Chapter 14. Radiation Therapy for Cancer

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Abstract

Radiation therapy (RT) is a key component of a comprehensive cancer treatment program, with the potential to contribute to effective and appropriate care in 50 percent of all cancer cases, alone or in combination with surgery and/or chemotherapy. The optimal deployment of radiotherapy requires the environment where the diagnostic services

Safe and effective RT requires trained staff, dedicated equipment, and a highly coordinated operational department. Numerous guidelines have been developed to guide safe equipment commissioning and radiotherapy facility operations. The global community offers resources to establish RT services. Countries at all economic levels have successfully developed RT initiatives, but access in low-income countries and low-and-middle-income countries is severely limited; only 20 percent of the population in Africa has access. Inadequate access to radiotherapy has also been observed in Europe, South America, and Asia. Although there are numerous barriers to radiotherapy, progress in establishing improved access has been observed in jurisdictions. It is important that radiotherapy be included in all population based cancer control plans as an essential element of cancer therapy armamentarium.

Introduction

Each year, more than 14 million new cases of cancer are diagnosed globally; radiation therapy (RT) has the potential to improve the rates of cure in 3.5 million cases and to provide palliative relief for another 3.5 million people. This conservative estimate is based on the fact that approximately 50 percent of all cancer patients can benefit from RT in the management of their disease (Barton, Frommer et al. 2006; Tyldesley, Delaney et al. 2011; Barton, Jacob et al. 2014) with approximately half of these patients presenting early enough to pursue curative intent.

Soon after the discovery of x-rays by Roentgen in 1895, ionizing radiation was applied to the treatment of cancer with remarkable results. Carefully controlled doses of ionizing radiation induce damage to the DNA in cells, with preferential effects on cancer cells compared to normal tissues, thereby saving lives and providing benefits in most types of cancer.

RT is now a central and essential element of an effective cancer care program throughout the world and regardless of economic status. RT is used to cure cancers that are localized and to provide local control (complete response with no recurrence in the treated area) or symptom relief in cancers that are locally advanced or disseminated (Gunderson and Tepper 2012**)**. It is frequently used in combination with surgery, either preoperatively or postoperatively, or in combination with systemic chemotherapy before, during, or subsequent to the course of RT (Barton, Jacob et al. 2014).

Because radiation affects both normal tissues and tumors, achieving an acceptable therapeutic ratio defined as the probability of tumor control versus probability of unacceptable toxicity**—** requires the radiation dose (in units of Gy, for example, J/kg) to be delivered within very tightly controlled tolerances with less than 5 percent deviation. This complex and controlled production and precise application of radiation requires specialized equipment that is maintained and operated by a team of trained personnel. The team includes, at a minimum, radiation oncologists to prescribe the appropriate dose, medical physicists to ensure accurate dose delivery, and radiation technologists to operate the equipment and guide patients through the radiation process. Radiation oncologists work within multidisciplinary teams with medical and surgical oncologists to coordinate a multidisciplinary approach to the management of cancer. A comprehensive cancer center usually provides the full scope of RT services, ranging from externally applied beams to the placement of sources within the tumor (see chapter 11).

RT is one of the more cost-effective cancer treatment modalities, despite the initial and substantial capital investment in the facilities and equipment. The investment, however, has resulted in severely limited access in most low- and middle- income countries (LMICs). Increasing the supply of RT services is critical to expanding cancer treatment in these settings and improving equity in access (Abdel-Wahab, Bourque et al. 2013; Goss, Lee et al. 2013; Rosenblatt, Izewska et al. 2013; Fisher, Daugherty et al. 2014; Jaffray and Gospodarowicz 2014; Rodin, Jaffray et al. 2014).

Uses of Radiation Therapy

RT is an essential element of curative treatment of breast, prostate, cervix, head and neck, lung, and brain cancers and sarcomas. The first four cancers are common in LMICs (Delaney, Jacob et al. 2005; Souchon, Wenz et al. 2009; Engstrom, Arnoletti et al. 2010; Gregoire, Lefebvre et al. 2010; Ramos, Benavente et al. 2010; Tyldesley, Delaney et al. 2011; Pfister, Ang et al. 2013; Barton, Jacob et al. 2014; Petrelli, De Stefani et al. 2014). RT is also used extensively in the management of prostate cancer (Delaney, Jacob et al. 2005; Tyldesley, Delaney et al. 2011).

