Radiotherapeutic Management of Non–Small Cell Lung Cancer in the Minimal Resource Setting

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ABSTRACT

Lung cancer is the most common cancer worldwide and the fifth most common cause of death globally. Its incidence continues to increase, especially within low- and middle-income countries (LMICs), which have limited capacity to address the growing need for treatment. The standard of care for lung cancer treatment often involves radiation therapy (RT), which plays an important therapeutic role in curative-intent treatment of early-stage to locally advanced disease, as well as in palliation. The infrastructure, equipment, and human resources required for RT may be limited in LMICs. However, this narrative review discusses the scope of the problem of lung cancer in LMICs, the role of RT technologies in lung cancer treatment, and RT capacity in developing countries. Strategies are presented for maximizing the availability and impact of RT in settings with minimal resource availability, and areas for potential future innovation are identified. Priorities for LMICs involve increasing access to RT equipment and trained health care professionals, ensuring quality of care, providing guidance on priority setting with limited resources, and encouraging innovation to increase the economic efficiency of RT delivery. Several international initiatives are currently under way and represent important first steps toward scaling up RT in LMICs to treat lung cancer.

Keywords: Lung cancer; Non–small cell lung cancer; Global health; Radiotherapy; Low- and middle-income countries; Quality

Introduction: scope of the problem

Since 1985, the global incidence of and mortality related to lung cancer have surpassed those of all other cancers.[1] In 2010, lung cancer (approximately 85% of which is non–small cell lung cancer [NSCLC][2]) was ranked as the fifth most common cause of death globally, ahead of HIV/AIDS (sixth), tuberculosis (10th), and malaria (11th).[3] The projected increases in total incidence of cancer over the next 15 years (to 2030) are expected to be proportionally higher in low- and middle-income countries (LMICs). The relatively recent

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and increasing spread of tobacco use in LMICs means that the current lung cancer epidemic in these regions has not yet reached its peak, and rates will likely continue to rise for the next few decades.[4,5] Environmental factors, including air pollution,[5] contamination of drinking water with arsenic, and workplace exposure to arsenic in industries such as mining,[6] are also contributing to this transition in the epidemiology of lung cancer.

RT plays a critical role in the treatment of lung cancer, with rates of RT use as high as 70% in some settings.[7] Global variation in the availability and use of RT is substantial, however. This article discusses the role of modern RT in treatment of NSCLC and reviews the availability of RT in developing countries, as well as in geographically underserviced regions of developed countries. Finally, strategies for maximizing the availability and impact of RT in settings with minimal resource availability are presented.

Role of RT in the treatment of NSCLC

RT plays an important role in the treatment of NSCLC throughout the continuum of care, including in radical treatment of early-stage and locally advanced disease and in palliative care. Although surgery has been the mainstay of treatment for early-stage lung cancer, early-stage disease probably represents a minority of cases in LMICs, as it does in high-income countries (HICs).[8] In order of increasing complexity, nonoperative options for curative-intent treatment of stage I NSCLC include conventional radiotherapy (i.e., 2 Gy delivered daily for several weeks), altered fractionation schemes, and stereotactic radiation. Delivery of curative-intent radiotherapy to patients who would otherwise go untreated is associated with improved survival.[9,10]

In patients with locally advanced disease, RT plays an important role as a component of dual-modality therapy alongside chemotherapy and, in very select patients, trimodality therapy, including surgery. RT also plays a key role in the palliation of disease in the thorax, as well as in the treatment of distant metastatic disease in the brain, bone, and other regions. Palliative RT has been found to improve symptoms of chest pain and hemoptysis by 60% to 80% and cough and dyspnea by 50% to 70%,[11] as well as to result in significant improvement in other symptoms of systemic disease. Palliative thoracic RT in doses of 30 Gy in 10 fractions or higher have been associated with improved survival in patients with good performance status,[12] but adequate symptom control can still be achieved with shorter regimens such as 20 Gy in five fractions or 10 Gy in a single fraction.[13]

RT technology

Before the mid-1990s, RT planning relied on two-dimensional imaging, with simple treatment fields designed using radiography or fluoroscopy (Fig. 1A).[14] Square or rectangular fields could be delivered without any modification of the beam, but more complex shaping of the beam required the creation of metal blocks (Fig. 2) that would be placed in the treatment field to attenuate the beam. In that era, patient setup before treatment was based on tattoo marks placed on the skin, with subsequent adjustment of the patient's position on the basis of radiographic images—called *portal images*

