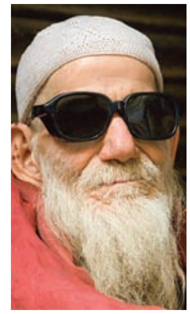

Chapter 14

Radiation Therapy for Cancer

David A. Jaffray and Mary K. Gospodarowicz

INTRODUCTION

More than 14 million new cases of cancer are diagnosed globally each year; radiation therapy (RT) has the potential to improve the rates of cure of 3.5 million people and provide palliative relief for an additional 3.5 million people. These conservative estimates are based on the fact that approximately 50 percent of all cancer patients can benefit from RT in the management of their disease (Barton, Frommer, and Shafiq 2006; Barton and others 2014; Tyldesley and others 2011); of these, approximately half present early enough to pursue curative intent.

Soon after Roentgen's discovery of X-rays 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 with normal tissues, providing treatment benefits in most types of cancer and saving lives.

RT is now recognized as an essential element of an effective cancer care program throughout the world, regardless of countries' economic status. RT is used to cure cancers that are localized; it also can 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, as well as in combination with systemic chemotherapy before, during, or subsequent to the course of RT (Barton and others 2014).

Because radiation affects normal tissues and tumors, achieving an acceptable therapeutic ratio—defined as the probability of tumor control versus the probability of unacceptable toxicity—requires that the radiation dose be delivered within very tightly controlled tolerances with less than 5 percent deviation. This 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 provides the full scope of RT services, ranging from externally applied beams of X-rays to the placement of radiation-emitting sources within tumors (see chapter 11 in this volume [Gospodarowicz and others 2015]).

RT is one of the more cost-effective cancer treatment modalities, despite the need for substantial capital investment in the facilities and equipment. Concerns about the initial investment, however, have resulted in severely limited access in most low- and middle-income countries (LMICs). Increasing the supply of RT services is critical to expanding effective cancer treatment in

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these settings and improving equity in access (Abdel-Wahab and others 2013; Fisher and others 2014; Goss and others 2013; Jaffray and Gospodarowicz 2014; Rodin and others 2014; Rosenblatt and others 2013).

USES OF RADIATION THERAPY

RT is an essential element of curative treatment of cancers of the breast, prostate, cervix, head and neck, lung, and brain, as well as sarcomas. The first four cancers are common in LMICs (Barton and others 2014; Delaney, Jacob, and Barton 2005b; Engstrom and others 2010; Gregoire and others 2010; Petrelli and others 2014; Pfister and others 2013; Ramos, Benavente, and Giralt 2010; Souchon and others 2009; Tyldesley and others 2011). RT is also used extensively in the management of prostate cancer (Delaney, Jacob, and Barton 2005a; Tyldesley and others 2011).

Patients with hematologic malignancies are primarily treated with chemotherapy, but they also access RT resources (Barton and others 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. In short, RT both saves lives and alleviates suffering associated with cancer.

Radiation Therapy Alone

RT as the sole therapy 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 (Hoppe and others 2012; Motzer and others 2009). 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.

Prior to the development of sophisticated computerized treatment planning systems, RT was planned using clinical information and conventional X-rays (2D RT) for field placement verification. This approach resulted in the use of large radiotherapy fields that assured coverage of the tumor, but also resulted in limiting toxicity. With the introduction of computerized tomography (CT) scanners and computerized treatment planning, fields were shaped (3D conformal radiation therapy, 3D CRT) to correspond to the tumors; the use of smaller fields resulted in less toxicity and the ability to escalate the radiation dose, with resulting improved outcomes and reduced toxicity. Now 3D CRT is the standard approach in most countries. However, in some low-income countries, the introduction of basic 2D radiotherapy would still save many lives and reduce suffering in thousands of patients with advanced cancers.

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 *critical normal structures*. Continued progress in computerization of RT planning and delivery allows shaping the radiation field to deposit higher doses to tumors and further sparing the surrounding normal tissues. These newer techniques—intensity modulated radiation therapy (IMRT) and stereotactic RT—allow a therapeutic dose of RT to be delivered in a few high-dose treatments and result in a higher probability of tumor eradication; they have been successfully applied in the management of brain metastasis and lung, bone, and paraspinal tumors. IMRT is being gradually introduced in many centers and is the preferred treatment for cancers of the prostate, as well as, head and neck, where it has been shown to improve outcomes significantly.

Concurrent Chemotherapy and Radiation Therapy

The use of concurrent chemotherapy and RT has significantly improved tumor eradication and survival in several 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 (Benson and others 2012; Chen and others 2013; Glynne-Jones and Renehan 2012; Gregoire and others 2010; Koh and others 2013; Petrelli and others 2014).