Patients with hematologic malignancies are primarily treated with chemotherapy, but they also access RT resources (Barton, Jacob et al. 2014). Total body irradiation is used in the treatment of leukemia in the context of bone marrow transplantation. Localized RT is applied in many lymphomas to optimize local disease control and cure; palliative RT is extremely useful in multiple myeloma and lymphomas. RT is increasingly used to control selected metastases.

Radiation Therapy Alone

RT alone is used in the treatment of localized tumors, such as early-stage cancer of the larynx or prostate; non-melanoma skin cancer; head and neck cancers; and radiosensitive tumor types, such as seminoma and lymphomas (Motzer, Agarwal et al. 2009; Hoppe, Advani et al. 2012). In more advanced disease stages, RT is used before, during, or after surgery and is frequently combined with chemotherapy, either as concurrent or adjuvant treatment. The use of high-dose RT has been limited by the dose delivered to adjacent normal tissues, especially those areas with limited radiation tolerance, called the *critical normal structures*. Progress in computerization of RT planning and delivery allows shaping the radiation field to deposit very high-dose radiation to tumors and sparing the surrounding normal tissues. These techniques — intensely modulated radiation therapy (IMRT) and stereotactic RT— allow a therapeutic dose of RT to be delivered in just a few high-dose treatments and result in the high probability of tumor eradication; they have been successfully applied in the management of brain metastasis, lung, bone, and paraspinal tumors.

Concurrent Chemotherapy and Radiation Therapy

The use of concurrent chemotherapy and RT has been shown to significantly improve tumor eradication and survival in a number of cancers. It may improve local control, result in organ preservation, and eradicate distant microscopic metastases. This combination therapy has proven beneficial in treating cancers of the lung, cervix, head and neck, vulva, and anal canal (Gregoire, Lefebvre et al. 2010; Benson, Arnoletti et al. 2012; Glynne-Jones and Renehan 2012; Chen, Shipley et al. 2013; Koh, Greer et al. 2013; Petrelli, De Stefani et al. 2014).

Radiation Therapy as Adjuvant Treatment

RT is commonly used as adjuvant treatment following surgery, especially in case of incomplete resection Postoperative radiation is commonly used in cancers of the head and neck, rectum, breast, and lung, as well as soft tissue sarcomas (Gunderson and Tepper 2012). RT is also used after chemotherapy as the mainstay of treatment when chemotherapy alone was not expected to result in cure, such as locally advanced breast cancer or bladder cancer, or as adjuvant treatment to potentially curative chemotherapy, such as Hodgkin and non-Hodgkin lymphomas.

Radiation Therapy in Metastatic Disease

RT is beneficial in providing palliation to patients with metastatic disease. It is highly effective in controlling bleeding and pain, as well as the symptoms resulting from compression of the nerves, spinal cord, or airways. The use of RT for pain relief is particularly valuable; a single dose of moderate intensity (8-10 Gy) achieves significant pain relief in 60 percent to 80 percent of patients. This benefit is of particular importance in LMICs, where many patients present with advanced and metastatic disease.

Delivering Radiation Therapy

RT is delivered in two ways:

- ***External beam radiation therapy***: applied externally through directed beams of radiation to treat the cancer deep within the body
- ***Brachytherapy***: applied through the insertion of radiation-emitting sources directly within the tumor or adjacent body cavity.

Externally applied radiation beams can be produced by several approaches: radioactive sources, such as Cobalt-60 that emit gamma rays; high energy x-rays or photons produced by linear accelerators; or particle beams—electrons, protons or heavier ions—accelerated by other types of accelerators. These machines are equipped with accessories that are able to dynamically shape the radiation beam according to beam direction, as well as onboard imaging devices that can verify the accuracy of treatment delivery. Linear accelerators are currently the backbone of external beam radiation therapy; multiple companies manufacture the technologies offering a range of high energy x-rays (4-25 MV) to enable treatment of deep-seated tumors.

