concerns lead to restrictions on the international transport of radioactive sources, which in turn result in higher costs. In this scenario, many centres opt to replace their old cobalt units with single energy linacs. A decline is foreseen in the use of cobalt-60 teletherapy units in the future as they continue to be replaced by single energy linacs in developing countries.

Image guidance during treatment, enabling real time tracking of moving tumours, is already part of the current technology [30.14]. Greater use of biological and molecular imaging targeted to show what is happening at

the cellular/molecular level will allow detection of very small tumours and metastases invisible to the eye. A further refinement will include the use of non-invasive imaging methods to measure tumour response during a course of treatment, for potential mid-course modifications to the treatment. The use of ultrasound for image guidance (for example in gynaecological brachytherapy) replacing computed tomography (CT) or magnetic resonance imaging (MRI) is convenient and saves resources [30.15]

A further increase in the routine use of four dimensional (4-D) CT scanning in the planning of moving targets, particularly in the chest and abdomen, is foreseen. Data will be used to plan small target volumes during the phases of the respiratory cycle and treat them with the assistance of breathing control or gated radiotherapy. Medical linacs that incorporate an MRI for image guidance in one unit are already being marketed and have been acquired by a small number of facilities [30.16].

Also anticipated is an increase in the use of functional imaging to improve radiotherapy treatment plans, with better delineation of the target volume and nearby organs at risk. Future treatment plans may take into account the biological characteristics of tumours, including tumour cell density, areas of hypoxia, areas of rapid growth, and differences in cell metabolism within a targeted tumour. Present and future imaging methods will allow an improved definition of targets and definition of subregions within the tumour that may require a preferential increased dose compared to the rest of the target volume in tumours that show a dose response relationship [30.17].

Incorporating metabolic information into radiotherapy planning to better define the target volume and for elective dose escalation can be achieved by using positron emission tomography–computed tomography (PET–CT) information for treatment planning [30.18]. The standardized uptake value of pre-treatment 18-fluordeoxyglucose PET is predictive of local recurrence after radiotherapy in various tumour types [30.19]. As suggested from the experience with glioblastoma, a more efficient delineation of the tumour volume could also emerge from information on viable hypoxic cells that take up 18-F-fluoromizonidazole PET. These areas could be targeted through specific hypoxic cell radiosensitizers or with high energy particles. The intrinsic radioresistance of glioblastomas, and the inability to improve clinical outcomes through various radiation modalities and fractionation schedules, emphasizes the critical need for improved understanding of the complex molecular biology of this disease, as evidenced by a recent molecular classification of glioblastomas, which may yield novel therapeutic insights [30.20]. Temozolomide, in combination with radiation, was the first treatment breakthrough in many years in the treatment of glioblastoma, and the elucidation of the MGMT (O(6)-methylguanine-DNA-methyl transferase) pathway [30.21] has provided an invaluable prognostic and predictive marker.

### 30.3.2. Brachytherapy

Low dose rate (LDR) brachytherapy is being gradually replaced by high dose rate (HDR) brachytherapy. In the developing world, and in particular in certain regions with a high incidence of cervical cancer, the potential for treating a larger number of patients on an ambulatory basis is clearly convenient and less resource intensive. The introduction of HDR brachytherapy based on cobalt-60 miniaturized sources represents an additional advantage because with these systems the source can be replaced every five years instead of every 3–4 months, as is the case with iridium-192, with the corresponding advantages of increased convenience, fewer regulatory and source installation procedures and lower costs [30.22]. Thus, the trend is towards a decline in cobalt-60 *teletherapy*, while HDR *brachytherapy* systems using cobalt-60 sources are becoming more popular in developing countries. Brachytherapy treatment planning based on cross-sectional imaging and delineation of volumes will become the standard.

### 30.3.3. Particle therapy

There are currently a total of 71 charged particle therapy facilities worldwide [30.23]. Of these, 61 offer treatment with proton beams and 10 offer treatment with carbon ion beams. But a more important fact is that at the time of writing, there are 42 additional facilities under construction around the world (11 of them in the United States of America) and 31 more in the planning phase. This indicates the keen interest and enthusiasm in this modality of treatment which has been technically refined and offers clinical results that are encouraging, notwithstanding the fact that these results are mostly single institution retrospective series. There is also a controversy regarding the need for prospective clinical trials comparing proton and photon therapy. Proponents of particle radiotherapy have cited the dose distribution characteristics of particle beams as evidence of its superiority over photon radiotherapy, thus arguing that prospective randomized trials are unnecessary or even unethical. Such trials are now being conducted with increasing frequency and it is hoped that they will shed light on the answers to many questions.

The cost of installation and operation of charged particle therapy facilities continues to be high, which has limited their use almost exclusively to high income countries. However, interest is being expressed and new projects are taking shape in developing countries as well. It is reasonable to expect that the use of charged particle therapy, in particular proton therapy, will become more widespread.

Technological developments will continue, and will certainly be important to improve the deposition of a well defined dose of ionizing radiation in a

well defined volume containing the malignant tumour and subclinical disease. Quality assurance processes will be redesigned and simplified in the face of more complex technologies in order to ensure that the correct dose is delivered to the correct tissue in the correct patient. Despite rapid technological advances, radiation oncologists should not 'view their patients through the opening of a collimator', but as patients with a complex array of multiple variables in mutual interaction — the natural history of the cancer as a disease; its impact on structure, on function and on cosmesis (i.e. the preservation, restoration or enhancement of physical appearance); the presence of co-morbidities; the effects of treatment interventions; symptomatic care and the psychosocial aspects.

## 30.4. DEVELOPMENTS IN BIOLOGY

A better understanding of the response of cancers to irradiation is slowly emerging, revealing the pathways employed by cancer cells for surviving after irradiation of different types, at different doses and at different dose rates. This, coupled with a deeper knowledge about molecular abnormalities in the cancers of specific patients, may offer opportunities for exploiting synthetic lethality. In other words, targeted drugs could selectively block certain pathways. That would permit repair of radiation injury by alternative pathways in healthy cells only, but not in malignant cells.

### 30.4.1. Targeted therapy

Molecular inhibition of epidermal growth factor receptor (EGFR) signalling represents one of the most promising current areas for the advancement of molecularly targeted cancer therapies. A series of EGFR inhibitors from both the monoclonal antibody and tyrosine kinase inhibitor class have shown clear clinical activity in the treatment of several common human cancers. Three EGFR inhibitors have recently gained the approval of the Food and Drug Administration (FDA) for cancer therapy in the United States of America, including the monoclonal antibody cetuximab and the small molecule tyrosine kinase inhibitors gefitinib and erlotinib. The rapidly increasing amount of preclinical and clinical data contributing to these FDA approvals confirms the central role of the EGFR as an important molecular target in epithelial malignancies. Indeed, one of the more striking clinical results in this field has been recently achieved by combining an EGFR inhibitor (cetuximab) with radiotherapy in the treatment of advanced head and neck cancer patients [30.24]. This experience is summarized here.