Radiation Therapy as Adjuvant Treatment

RT is commonly used as adjuvant treatment following surgery, especially in the 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 for locally advanced breast cancer or bladder cancer, or as adjuvant treatment to potentially curative chemotherapy, such as for 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 moderate dose (8–10 Gy) achieves significant pain relief in 60–80 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 three 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.
- *Radioisotope therapy:* applied through the systemic injection of a radioisotope that has been designed to target disease.

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 shape dynamically 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 RT; 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 tumors within preplaced interstitial or intracavitary catheters. The source and applicators are removed after delivery of the prescribed dose of radiation. These removable radiation sources can provide either *low-dose rate brachytherapy*, where the source remains in the tissues for several days, or *high-dose rate brachytherapy*, where the single dose of radiation is delivered within minutes.

Radioisotope therapy may be applied in the radiotherapy department or in the nuclear medicine department. The most common application of radioisotope therapy is in the treatment of thyroid cancer using radioactive iodine or in the palliation of pain from bone metastasis using a radioactive isotope of strontium. Less common indications employ a conjugated radioisotope such as lutetium (^{177}Lu) DOTA-TATE to target somatostatin-expressing neuroendocrine tumors.

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 areas
- 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 testing laboratory, equipment storage, and dedicated environmentally controlled computer 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. Linear accelerators use electric power to generate an electron beam that is accelerated to produce 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 multileaf collimators that allow motorized shaping and/or modulation of the beam shape and intensity during treatment delivery, thereby 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 therapists to guide the placement of the radiation with increased precision and accuracy.

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 develop 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 the 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 a specifically designed 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 are 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 delivered through a series of treatments (fractions) in a prearranged schedule of sessions, usually daily over several weeks, as specified in the prescription.
- *Treatment delivery.* Once the treatment plan is developed by a 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 the 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 hypofractionated 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.

Safe and Effective Operation

The staff processes and equipment need to be well managed to ensure safe and effective care that adheres to 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:

- Ensuring that the radiation systems are safe for patients, the public, and staff members
- Ensuring that the radiation equipment is appropriately calibrated, tested, and maintained
- Ensuring that the each patient receives appropriate care through peer review of the treatment plan and independent checks of the calculations
- Monitoring and responding 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 extent (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 applied not only accurately, but also appropriately 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 providing a 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 and others 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 emergence of cloud-based treatment planning and peer review is likely to fuse with modern telemedicine approaches to create more efficient delivery and 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 that promise to advance clinical practice (Lambin and others 2013).

EQUITABLE ACCESS TO RADIATION THERAPY

The World Health Organization 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, and chemotherapy; and palliative and supportive care.

Planning RT resource provision requires detailed knowledge of the patterns of cancer, including different disease entities and distribution by stage. National 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, training programs for support staff, and ongoing refreshment of equipment and infrastructure. Specific elements that need attention include the following:

- *Medical education system.* The training of radiation oncologists, medical physicists, and radiation therapists is a critical element. 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 cancer services are ramped up to reach the level of appropriate use.
- *Regulatory structure.* The presence of external accreditation and regulation frameworks helps to standardize the operation of RT departments and secure high-quality practice. Establishing these frameworks can be particularly challenging in resource-constrained economies, where infrastructure is limited and political stability is an issue.
- *Societal infrastructure.* 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 impede capacity building. These innovations need to come from the technological, educational, operational, and clinical practice domains to avoid unnecessary suffering and loss of human life.

Efforts to Address the Equity Gap

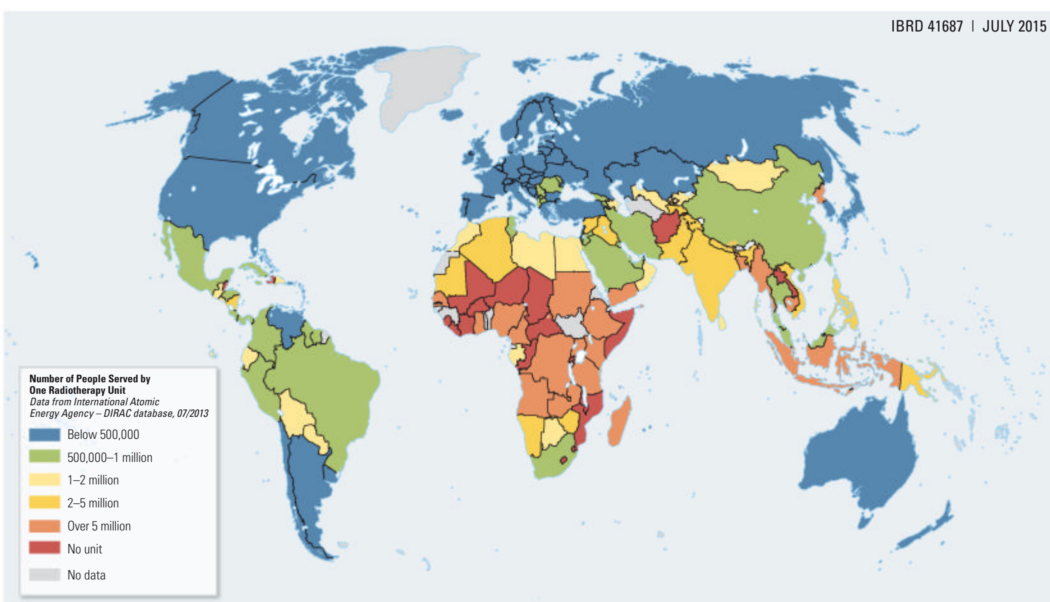
Ample evidence indicates severe gaps in access to RT in large areas of the world. The International Atomic Energy Agency (IAEA) maintains a directory of all RT facilities (http://www-naweb.iaea.org/nahu/dirac/).