Brachytherapy involves either temporarily or permanently placing radiation-emitting sources directly within tissues or body cavities. Permanent sources decay rapidly, depositing the dose and remaining in the body; temporary placement uses higher activity sources that are electromechanically guided to the tumor within pre-placed interstitial or intracavitary catheters. The source and applicators are removed after the prescribed dose of radiation has been delivered.

These removable radiation sources can provide either *low-dose rate brachytherapy*, where the source remains in the tissues for a period of day, or *high-dose brachytherapy*, where the single-dose of radiation is delivered within minutes.

Personnel

RT requires a specially trained team of professionals that includes radiation oncologists to prescribe the dose; medical physicists, trained to commission and maintain the equipment and develops treatment plans; radiation technologists or therapists to operate the treatment units; and nurses experienced in managing patients undergoing therapy. Biomedical engineers and computer or information technology experts complement the team.

Once a decision to treat a patient has been made, the team develops a treatment plan and proceeds with delivery. The plan is based on accepted clinical guidelines that describe the indications for RT; the target tissues to be irradiated; the dose and fractionation prescriptions; support for patients during treatment; and management of patients after treatment, including acute and late complications of treatment.

The safe and effective management of the RT system requires a high level of communication and coordination of the processes and systems employed in the prescription, design, and delivery of radiation. Local, national, and international bodies provide regulations and guidelines for radiation safety, dose calibration, and quality assurance of devices, clinical practice, and monitoring of compliance.

Process

The *process* refers to all the steps from the decision to treat a patient with radiation to the completion of the course of radiation treatment.

- **Prescription**: The first step is completion of the radiation prescription, which indicates the exact part of the body to be treated; as well as the dose/fractionation schedule, including the total radiation dose to be delivered in how many fractions, at what intervals, and in what overall time period.
- **Planning**: The second step is initiation of the planning process. Patients are positioned on an x-ray imaging machine that simulates the geometry of treatment machine, or in more modern settings on a specially adapted CT

scanner (CT-simulator). A desired position is determined (supine, prone, arms up or by the side of the body); if needed, the patient is immobilized with specifically designed immobilization device to secure the reproducibility of the position. The set-up information is documented in the RT chart or electronic medical record. Images of the part of the body to be treated are obtained and stored.

- **Treatment Plan**: Once the set-up and imaging is complete, the radiation oncologist outlines the tissues that must be irradiated on images and a radiation technologist/dosimetrist or a medical physicist develops the treatment plan, using specialized planning software that models the placement of radiation beams and the dose contributed by each beam to ensure that the prescribed dose is delivered to the disease, while the dose to other tissues is minimized, especially critical and particularly sensitive organs. The individualized treatment plan is independently verified and the total dose is gradually delivered through a series of treatments (fractions) in a pre-arranged schedule of sessions, usually daily over several weeks, as specified in the prescription.
- **Treatment delivery**: Once the treatment plan is developed by medical physicist and dosimetrist and reviewed and approved by a radiation oncologist, the treatment can begin. In each session, the patient is positioned exactly as during simulation. After verifying the prescription, treatment plan and patient's position, the radiation dose is delivered. Treatments are frequently given five days per week; in curative settings, they may continue for four to six weeks. Daily treatments are commonly delivered during a session lasting 10-20 minutes.

In specific circumstances, RT is applied in a shorter schedule consisting of one to three high-dose fractions. These hypo-fractionationed treatments can be applied with generous margins for symptom relief for palliation rather than local disease control. Alternatively, they can be applied for curative intent, using high precision (also called *stereotactic*) methods, wherein the targeted volume is very small and surrounding normal tissues are avoided.

During each session, specific verification steps are taken before the dose is applied. During the course of RT, the patient is monitored daily by technologists and at least weekly by a physician; patients with acute side effects receive supportive care, as needed. The radiation records are kept for decades and made available for review in case further RT or other interventions, such as surgery, are planned for the previously irradiated part of the body.

Facilities

RT is delivered in a specially designed facility that contains specialized equipment for imaging, treatment planning, and radiation delivery. Modern RT departments are designed to optimize patient flow through the process and contain the following elements:

- Waiting area
- Examination rooms
- Imaging suites with simulators/CT-simulators
- Computer planning workrooms
- Shielded treatment rooms for linear accelerators or ^{60}Co treatment units
- Shielded high dose rate brachytherapy suites.