Only one randomized phase III study has shown that enhancing radiation sensitivity through a targeted molecular agent could translate into a clinical

benefit. Bonner et al. [30.25] compared radiotherapy alone with radiotherapy plus cetuximab, a monoclonal antibody targeting the EGFR, in the treatment of locoregionally advanced head and neck squamous carcinoma. The median duration of locoregional control and survival were both improved in the cetuximab group (24.4 versus 14.9 months, $p = 0.005$ and 49 versus 30.3 months, $p = 0.03$, respectively). Cetuximab is the only example of successful development of a targeted agent from the preclinical data to a positive phase III trial leading to FDA approval of the drug for combination therapy. The survival benefit of cetuximab was clearly attributable to improved local control, since there was no difference in distant metastases according to the treatment group. It should be pointed out though that the addition of cisplatin based chemotherapy to radiotherapy in head and neck cancer also results in a hazard ratio of death of 0.81 ($p = 0.0001$) and an absolute benefit of 6.5% at five years [30.26], thus confirming the value of combined chemoradiotherapy in this clinical setting.

All other controlled studies with cetuximab or other targeted agents were disappointing, with only slight improvement over existing drugs. The overall clinical gains realized to date with the EGFR inhibitors are modest for the global cancer population. Much remains to be learned regarding the rational integration of EGFR inhibitors into cancer treatment regimens as well as methods to optimize the selection of patients most likely to benefit from EGFR inhibition strategies. A better understanding of the underlying biological pathways and optimal sequencing will be mandatory for improving the development of anti-EGFR agents in combination with radiotherapy.

Future clinical trials should incorporate biomarkers to identify patients who are most likely to benefit from molecular targeting agents. Some biomarkers have already shown their ability to predict a response to certain chemotherapy or targeting agents such as DPC4 for chemoradiation in advanced pancreatic cancer [30.27], K-ras in colorectal carcinoma [30.28] or exon-9 activating mutation in non-small cell lung cancer and others.

### 30.4.2. Anti-angiogenesis

Angiogenesis is critical for a number of physiological and pathophysiological processes, and angiogenesis inhibitors are now being tested in the treatment of cancer [30.29]. Although anti-angiogenic agents offer great therapeutic potential, preclinical and clinical trial results suggest that these agents have a delayed onset of activity and may only induce disease stabilization for patients with advanced malignancy. The use of radiotherapy for cancer is also associated with therapeutic challenges that are distinct from those that might be expected with antiangiogenic agents. Thus, the use of angiogenesis inhibitors in combination with radiotherapy should help to overcome the limitations of each,

leading to enhanced efficacy and diminished toxicity. Translating the preclinical successes into clinical practice, identifying the optimal clinical indications, and maximizing the efficacy of anti-angiogenic therapy for cancer patients have been more challenging than anticipated. Long term clinical experience with the use of anti-angiogenic factors has failed to show a significant survival advantage in treated patients [30.30].

The development of targeted therapeutics against cancer, with improved discrimination between tumour cells and non-malignant counterparts, is one of the major goals of current anti-cancer research. Tumour angiogenesis has been considered a particularly useful target for therapy and the effect of anti-angiogenic therapy has improved the therapeutic index. At present, angiogenesis inhibitors have been shown to prolong progression free survival, but only have a small effect on overall survival in patients with cancer [30.31].

### 30.4.3. Regenerative medicine

Supralethal irradiation to the diseased bone marrow followed by allogeneic stem cell transplantation to regenerate healthy marrow has saved many patients with haematological malignancies. The same principle can be applied in the field of regenerative medicine for generating healthy liver tissue [30.32], pancreatic tissue and neurological tissue. The feasibility has already been established by animal studies in the case of the liver and the first human trials are under way [30.33, 30.34].

### 30.4.4. Paracrine signalling

Some currently available drugs do affect various cell signalling processes including paracrine signalling. For example, Berbée [30.35] has shown that the radioprotective drug combination gamma-tocotrienol and pentoxifylline improves post-irradiation haematopoietic recovery. The drug combination was shown to induce the availability of a number of pro-regenerative cytokines in the bone marrow microenvironment, indicating that paracrine signalling may be of importance. Increasing the knowledge of post-irradiation and therapy induced paracrine responses is essential to develop new insights to decrease radiation induced normal tissue injury. Hence, future studies should include adequate assays to measure the local presence or release of paracrine factors, as opposed to only measuring systemic effects. In summary, paracrine signalling may play an important role in tissue repair.

### 30.4.5. Stem cell therapeutics

Normal tissue damage after radiotherapy is still a major problem in cancer treatment. Stem cell therapy may in the future provide a means to reduce radiation induced side effects and improve the quality of life of patients. A number of different types of stem cells are being investigated for their potential to treat a variety of disorders. Their current status, localization, characterization, isolation and potential in stem cell based therapies are the subject of active research. Although clinical adult stem cell research is still at an early stage, preclinical experiments show the potential these therapies may have. Based on the major advances made in this field, stem cell based therapy has great potential to allow prevention or treatment of normal tissue damage after radiotherapy [30.36].

Preclinical studies have shown that the remaining stem cells can be stimulated to enhance regeneration in irradiated tissues by the application of growth factors and bone marrow derived cells. These therapies, however, only have therapeutic potential when a sufficient number of stem/progenitor cells have survived the radiation. If not, stem cell therapy could be an option. The use of embryonic stem cells or induced pluripotent stem cells, however, is still in its infancy. Therefore, adult stem cell therapy is more feasible in the near future. For patients receiving radiotherapy, the collection of tissue stem cells before treatment is feasible. In fact, bone marrow transplantation has been used for many years to re-establish haematopoiesis. Adult stem cells have now been isolated and characterized for several organs.

Radiation induced organ failure often occurs as a result of reduced functioning of the tissue stem cells that can no longer replace terminally differentiated functional cells, resulting in a loss of homeostasis. The lack of replenishment of these functional cells is thought to be due to radiation induced sterilization of endogenous stem cells. Replenishment of the depleted stem cell compartment should allow regeneration of irradiated tissues. New scientific knowledge and biotechnological developments indicate that stem cell therapy may rescue damaged or diseased organs [30.37].