Significant inequity exists in access to RT across the world. Map 14.1 shows one descriptor. By comparison, access rates in high-income countries would correspond to approximately 100,000 people served by one radiation treatment machine.

IAEA has brought attention to the lack of adequate RT resources for several decades. Comprehensive reviews of the resources in Europe, Latin America and the Caribbean, and Sub-Saharan Africa describe the limitations in centers, equipment, and staff. One publication on cancer in Sub-Saharan Africa stated that 29 of 52 countries have no RT facilities; those that have facilities face severe shortages. Less than 10 percent of the population in the region has access (Zubizarreta and others 2015).

The barriers to the implementation of RT are numerous. They include perceptions that it is expensive, complex, and unlikely to succeed because of the

Map 14.1 Number of People Served by One Radiotherapy Unit



Source: Based on data from the Directory of Radiotherapy Centres (DIRAC) database of radiation therapy equipment, International Atomic Energy Agency, Vienna, http://www-naweb.iaea.org/nahu/dirac/.

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, leaving countries and patients to wrestle with dysfunctional cancer services.

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 Programme of Action for Cancer Therapy, 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 can be realized only in the presence of adequate diagnostic facilities, surgery, chemotherapy, and supportive and palliative care. IAEA can advise governments on the optimal ways to proceed, but the implementation depends on the political will and resources devoted to cancer control.

Effective cancer planning has improved access in a number of areas, including Brazil; Ireland; Ontario, Canada; and Poland (Chalubinska-Fendler and others 2014). Overall, however, such progress is lacking in LMICs, and international partnerships and assistance are needed to accelerate progress to close the access gap. The U.S.-based AMPATH Program is building a new cancer center in Eldoret, Kenya, and has included plans to implement RT 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 RT in the region (http://www2.rinc-unasur.org/wps/wcm/connect/rinc/site/home). The Network of National Cancer Institutions of Latin America (RINC) initiative draws together 18 countries to organize a regional community of best practices; exchange information and knowledge; identify needs, opportunities, and common interests; foster coordination among member countries; and promote the commitment of every country's corresponding levels of government, with emphasis on the availability of the financial, human, and legislative resources necessary for the development of cancer control.

Ongoing efforts in India and Turkey offer promise, but to date fall short of addressing the limited access to effective RT for their populations (Banerjee, Mahantshetty, and Shrivastava 2014; Goksel and others 2011).

Although ample data describe the benefits of RT for cancer control, the cost of 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 resultant benefits of RT so that decision makers can make informed choices. Such approaches have been applied in advancing the global HIV/AIDS effort and are being pursued by the Union for International Cancer Control Global Task Force on Radiotherapy for Cancer Control (http://www.gtfrcc.org). Such approaches are the key to articulating the importance and value of financial investments in cancer control. Moreover, these approaches immediately lead to the development of novel financing schemes to overcome the reluctance to commit the funds for the capital investment required to improve access globally (chapter 17 in this volume [Knaul and others 2015]).

CONCLUSIONS

Cancer is projected to become the number one cause of death across the globe in the next 20 years. The evidence demonstrates that more than 40 percent of patients with cancer would benefit from RT; the lack of access will compromise the care of millions of people suffering from cancer if not addressed through immediate action. The global community has been working hard to ensure 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 acknowledged as an essential element of an effective cancer control plan—and that the critical equipment, operations, and educational investments be provided to ensure that RT is in place to respond to the growing cancer burden.

NOTE

World Bank income classifications as of July 2014 are as follows, based on estimates of gross national income per capita for 2013:

- Low-income countries (LICs): US$1,045 or less
- Middle-income countries are subdivided:
  a) Lower-middle-income: US$1,046–US$4,125
  b) Upper-middle-income (UMICs): US$4,126–US$12,745
- High-income countries (HICs): US$12,746 or more.

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