Additional support space is required for a physics laboratory, equipment storage, and dedicated environmentally controlled server rooms.

External beam RT is delivered using machines that produce high-energy x-ray or electron beams. The two main types of photon beams are ^{60}Co machines or x-ray generating linear accelerators. Cobalt units contain radioactive cobalt sources in the head of the unit that emit photons with a mean energy of 1.25 MeV. The source is constantly emitting and requires constant radiation protection; it decays gradually and requires replacement every three to five years. The linear accelerators use electric power to generate an electron beam that is accelerated and produces a high-energy photon beam. Linear accelerators require a stable power supply for reliable operation. Both units have collimators and filters to shape the radiation beam, including the multileaf collimators that allow motorized shaping and/or modulation of the beam shape and intensity during treatment delivery, producing more conformal irradiation of the target tissues while minimizing normal tissue exposure. In the past 10 years, x-ray and CT imaging capabilities have been added to these machines to allow the therapists to guide the placement of the radiation with increased precision and accuracy.

Safe and Effective Operation

The staff processes and equipment need to be well managed to ensure safe and effective care that adheres to the best practices and evidence-based medicine. Specially trained and certified personnel are essential for safe and effective treatments, as well as, safe operation of the facility. The medical specialization requires a residency in radiation oncology to learn evidence-based practice, radiation biology, and the principles of radiation physics. Typically, an experienced radiation oncologist oversees the operations of the RT department. The technological and treatment design activities are supported by specially trained physicists, called *medical physicists*, with a degree in physics and additional training to acquire the specific skills required to practice RT.

Trained technologists interact with patients and operate the treatment machines to deliver the radiation doses. Dedicated education programs have been developed to train these staff members in a range of topics, including, patient care, technology, and radiation physics.

The operational team of the department has several key responsibilities:

- Ensure that the radiation systems are safe for patients, public, and staff members
- Ensure that the radiation equipment is appropriately calibrated and tested
- Ensure that the each patient receives appropriate care through peer-review of the treatment plan and independent checks of the calculations
- Monitor and respond to errors or variations in the delivery of care.

Depending on the local, national, and international context, these activities may need to comply with regulations.

Integration into Cancer Centers

RT departments collaborate closely with departments of pathology and laboratory medicine, diagnostic imaging, surgery or surgical oncology, medical oncology, and palliative care to ensure that treatment plans are created based on correct diagnosis, full assessment of disease extend (stage) and the medical condition of the patient. Modern clinical practice ensures the physical and operational infrastructure is in place to allow multidisciplinary cancer care. This infrastructure may include multidisciplinary clinics and conferences where the management of the patient is discussed with all appropriate experts— for example, oncologists, pathologists, and radiologists—and the amalgamation of medical records to facilitate communication and coordination of care.

RT has evolved from the direct application of a single beam of ionizing radiation to a cancerous lesion, to image-guided, computer-optimized, robotically controlled systems that work to maximize the therapeutic ratio for each patient. This evolution has resulted in significant increases in the complexity of the treatment, which is characterized by hundreds of megabytes of treatment data and detailed quality control activities to ensure that the prescription is not only applied but is also appropriate for each patient. In the interest of reducing costs and standardizing interventions, the field is developing automated methods that allow high quality treatment plans to be designed in a few minutes. These approaches promise to ‘bury the complexity’ of the current RT process, while still provide the high degree of safety and personalization (Jaffray 2012).

The adoption of expert systems and machine learning methods allows the treatment team to design and deliver highly personalized RT (Purdie, Dinniwell et al. 2014). This degree of automation provides a valuable form of peer review that is inexpensive and can learn from experts around the world by drawing on the clinical expertise that has gone into large databases of existing treatment plans. The emerging advancement of cloud-based treatment designs, planning, and peer review is likely to fuse with modern telemedicine approaches to create more efficient learning platforms. An additional advantage of these cost-saving methods is that they require a standardization in the nomenclature used to describe the treatment intent and treatment record—a benefit that is highly synergistic with the adoption of medical and bioinformatics efforts (Lambin, van Stiphout et al. 2013).