Currently, a wide variety of stem cell therapies are being investigated for their potential to treat radiation induced normal tissue damage. Stem cell therapy may include: local induction of stem cell proliferation in irradiated/damaged tissues (i.e. local administration of growth factors such as keratinocyte growth factor), local delivery of molecular/viral vectors to express stem cell growth factors in situ, and/or transplantation of stem cells in the damaged area.

Positive results with stem cell therapy after irradiation of different tissues (including the salivary gland, skin, muscle, intestine and spinal cord) showing functional and pathohistological improvement were obtained in different animal models. A reduction in radiation induced myelopathy (remyelination)

was observed after transplantation of genetically altered stem cells. Also, post-irradiation muscle was formed after transplantation of myoblasts [30.38] or adult bone marrow derived cells [30.39].

Although the first results of stem cell therapy after irradiation look encouraging (positive proof of principle), knowledge regarding stem cell therapy is not yet sufficient for its clinical application. To successfully use stem cells, it is important to understand their nature and qualities, the mechanism by which they differentiate into mature, functional cells and their capacity to repair damaged tissues in animal models. In order to develop experimental protocols for the amelioration of radiotherapy induced side effects by stem cell therapy, a number of questions need to be answered, such as:

(a) What are the optimal time point(s) for stem cell therapy?
(b) Which cells/compounds or combinations have the highest potential of reducing radiation induced tissue toxicity in a specific tissue?
(c) What are the risks of stem cell therapy?

Successful replacement of stem cells and the subsequent amelioration or reduction of radiation induced complications may open the road to completely new strategies in radiotherapy and can help in combating cancer.

### 30.4.6. Nanotechnology

The use of nanotechnology for medical applications is a rapidly expanding field [30.40]. Increasing numbers of novel diagnostic and therapeutic schemes are emerging, including many in the area of cancer medicine. Nanomedicine is the interaction of cellular and molecular components with nanoparticles. Such particles can be made of lipids, polymers, semiconductors or metals, created in the form of particles, shells, rods, tubes or quantum dots, among others. The linking factor is scale — such particles are up to 100 nm in size, similar in size to large biological molecules and structures inside cells. The advantage of nanoscale technology in cancer medicine is that if the particles are less than 50 nm, they can enter cells. If they are less than 20 nm, they can also move out of small blood vessels. There may be potential applications of nanotechnology in radiotherapy, including target selection, volume delineation, radiation sensitization, combined chemo- and radiotherapy schemes, and radiation protection of normal tissue. Along these lines, nanotechnology could potentially play a role in radiation oncology. Employing nanoparticle enhanced imaging techniques to better define target volumes, for example, could enhance the quality of the ensuing radiation treatment.

Nanotechnologies offer a new world of therapeutic possibilities for cancer. For example in radiotherapy, novel radiosensitization strategies are under investigation [30.41–30.43].

Gold nanoparticles have many properties that are attractive for use in cancer therapy. They are small and can penetrate widely throughout the body, preferentially accumulating at tumour sites due to the enhanced permeability of tumour endothelium. Importantly, they can bind many proteins and drugs and can be actively targeted to cancer cells overexpressing cell surface receptors. While they are biocompatible, it is clear that gold nanoparticle preparations can be toxic in in vitro and in vivo systems. Gold nanoparticles have a high atomic number, which leads to greater absorption of kilovoltage (kV) X rays and provides greater contrast than standard agents [30.42].

Research has already shown that gold nanoparticles can enhance the efficacy of low energy X rays in irradiated cells [30.40]. However, for use in humans, the key consideration is safety.

The proof of principle was made in 2004 when Hainfeld et al. [30.45] published in vivo results of radiation enhancement using 1.9 nm gold nanoparticles administered intravenously to EMT-6 mammary carcinoma bearing mice. Since these experiments, the clinical application remains limited. A better understanding of the pharmacology of gold nanoparticles is needed, including an evaluation of the benefit of targeted versus passive distribution, an evaluation of the pharmacokinetics at the tissue and cellular levels (defining where the nanoparticles are located and for how long), as well as the evaluation of potential toxicities.

Nanoparticles of amifostine, for example, have been shown to provide significant protection from acute whole body gamma irradiation injury in mice [30.46]. Some unresolved issues that need to be addressed in the future include the need for further work on selective targeting of cancer cells, methods of nanoparticle delivery and studies into long term toxicity.

### 30.4.7. Genomics

This is an age of massive genomic surveys. More than a decade after the completion of the Human Genome Project, large scale genomic sequencing efforts directed at cancer and congenital syndromes are under way. There is a wealth of data produced by international research teams supported by private and public funding agencies that have enlarged the catalogue of genetic changes associated with neoplasia and other diseases using sequencing methods and heavy duty bioinformatics. The Cancer Genome Atlas [30.47, 30.48] has provided detailed information on more than 10 000 cancer genomes. The impact of cancer genomics research on the radiosensitivity of tumours and normal tissues can

only be anticipated, and the use of genomics in quotidian practice lies in the near future.

## 30.5. THE FUTURE

Damage to the DNA molecule appears to be the fundamental cause of cancer at the molecular level. However, factors that occur at the cell population level (tissues) seem to play an important role as well. It is unlikely that there will be a single 'curative' treatment, since what we call 'cancer' is in reality about 200 different diseases. While survival rates have doubled since the 1970s, too many types of cancer and metastatic spread are still beyond realistic control or cure.

Eventually, individualized forms of cancer treatment will use comprehensive physiological, anatomical, cellular and metabolic image data to design a patient's treatment. New, optimized combinations of radiation, surgery, and targeted chemotherapy, including radioresponse enhancers, will have to be worked out for the different forms of cancer. To make significant progress into individualized radiation oncology, technological development, biological research and clinical experience will need to be better integrated.

This discussion has focused on the future of radiation oncology as a discipline based on developments in technology and biological research. The discussion cannot end without a reference to the main topic of this book, namely the role of radiotherapy in cancer care from a global perspective. This book (Chapter 5) and others have described the current unequal level of access to adequate radiotherapy services between high income and lower income countries. But the inequality exists also inside many countries between affluent and impoverished sectors of the population. This inequality in access is another manifestation of inadequate access to health care services in general, and of economic inequality in the broader sense.

Health and non-communicable diseases have been brought to the attention of the international community and a number of actions and plans are under way to address this problem. In the particular field of radiotherapy of cancer — and looking at the international response to the HIV/AIDS epidemic — it seems clear that only concerted, international effort can induce change in the current situation. Governments should assume their responsibility to ensure that adequate services are available and to facilitate access to these services to the impoverished sectors of society, while at the same time establishing educational campaigns, prevention and early detection programmes, adequate diagnostic and treatment services and palliative care programmes within the framework of national cancer control plans.