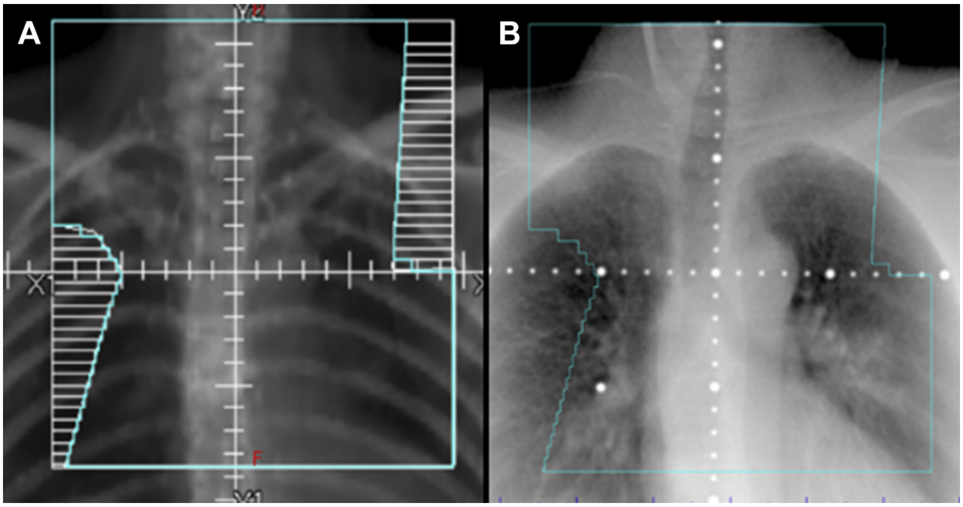

Figure 1. (*A*) An illustration of the concept of two-dimensional treatment planning. The field borders (*blue line*) encompass the upper mediastinum and neck and would be placed using anatomy visible on radiographs or fluoroscopy. The patient would be treated with opposing anterior and posterior beams. (*B*) An electronic portal image showing a patient at the time of treatment, with the field borders (*blue*) superimposed.

Figure 2. Blocks used for beam shaping. These hand-poured metal blocks are placed into the treatment machine to attenuate the beam in selected areas.

(see Fig. 1B)—taken on the treatment machine. Although most centers in HICs now use more advanced techniques, even RT with two-dimensional (2D) planning and block creation is still unavailable in some LMICs and underserviced areas.

The development of three-dimensional conformal RT (3D-CRT) and intensity-modulated RT (IMRT) in the 1990s allowed better delineation of normal structures (termed *organs at risk*) and target volumes (see Fig. 3).[15] Although IMRT allows more advanced manipulation of the radiation beam to provide more conformal radiation plans, randomized data to confirm its clinical superiority over 3D-CRT techniques are not available. In many cases, good outcomes can be achieved with less-advanced techniques; for example, a prospective study of hypofractionation using 3D-CRT in patients with medically inoperable stage I (T1–2N0, <4 cm) NSCLC yielded results that were comparable to those reported with stereotactic body RT and limited resection.[16]

Technologies for patient positioning have also improved, with several imaging modalities available to ensure accurate setup. Although tattoos and matching to bony structures by means of electronic portal images are still used, more advanced technologies involve orthogonal radiographs with automated repositioning or cone beam computed tomography (see Fig. 3C), which allows visualization and matching of soft tissues. The application of advanced technologies in settings with insufficient training or experience has been associated with outcomes inferior to those of older, traditional approaches, however.[17] Furthermore, the incremental benefit of each small improvement in RT technology is often not quantified.

RT capacity

Sufficient RT capacity is necessary for cancer treatment globally and in LMICs in particular, where only one-third of RT machines, but 60% of the world's patients with cancer, are located.[18] The modern delivery of RT is also dependent on broader health system resources, including imaging, pathology, laboratory medicine, and surgical facilities, to facilitate staging and diagnosis and complete the continuum of care.[19] Increasing the infrastructure, equipment, and human personnel able to deliver RT is a critical step.[18,20,21] We therefore summarize RT capacity in the global regions of Europe, Africa, Asia, Latin America, and North America from the standpoint of these three key elements (Table 1). The numbers are based on available published data and are subject to change.