Equitable Access to Radiation Therapy

The WHO recommends that all countries develop and implement a population-based cancer control plan. These plans are based on the information provided by cancer registries and include plans for prevention; screening and early detection; timely access to high-quality treatment, including surgery, radiotherapy, chemotherapy; and palliative and supportive care.

Planning RT requires detailed knowledge of the patterns of cancer, including different disease entities and distribution by stage. The cancer plans should define the number of departments and treatment machines that are appropriate for the current and projected cancer burden. The distribution of cancer facilities needs to consider not only the burden but also the geographic distribution of the population to facilitate access.

Requisite elements of effective RT include medical and professional education, support staff training programs, and improved infrastructure capacity.

- The medical education system needs to support training of professionals, including radiation oncologists, medical physicists, and radiation therapists. Without this foundation, shortages of professionals will lead to long waiting lists, treatment delays, and compromised outcomes. In addition, the lack of local training programs prevents the establishment of a stable supply of staff to operate the facilities. This lack is not only a challenge during initiation of a program; it will persist as the cancer services are ramped up to reach the level of appropriate use.
- The presence of external accreditation and regulation frameworks help to standardize the operation of RT departments and to secure a high quality practice. Establishing these frameworks can be particularly challenging in resource-constrained economies where infrastructure is limited and political stability is an issue.

- Limitations in access to a reliable supply of electric power, climate control, service infrastructure, and complex procurement settings affected by such factors as political instability and transportation are problematic.

Innovative approaches need to be pursued to address the numerous challenges that impeded capacity building. These innovations need to include technological, educational, operational, and clinical practice domains to avoid unnecessary suffering and loss of human life.

Efforts to Address the Equity Gap

Ample evidence indicates severe gaps in access to RT in large parts of the world. The International Atomic Energy Agency (IAEA) maintains a directory of all the RT facilities in the world (http://www-naweb.iaea.org/nahu/dirac/).

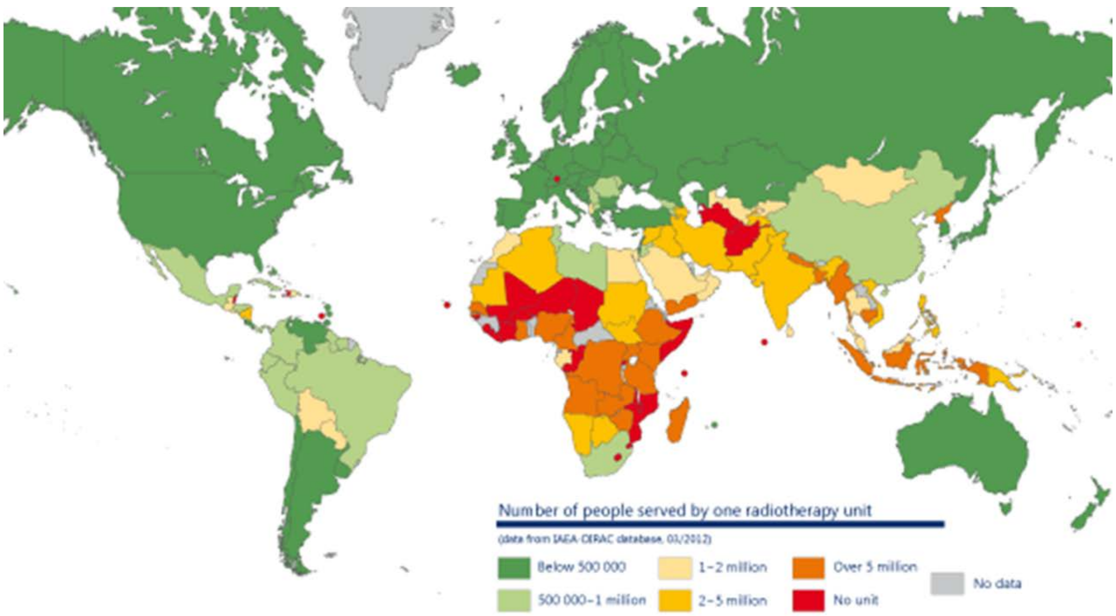

Figure 14.1: World map showing the number of people served by one radiotherapy unit according to the IAEA's DIRAC database of radiation therapy equipment (http://www-naweb.iaea.org/nahu/dirac/).