The practice of radiation oncology should not be technology/industry driven, but should have oncology and biology driving the care of the cancer patient. With further advances the hope is to turn what was once a sure killer into a manageable disease.

## 30.6. KEY POINTS

— Epidemiology projections suggest that cancer incidence will increase in the near future, and with it the need for cancer treatment modalities, including radiotherapy.
— A decline is foreseen in the use of cobalt-60 teletherapy units in the future as they continue to be replaced by single energy linacs in developing countries.
— Linacs that incorporate an MRI for image guidance in one unit are already being tested.
— Molecular inhibition of epidermal growth factor receptor (EGFR) signalling represents one of the most promising areas for the advancement of molecularly targeted cancer therapies.
— Paracrine signalling may play an important role in tissue repair.
— Successful replacement of stem cells and subsequent amelioration or reduction of radiation induced complications may open the road to completely new strategies in radiotherapy.
— Nanotechnologies offer a new world of therapeutic possibilities for cancer. For example in radiotherapy, improved target definition and novel radiosensitization strategies are under investigation.
— The impact of cancer genomics research on the radiosensitivity of tumours and normal tissues can only be anticipated; the use of genomics in quotidian practice lies in the near future.
— To make significant progress into individualized radiation oncology, technological development, biological research and clinical experience need to be better integrated.

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# ABBREVIATIONS

| | |
|---|---|
| 2-D | two dimensional |
| 3-D | three dimensional |
| 3-D CRT | three dimensional conformal radiotherapy |
| 5-FU | 5-fluorouracil |
| ABC | activity based costing model |
| ABMS | American Board of Medical Specialties |
| ACE | angiotensin converting enzyme |
| ACGME | Accreditation Council for Graduate Medical Education |
| ACHS | Australian Council for Health Standards |
| ACPSEM | Australasian College of Physical Scientists and Engineers in Medicine |
| ADT | androgen deprivation therapy |
| AIDS | acquired immunodeficiency syndrome |
| AIRO | Italian Association of Radiation Oncology |
| AORTIC | African Organisation for Research and Training in Cancer |
| ALATRO | Latin American Association for Radiation Oncology |
| APBI | accelerated partial breast irradiation |
| APR | abdominoperineal resection |
| ARCAL | Regional Cooperation Agreement for the Promotion of Nuclear Science and Technology in Latin America and the Caribbean |
| ASCO | American Society of Clinical Oncology |
| ASN | French Nuclear Safety Authority |
| ASR | age standardized rate |
| ASTRO | American Society for Radiation Oncology |
| CanMEDS | Canadian Medical Education Directives for Specialists |
| CD4 | cluster of differentiation 4-lymphocytes |
| CDH | Cancer Diseases Hospital (Zambia) |
| CGE | cobalt gray equivalent |
| CHART | continuous hyperfractionated accelerated radiotherapy |
| CI | confidence interval |
| CMJAH | Charlotte Maxeke Johannesburg Academic Hospital |
| CNS | central nervous system |
| CPD | continuing professional development |
| CQMP | clinically qualified medical physicist |
| CRP | coordinated research project |
| CSI | craniospinal irradiation |
| CSTRO | Chinese Society of Radiation Oncology |
| CT | computed tomography |

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|---|---|
| CTBP1 | C-terminal-binding protein 1 |
| DICOM | digital imaging and communications in medicine |
| DIRAC | Directory of Radiotherapy Centres (IAEA) |
| DNA | deoxyribonucleic acid |
| DSB | double strand break |
| EBRT | external beam radiotherapy |
| EC | European Commission |
| ECRI | Emergency Care Research Institute |
| EEA | European Economic Area |
| EGFR | epidermal growth factor receptor |
| ELISA | enzyme-linked immunosorbent assay |
| EPID | electronic portal imaging device |
| ESTRO | European Society for Radiotherapy and Oncology |
| EU | European Union |
| FDA | Food and Drug Administration (USA) |
| FDG-PET | fluordeoxyglucose positron emission tomography |
| FMEA | failure mode and effect analysis |
| FS | fractionation schedules |
| FTE | full time equivalent |
| GDP | gross domestic product |
| GEC–ESTRO | Groupe Européen de Curiethérapie (GEC) — European Society for Radiotherapy and Oncology (ESTRO) |
| GSI | Gesellschaft für Schwerionenforschung (Germany) |
| GTV | gross tumour volume |
| Gy | gray (a unit of absorbed radiation dose) |
| HAART | highly active antiretroviral therapy |
| HDI | Human Development Index (United Nations) |
| HDR | high dose rate |
| HDRBT | high dose rate brachytherapy |
| HHV-8 | human herpes virus 8 |
| HI | high income (countries) |
| HIBMC | Hyogo Ion Beam Medical Center (Japan) |
| HIF | hypoxia inducible factor |
| HIOB | intra-operative electron boost and hypofractionated whole-breast irradiation during breast-conserving treatment |
| HIT | Heidelberg Ion-Beam Therapy Center (Germany) |
| HIV | human immunodeficiency virus |
| HPV | human papillomavirus |
| HR | homologous recombination |
| ICRU | International Commission on Radiation Units and Measurements |

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|---|---|
| IGRT | image guided radiation therapy |
| IHE-RO | Integrating the Healthcare Enterprise in Radiation Oncology |
| IHSDN | integrated health service delivery network |
| IMP | Institute of Modern Physics (China) |
| IMRT | intensity modulated radiation therapy |
| INES | International Nuclear and Radiological Event Scale (IAEA–OECD/NEA) |
| IOERT | intraoperative electron radiotherapy |
| IOMP | International Organization for Medical Physics |
| IORT | intraoperative radiotherapy |
| ISIORT | International Society of Intraoperative Radiotherapy |
| ISIORT Europe | International Society of Intraoperative Radiotherapy European Group |
| ISO | International Organization for Standardization |
| KS | Kaposi's sarcoma |
| LAR | low anterior resection |
| LBNL | Lawrence Berkeley National Laboratory |
| LDR | low dose rate |
| LET | linear energy transfer |
| LMICs | low and middle income countries |
| MCQ | multiple choice questions |
| MDG | Millennium Development Goals (United Nations) |
| MGMT | O(6)-methylguanine-DNA-methyltransferase pathway |
| MLC | multileaf collimator |
| MM | multimodality |
| MRI | magnetic resonance imaging |
| MRN | Mre11, Rad50 and Nbs1 protein complex |
| MV | megavoltage |
| NCCP | national cancer control programme |
| NCD | non-communicable disease |
| NGO | non-governmental organization |
| NHEJ | non-homologous end joining |
| NHL | non-Hodgkin's lymphoma |
| NICE | National Institute for Health and Care Excellence |
| NIRS | National Institute of Radiological Sciences (Japan) |
| NSAID | non-steroidal anti-inflammatory drug |
| NSCLC | non-small cell lung cancer |
| NTCP | normal tissue complication probability |
| OAR | organs at risk |
| OER | oxygen enhancement ratio |
| OFID | OPEC Fund for International Development |

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|---|---|
| OPEC | Organization of the Petroleum Exporting Countries |
| OSCE | Objective Structured Clinical Examination |
| PACT | Programme of Action for Cancer Therapy (IAEA) |
| PAHO | Pan American Health Organization |
| PET | positron emission tomography |
| PIR | projected incidence rate |
| PNG | Papua New Guinea |
| PORTEC | Post-Operative Radiation Therapy in Endometrial Carcinoma |
| PSA | prostate-specific antigen |
| PTCOG | Particle Therapy Co-operative Group |
| PTV | planning target volume |
| QA | quality assurance |
| QA/QC | quality assurance/quality control |
| QC | quality control |
| QGUH | Queen Giovanna University Hospital (Bulgaria) |
| QUALY | quality adjusted life year |
| QUATRO | Quality Assurance Team for Radiation Oncology (IAEA) |
| RBE | relative biological effectiveness |
| RNA | ribonucleic acid |
| ROMP | radiation oncology medical physics |
| ROSIS | Radiation Oncology Safety Information System |
| RPA | replication protein A |
| RR | relative risk |
| RT | radiotherapy |
| RTE | IAEA Radiotherapy Cost Estimator |
| RTOG | Radiation Therapy Oncology Group |
| RTT | radiotherapist |
| RTU rate | radiotherapy utilization rate |
| RVS | record and verify system |
| SANTRO | Sino-American Network for Therapeutic Radiology and Oncology |
| SBRT | stereotactic body radiotherapy |
| SSB | single strand break |
| SSDL | secondary standards dosimetry laboratory (IAEA) |
| TA-GVHD | transfusion-associated graft-versus-host disease |
| TARGIT | targeted intraoperative radiotherapy |
| TBI | total body irradiation |
| TCP | tumour control probability |
| TDS | treatment delivery system |
| TMS | treatment management system |
| TPS | treatment planning system |

| | |
|---|---|
| TROG | Trans-Tasman Radiation Oncology Group |
| UICC | Union for International Cancer Control |
| UN | United Nations |
| UNAIDS | Joint United Nations Programme on HIV/AIDS |
| V-MAT | volumetric modulated arc therapy |
| WBRT | whole breast radiotherapy |
| WHO | World Health Organization |

# GLOSSARY

*The following definitions are from the United States National Cancer Institute web site (www.cancer.gov).*

**accelerated radiotherapy.** Radiation treatment, in which the total dose of radiation is given over a shorter period of time (fewer days) compared with standard radiotherapy.

**adjuvant therapy.** Additional cancer treatment given after the primary treatment to reduce the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiotherapy, hormone therapy, targeted therapy or biological therapy.

**adverse effect.** An unexpected medical problem that occurs during treatment with a drug or other therapy. Adverse effects do not have to be caused by the drug or therapy, and they may be mild, moderate, or severe. Also called adverse event.

**anaesthesia.** The loss of feeling or sensation as a result of drugs. General anaesthesia causes temporary loss of consciousness. Local or regional anaesthesia numbs only a certain area.

**anticancer therapy.** Treatment to stop or prevent cancer.

**barrier.** Something that blocks, prevents, separates or limits.

**benign tumour.** An abnormal non-cancerous growth that does not spread to other places in the body.

**biopsy.** The removal of a sample of tissue to see whether cancer cells are present. There are several kinds of biopsy. In some, a very thin needle is used to draw fluid and cells from a lump. In a core biopsy, a larger needle is used to remove significantly more tissue.

**boron neutron capture therapy (BNCT).** A type of radiotherapy. A substance that contains boron is injected into a blood vessel. The boron collects in tumour cells. The patient then receives radiotherapy with atomic particles called neutrons. The neutrons react with the boron to kill the tumour cells without harming normal cells. BNCT is being studied as a treatment for glioblastoma multiforme and recurrent head and neck cancer.

**brachytherapy.** A type of radiotherapy in which radioactive material sealed in needles, seeds, wires or catheters is placed directly into or near a tumour. Also called implant radiotherapy, internal radiotherapy and radiation brachytherapy.

**brain metastasis.** Cancer that has spread from the original (primary) tumour to the brain.

**cancer.** Cancer develops when cells in the body begin to grow out of control. Normal cells grow, divide and die. Instead of dying, cancer cells continue to grow and form new abnormal cells. Cancer cells often travel to other body parts where they grow and replace normal tissue. This process, called metastasis, occurs as the cancer cells get into the bloodstream or lymph vessels.

**carcinogen.** A substance known to cause cancer.

**carcinoma.** A malignant tumour that begins in the lining layer (epithelial cells) of organs. At least 80% of all cancers are carcinomas.

**catheter.** A thin, flexible hollow tube. Catheters can be used to allow fluids to enter or leave the body. Catheters can also be used to temporarily insert radioactive sources into tumours, as in breast brachytherapy or high dose rate prostate brachytherapy.

**cell cycle.** The process a cell goes through each time it divides. The cell cycle consists of a series of steps during which the chromosomes and other cell material double to make two copies. The cell then divides into two daughter cells, each receiving one copy of the doubled material. The cell cycle is complete when each daughter cell is surrounded by its own outer membrane. Also called mitotic cycle.

**cervix.** The lower, narrow end of the uterus that forms a canal between the uterus and vagina.

**chemoradiotherapy.** Treatment that combines chemotherapy with radiotherapy. Also called chemoradiation.

**clinical trial.** A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or treatment of a disease. Also called clinical study.

**conventional treatment.** Treatment that is widely accepted and used by most health care professionals. It is different from alternative or complementary therapies, which are not as widely used. Examples of conventional treatment for cancer include chemotherapy, radiotherapy and surgery. Also called conventional therapy.

**computed tomography (CT) scan.** A series of detailed pictures of areas inside the body taken from different angles; the pictures are created by a computer linked to an X ray machine. Also called computerized tomography and computerized axial tomography (CAT) scan.

**dose.** The amount of medicine taken, or radiation given, at one time.

**dosimetrist.** A person who determines the proper radiation dose for treatment.

**dosimetry.** Measurement of radiation exposure from X rays, gamma rays or other types of radiation used in the treatment or detection of diseases, including cancer.