There is significant inequity in access to radiotherapy across the world. Figure 14.1 shows one factor – the number of people served by one radiotherapy unit according to the IAEA's DIRAC database of radiation therapy equipment (http://www-naweb.iaea.org/nahu/dirac/). For comparison, full access rates in developed countries would correspond to approximately 100,000 people served by one radiation treatment machine.

The IAEA has brought attention to the lack of adequate RT resources for several decades. A number of comprehensive reviews of the resources in Europe, Latin America and the Caribbean, Africa, describe the limitations in the number of centers, equipment, and staff. The recent publication on cancer in Africa stated that 29 of 52 countries have no RT facilities; those that have facilities face severe shortages. Only 20 percent of the population in Africa has access.

The barriers to the implementation of RT are numerous. They include perceptions that it is expensive, complex, and unlikely to succeed because of the shortage of qualified personnel and funding. With many competing demands for cancer control activities, there is a risk that the appropriate investment in RT may not be made, thereby, leaving countries and patients to wrestle with dysfunctional cancer services.

The IAEA has provided technical assistance, training and education, and financing for equipment. Unfortunately, these efforts have not resolved the severe limitations in access. The IAEA PACT Programme established in 2004 (http://cancer.iaea.org/) organized a large number of missions to assess the readiness of a country to develop new RT facilities. These missions assess all aspects of cancer control since the potential benefit offered by RT is enhanced by the presence of adequate diagnostic facilities, surgery, chemotherapy, and supportive and palliative care. The IAEA is able to advise the governments of the optimal way to proceed, but the implementation depends on the political will and resources being devoted to cancer control. Effective cancer planning has improved the access in a number of areas, including Brazil; Ontario, Canada{REF_CCO_Plan}; Ireland; and Poland (Chalubinska-Fendler et al. 2014 }; but such progress is lacking in LMICs. International partnerships and assistance are needed to accelerate the progress in closing the gaps. The U.S.-based AMPATH Program is building a new cancer center in Eldoret, Kenya, and has included plans to implement radiotherapy as soon as possible (http://www.ampathkenya.org/our-programs/primary-care-chronic-diseases/oncology/).

In Latin America and the Caribbean, a unique network of national cancer institutes has embarked on an initiative to improve the quality of radiotherapy in the region (http://www2.rinc-unasur.org/wps/wcm/connect/rinc/site/home). The RINC initiative draws together 18 countries to organize a regional community of best practices; exchange information and knowledge; identify the needs, opportunities and common interests; promote coordination among member countries; and, promote the commitment of every countries' corresponding levels of government with emphasis on the availability of financial, human and legislative resources necessary for the development of cancer control.

Access is not only an issue for lower income countries, professional societies in Australia, Europe (ESTRO-HERO project), and the United Kingdom are studying the existing RT resources and advocating improved access within their own countries.

Although ample data describe the benefits of RT for cancer control, the cost of the equipment and development of skills seem an overwhelming challenge. This does not need to be the case – any return begins with an investment. Real effort needs to be put into calculating the true cost and the associate benefit of RT so decision makers in the government can make informed choices. Such approaches has been applied in advancing the global HIV/AIDS effort and is being pursued by the Union International for Cancer Control (UICC) Global Task Force on Radiotherapy for Cancer Control (GTFRCC) (www.gtfrcc.org) Such approaches are key in articulating effective messages regarding the importance and value of financial investments in cancer control. In addition, these approaches immediately lead to the development of novel financing schemes to overcome the reluctance to commit the funds for capital investment required to improve access globally (chapter 17; Atun XX).

Conclusions

Cancer will become the number one cause of death across the globe in the next 20 years. RT is a critical component of an effective cancer treatment program if current cure rates are to be achieved, and cost-effective palliation is a priority. The evidence demonstrates that in excess of 40 percent of cancer patients benefit from RT; the lack of access will compromise the care millions of people suffering from cancer if not addressed through immediate action. The global community has been working hard to assure quality through standardization in RT practices and provide guidance in the establishment of new treatment capacity (IAEA 2008). It is now critical that RT be seen for what it is - *an essential element of an effective cancer control plan* – and the critical equipment, operating, and educational investments be made to assure it is in place to respond to the growing cancer burden.

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