**electromagnetic radiation.** Radiation that has both electric and magnetic fields and travels in waves. It comes from natural and human-made sources. Electromagnetic radiation can vary in strength from low energy to high energy. It includes radio waves, microwaves, infrared light, visible light, ultraviolet light, X rays and gamma rays. Also called EMR.

**electron.** A small particle with a negative charge that is found in all atoms. Streams of electrons made by special equipment can be used for radiation treatment.

**electron beam.** A stream of electrons (small negatively charged particles found in atoms) that can be used for radiotherapy.

**external radiotherapy.** A type of radiotherapy that uses a machine to aim high energy rays at the cancer from outside of the body. Also called external beam radiotherapy.

**event free survival.** The length of time after primary cancer treatment ends that the patient remains free of certain complications or events that the treatment was intended to prevent or delay. These events may include the return of the cancer or the onset of certain symptoms, such as bone pain from cancer that

has spread to the bone. In a clinical trial, measuring the event free survival is one way to see how well a new treatment works. Also called EFS.

**fibrosis.** The growth of fibrous tissue.

**fractionation.** Dividing the total dose of radiotherapy into several smaller, equal doses delivered over a period of several days.

**five year survival rate.** The percentage of people in a study or treatment group who are alive five years after they were diagnosed with or started treatment for a disease, such as cancer. The disease may or may not have come back.

**gamma irradiation.** A type of radiotherapy that uses gamma radiation. Gamma radiation is a type of high energy radiation that is different from X rays.

**Gleason score.** A system of grading prostate cancer cells describing how aggressive the cancer appears. It is used to determine the best treatment and to predict how well a person is likely to respond to treatment. The lower the Gleason score, the closer the cancer cells are to normal cells; the higher the Gleason score, the more abnormal the cancer cells.

**hazard ratio.** A measure of how often a particular event occurs in one group compared with how often it occurs in another group, over time. In cancer research, hazard ratios are often used in clinical trials to measure survival at any point in time in a group of patients who have been given a specific treatment compared with a control group given another treatment or a placebo. A hazard ratio of one means that there is no difference in survival between the two groups. A hazard ratio of greater than one or less than one means that survival was better in one of the groups.

**helical tomotherapy.** A type of therapy in which radiation is aimed at a tumour from many different directions. The patient lies on a table and is moved through a doughnut shaped machine. The radiation source in the machine rotates around the patient in a spiral pattern. Before irradiation, a 3-D image of the tumour is taken. This helps doctors find the highest dose of radiation that can be used to kill tumour cells while causing less damage to nearby tissue. Helical tomotherapy is a type of intensity modulated radiation therapy (IMRT). Also called tomotherapy.

**high dose rate (HDR) brachytherapy.** A modality of brachytherapy using a high activity source and delivering a radiation dose rate of more than 12

Gy/h, although the usual dose rate delivered in practice is approximately 100–300 Gy/h.

**human papillomavirus (HPV).** A type of virus that can cause abnormal tissue growth (for example, warts) and other changes to cells. Infection for a long time with certain types of HPV can cause cervical cancer. HPV may also play a role in some other types of cancer, such as anal, vaginal, vulvar, penile, oropharyngeal and squamous cell skin cancers.

**hypofractionated radiotherapy.** Radiation treatment in which the total dose of radiation is divided into large doses and treatments are administered less than once a day. Also called hypofractionation.

**image guided radiation therapy (IGRT).** A procedure that uses a computer to create a picture of a tumour to help guide the radiation beam during radiotherapy. The pictures are made using CT, ultrasound, X ray or other imaging techniques. Image guided radiation therapy makes radiotherapy more accurate and causes less damage to healthy tissue.

**implant radiotherapy.** A type of radiotherapy in which radioactive material sealed in needles, seeds, wires, or catheters is placed directly into or near a tumour. Also called brachytherapy, internal radiotherapy and radiation brachytherapy.

**intensity modulated radiation therapy (IMRT).** A type of 3-D radiotherapy that uses computer generated images to show the size and shape of the tumour. Thin beams of radiation of different intensities are aimed at the tumour from many angles. This type of radiotherapy reduces the damage to healthy tissue near the tumour.

**in vivo.** In the body. The opposite of in vitro (outside the body or in the laboratory).

**intracavitary radiotherapy.** A type of internal radiotherapy in which radioactive material sealed in needles, seeds, wires or catheters is placed directly into a body cavity such as the chest cavity or the vagina.

**ionizing radiation.** A type of radiation made (or emitted) by X ray procedures, radioactive substances, rays that enter the Earth's atmosphere from outer space and other sources. At high doses, ionizing radiation increases chemical activity inside cells and can lead to health risks, including cancer.

**intraoperative radiotherapy (IORT).** Radiation treatment aimed directly at a tumour during surgery.

**irradiation.** The use of high energy radiation from X rays, gamma rays, neutrons, protons and other sources to kill cancer cells and shrink tumours. Radiation may come from a machine outside the body (external beam radiotherapy), or it may come from radioactive material placed in the body near cancer cells (internal radiotherapy). Systemic irradiation uses a radioactive substance, such as a radiolabelled monoclonal antibody, that travels in the blood to tissues throughout the body. Also called radiation therapy and radiotherapy.

**joint.** In medicine, the place where two or more bones are connected. Examples include the shoulder, elbow, knee and jaw.

**kidney cancer.** Cancer that forms in tissues of the kidneys. Kidney cancer includes renal cell carcinoma (cancer that forms in the lining of very small tubes in the kidney that filter the blood and remove waste products) and renal pelvis carcinoma (cancer that forms in the centre of the kidney where urine collects). It also includes Wilms tumour, which is a type of kidney cancer that usually develops in children under the age of 5.

**larynx.** The area of the throat containing the vocal cords and used for breathing, swallowing and talking. Also called voice box.

**late effect.** A health problem that occurs months or years after a disease is diagnosed, or after treatment has ended. Late effects may be caused by cancer or cancer treatment. They may include physical, mental and social problems and second cancers.

**linear accelerator (linac).** A machine that uses electricity to form a stream of fast moving subatomic particles. This creates high energy radiation that may be used to treat cancer. Also called megavoltage linac and MV linac.

**local therapy.** Treatment that affects cells in the tumour and the area close to it.

**localization.** The process of determining or marking the location or site of a lesion or disease. May also refer to the process of keeping a lesion or disease in a specific location or site.

**long term side effect.** A problem that is caused by a disease or treatment of a disease and may continue for months or years. Long term side effects of cancer treatment include heart, lung, kidney or gastrointestinal tract problems; pain, numbness, tingling, loss of feeling, or heat or cold sensitivity in the hands or feet; fatigue; hearing loss; cataracts; and dry eyes or dry mouth.

**low dose rate (LDR) brachytherapy.** Brachytherapy in which sources are left in place for the duration of treatment. This includes temporary LDR brachytherapy treatment, in which patients are hospitalized for several days of temporary brachytherapy. It also includes permanent LDR brachytherapy treatment in which seeds are permanently placed.

**lymph node (lymph gland).** A rounded mass of lymphatic tissue that is surrounded by a capsule of connective tissue. Lymph nodes are spread out along lymphatic vessels and contain many lymphocytes, which filter the lymphatic fluid (lymph). Lymph nodes are part of the body's immune system.

**magnetic resonance imaging (MRI).** A procedure in which radio waves and a powerful magnet linked to a computer are used to create detailed pictures of areas inside the body. These pictures can show the difference between normal and diseased tissue. MRI provides better images of organs and soft tissue than other scanning techniques, such as CT or X rays. MRI is especially useful for imaging the brain, the spine, the soft tissue of joints and the inside of bones.

**malignancy.** A term for diseases in which abnormal cells divide without control and can invade nearby tissues. Malignant cells can also spread to other parts of the body through the blood and lymph systems. There are several main types of malignancy. Carcinoma is a malignancy that begins in the skin or in tissues that line or cover internal organs. Sarcoma is a malignancy that begins in bone, cartilage, fat, muscle, blood vessels or other connective or supportive tissue. Leukaemia is a malignancy that starts in blood forming tissue, such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the blood. Lymphoma and multiple myeloma are malignancies that begin in the cells of the immune system. Central nervous system cancers are malignancies that begin in the tissues of the brain and spinal cord. Also called cancer.

**median survival.** The length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that half of the patients in a group of patients diagnosed with the disease are still alive. In a clinical trial, measuring the median survival is one way to see how well a new treatment is working. Also called median overall survival.

**medical oncologist.** A doctor who specializes in diagnosing and treating cancer using chemotherapy, hormonal therapy and biological therapy.

**meta-analysis.** A process that analyses data from different studies done about the same subject. The results of a meta-analysis are usually stronger than the results of any study by itself.

**metastasis.** The spread of cancer from one part of the body to another. Tumours formed from cells that have spread are called secondary tumours and contain cells that are like those in the original (primary) tumour.

**multidisciplinary care.** Multidisciplinary care is a team approach to the provision of health care by all relevant medical and allied health disciplines as a means of achieving best practice. Through their combined understanding, all members of the team liaise and cooperate with each other and with the patient to diagnose, treat and manage the condition to the highest possible standard of care. In the case of the cancer patient, the multidisciplinary team normally includes the radiation oncologist, surgeon, medical oncologist, medical physicist, radiation oncology nurse, radiotherapist, psychologist, social worker and/or other specialists.

**mutation.** Any change in the DNA sequence of a cell. Mutations may be caused by mistakes during cell division, or they may be caused by exposure to DNA damaging agents in the environment. Mutations can be harmful, beneficial or have no effect. If they occur in cells that make eggs or sperm, they can be inherited; if mutations occur in other types of cells, they are not inherited. Certain mutations may lead to cancer or other diseases.

**nasopharyngeal cancer.** Cancer that forms in tissues of the nasopharynx (upper part of the throat behind the nose). Most nasopharyngeal cancers are squamous cell carcinomas (cancer that begins in flat cells lining the nasopharynx).

**non-steroidal anti-inflammatory drug (NSAID).** A drug that decreases fever, swelling, pain and redness.

**oncologist.** A doctor who specializes in treating cancer. Some oncologists specialize in a particular type of cancer treatment. For example, a radiation oncologist specializes in treating cancer with radiation.

**oncology nurse.** A nurse who specializes in treating and caring for people who have cancer.

**opioid.** A substance used to treat moderate to severe pain. Opioids are like opiates, such as morphine and codeine, but are not made from opium. Opioids bind to opioid receptors in the central nervous system. Opioids used to be called narcotics. An opioid is a type of alkaloid.

**optic chiasm.** The place in the brain where some of the optic nerve fibres coming from one eye cross optic nerve fibres from the other eye.

**palliation.** Relief of symptoms and suffering caused by cancer and other life threatening diseases. Palliation helps a patient feel more comfortable and improves the quality of life, but does not cure the disease.

**palliative care.** The physical, social, psychological and spiritual care of patients with life limiting illnesses that is delivered by a multidisciplinary team. Palliative care is an approach to improving the quality of life of patients and their families facing problems associated with life threatening disease through the prevention and relief of suffering by means of the early identification and accurate assessment and treatment of pain and other physical, psychological and spiritual problems.

**performance status.** A measure of how well a patient is able to perform ordinary tasks and carry out daily activities.

**photon beam radiotherapy.** A type of radiotherapy that uses X rays or gamma rays that come from a linear accelerator. The radiation dose is delivered at the surface of the body and goes into the tumour and through the body. Photon beam radiotherapy is different from proton beam radiotherapy.

**positron emission tomography–computed tomography (PET–CT) scan.** A procedure that combines the images from a PET scan and a CT scan. The PET and CT scans are performed at the same time with the same machine. The combined scans give more detailed images of areas inside the body than either scan gives by itself. A PET–CT scan may be used to

help diagnose disease, such as cancer, plan treatment, or find out how well treatment is working.

**prostate.** A gland in the male reproductive system just below the bladder. The prostate surrounds part of the urethra, the canal that empties the bladder, and produces a fluid that forms part of semen.

**proton beam radiotherapy.** A type of radiotherapy that uses streams of protons (tiny particles with a positive charge) to kill tumour cells. This type of treatment can reduce the amount of radiation damage to healthy tissue near a tumour. It is used to treat cancers of the head and neck, and organs such as the brain, eye, lung, spine and prostate. Proton beam radiation is different from X ray radiation.

**quality assurance (QA).** A process that looks at activities or products on a regular basis to make sure they are being completed at the required level of excellence. In clinical trials, QA makes sure that all parts of the trial follow the law and the good clinical practice guidelines.

**quality of life.** The overall enjoyment of life. Many clinical trials assess the effects of cancer and its treatment on the quality of life. These studies measure aspects of an individual's sense of well-being and ability to carry out various activities.

**radiation.** Energy released in the form of particle waves or electromagnetic waves. Common sources of radiation include radon gas, cosmic rays from outer space, medical X rays and energy given off by a radioisotope (unstable form of a chemical element that releases radiation as it breaks down and becomes more stable).

**radiation oncologist.** A doctor who specializes in using radiation to treat cancer.

**radiation physicist.** A person who ensures that the radiation machine delivers the required amount of radiation to the correct site in the body. The physicist works with the radiation oncologist to choose the treatment schedule and dose that has the best chance of killing the most cancer cells.

**radiosurgery.** A type of external radiotherapy that uses special equipment to position the patient and precisely administer a single large dose of radiation to a tumour. It is used to treat brain tumours and other brain disorders that cannot be treated by regular surgery. It is also being studied in the

treatment of other types of cancer. Also called stereotactic radiosurgery and stereotaxic radiosurgery.

**radiotherapist.** A health professional who administers radiation treatment.

**radiotherapy.** The use of high energy radiation from X rays, gamma rays, neutrons, protons and other sources to kill cancer cells and shrink tumours. Radiation may come from a machine outside the body (external beam radiotherapy), or it may come from radioactive material placed in the body near cancer cells (internal radiotherapy). Systemic radiotherapy uses a radioactive substance, such as a radiolabelled monoclonal antibody, that travels in the blood to tissues throughout the body. Also called irradiation and radiation therapy.

**radioactive.** Emitting radiation.

**radiopharmaceutical.** A drug that contains a radioactive substance and is used to diagnose or treat disease, including cancer. Also called radioactive drug.

**radiosensitizer.** Any substance that makes tumour cells easier to kill with radiotherapy. Some radiosensitizers are being studied in the treatment of cancer. Also called radiosensitizing agent.

**samarium-153 lexidronam pentasodium.** A type of radiopharmaceutical used to treat bone pain caused by bone cancer and other cancers that have spread to the bone. It contains a radioactive substance called samarium-153. Samarium-153 lexidronam pentasodium collects in bone and gives off radiation that may kill cancer cells. Also called Quadramet.

**simulation.** In cancer treatment, a process used to plan radiotherapy so that the target area is precisely located and marked.

**spinal cord compression.** Pressure on the spinal cord that may be caused by a tumour, a spinal fracture or other conditions. Spinal cord compression may cause pain, weakness, loss of feeling, paralysis, incontinence (inability to control urine or stool) or impotence (inability to have an erection of the penis).

**stage.** The extent of a cancer within the body, especially whether the disease has spread from the original site to other parts of the body.

**stent.** A device placed in a body structure (such as a blood vessel or the gastrointestinal tract) to provide support and keep the structure open.

**stereotactic body radiotherapy.** A type of external radiotherapy that uses special equipment to position a patient and precisely deliver radiation to tumours in the body (except the brain). The total dose of radiation is divided into smaller doses given over several days. This type of radiotherapy helps spare normal tissue.

**stereotactic radiotherapy.** A type of external radiotherapy that uses special equipment to position the patient and precisely deliver radiation to a tumour. The total dose of radiation is divided into several smaller doses given over several days. Stereotactic external beam radiotherapy is used to treat brain tumours and other brain disorders. It is also being studied in the treatment of other types of cancer, such as lung cancer. Also called stereotactic external beam radiotherapy and stereotaxic radiotherapy.

**stereotactic radiosurgery.** A type of external radiotherapy that uses special equipment to position the patient and precisely administer a single large dose of radiation to a tumour. It is used to treat brain tumours and other brain disorders that cannot be treated by regular surgery. It is also being studied in the treatment of other types of cancer. Also called radiation surgery, radiosurgery and stereotaxic radiosurgery.

**supportive care.** The treatment of the adverse effects of cancer treatment, such as nausea, vomiting, infections, cytopenia, mucositis, malignant effusions, paraneoplastic syndromes, oncological emergencies and nutritional support. It aims to optimize the comfort, function and social support of patients and their families at all stages of disease.

**tomotherapy.** A type of therapy in which radiation is aimed at a tumour from many different directions. The patient lies on a table and is moved through a doughnut shaped machine. The radiation source in the machine rotates around the patient in a spiral pattern. Before irradiation, a 3-D image of the tumour is taken. This helps doctors find the highest dose of radiation that can be used to kill tumour cells while causing less damage to nearby tissue. Tomotherapy is a type of IMRT. Also called helical tomotherapy.

**total body irradiation.** Radiotherapy to the entire body. It is usually followed by bone marrow or peripheral stem cell transplantation.

**treatment field.** In radiotherapy, the place on the body where the radiation beam is aimed.

**tumour.** An abnormal mass of tissue that results from excessive cell division. Tumours perform no useful body function. They may be benign (not cancerous) or malignant (cancerous).

**tumour staging.** An important step in the management of cancer. Typically, several tests are performed to determine three things. The first part is to quantify the size and extent of a primary cancer. The second is to determine whether nearby lymph nodes are involved by the cancer. The third is to check whether cancer has spread through the bloodstream to other parts of the body. Using this information, people with cancer are assigned a stage. This helps to determine the best course of treatment and it also predicts the response to treatment. Each type of cancer has a specific staging system.

**ultrasound.** A test that bounces sound waves off tissues and internal organs and changes the echoes into sonograms (pictures).

**ultraviolet (UV) radiation.** Invisible rays that are part of the energy that comes from the sun. Ultraviolet radiation that reaches the Earth's surface is made up of two types of rays, UVA and UVB. Ultraviolet radiation also comes from sun lamps and tanning beds. It can cause skin damage, premature ageing, melanoma and other types of skin cancer. It can also cause problems with the eyes and the immune system. Skin specialists recommend that people use sunscreens that protect the skin from both kinds of ultraviolet radiation. In medicine, ultraviolet radiation also comes from special lamps or a laser and is used to treat certain skin conditions such as psoriasis, vitiligo and skin tumours of cutaneous T-cell lymphoma.

**vascular.** Relating to or containing blood vessels.

**whole brain radiotherapy.** A type of external radiotherapy used to treat patients who have cancer in the brain. It is often used to treat patients whose cancer has spread to the brain, or who have more than one tumour or tumours that cannot be removed by surgery. Radiation is given to the whole brain over a period of many weeks.

**X ray.** A type of radiation used in the diagnosis and treatment of cancer and other diseases. In low doses, X rays are used to diagnose diseases by generating

images of the inside of the body. At high doses, X rays are used to treat cancer.

**X ray therapy.** A type of radiotherapy that uses high energy radiation from X rays to kill cancer cells and shrink tumours.

**yttrium-90.** A radioactive form of the rare metal yttrium that is used in radiation therapy to treat some types of tumours. Yttrium-90 can be linked to a molecule, such as a monoclonal antibody, to help it locate and bind to certain substances in the body, including cancer cells. The radiation may kill the cancer cells

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