Europe

Infrastructure. Major RT differences in capacity exist between Western Europe and Southern/Eastern Europe.[22] Of the 1286 active RT centers registered with the Directory of Radiotherapy Centres (DIRAC) database in 2012, more than two-thirds were located in five Western European countries: Germany, Italy, France, the United Kingdom, and Spain. The remaining RT centers were in smaller countries with lower gross national income (GNI) in southern and Eastern Europe. This socioeconomic

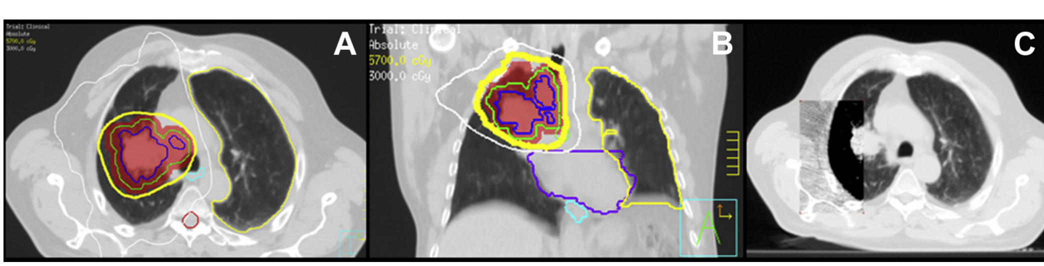

Figure 3. Radiation treatment planning and delivery for stage III non-small cell lung cancer. Normal tissues and tumor target volumes are outlined on a planning computed tomography (CT) scan (*Panel A*, axial; *Panel B*, coronal). The tumor and involved nodes are outlined (*blue*), and margins added for microscopic extension (*green*) and setup error produce the planning target volume (*red color wash*). The prescription dose is 60 Gy in 30 fractions, and the 95% dose line (*thick yellow*) and 50% dose line (*thin white*) are shown. Normal structures are also outlined (left lung, esophagus, heart, and spinal cord are shown). For treatment delivery, a cone beam computed tomographic image (*Panel C*, *inset*) is acquired aligned to the planning computed tomographic image (*Panel C*, *main image*) to confirm positioning.

Table 1. Summary of radiotherapy capacity in Europe, Africa, Asia, Latin America and the Caribbean, and North America

	Infrastructure	Equipment	Human resources	Comments
Europe	1286 RT centers; more than two-thirds in Germany, Italy, France, the United Kingdom, and Spain	3157 MV machines represent 19% of unmet need; 92% of machines are linear accelerators	6000 radiation oncologists, 3000 medical physicists, and 10,000 RT technologists	Range of RT capacity follows GNI distribution; many centers perform advanced RT techniques (IMRT, SABR)
Africa	160 RT centers; 29 countries (20% of population) do not have any machines	277 MV machines, 68% linear accelerators; machines weighted heavily toward South Africa (33%) and Egypt (27%)	No up-to-date data on number of RT professionals; presence of training facilities noted in only 7 countries	Little known about types of plans delivered
Asia	1462 RT centers; 86% of centers located in Japan, China, and India	3051 MV machines identified, high country-to-country disparity in number of machines per million population	Radiation oncologists and therapists serve in multiple roles; only 17 countries meet human personnel guidelines	Little known about types of plans delivered
Latin America & Caribbean	470 RT centers, most densely available in Argentina, Chile, Panama, Uruguay, and Venezuela	710 MV machines, 44% linear accelerators; estimated 100 more machines needed	69% more radiation oncologists, 146% more medical physicists, and 109% more RT technologists needed	Only 3% of centers able to generate IMRT plans
North America	3388 RT centers between United States (3331) and Canada (57)	4240 MV machines between United States (3956) and Canada (284), 96% are linear accelerators	4236 radiation oncologists, robust medical physics training programs	Quality assurance measures not well described; many centers perform advanced RT techniques (IMRT, SABR)

RT, radiotherapy; MV, megavoltage; GNI, gross national income; IMRT, intensity-modulated radiotherapy; SABR, stereotactic ablative radiotherapy.

disparity in distribution of RT capacity was also noted in the Health Economics in Radiation Oncology project.[23]

Equipment. A total of 3157 megavoltage machines serve an anticipated 2.8 million European patients with cancer. On the basis of the Quantification of Radiotherapy Infrastructure and Staffing Needs benchmarks, this represents a 19% unmet need for RT throughout Europe.[24] Countries with a higher GNI (>$12,476 [U.S.] per capita per year) serve approximately 400 to 450 patients per machine per year, whereas countries with a lower GNI treat significantly more patients per machine. Although 92% of machines in Europe are linear accelerators, the quality of machines (e.g., age, condition, treatment techniques such as IMRT) and quality assurance measures used are not well described.[25]

Human Resources. There are approximately 6000 radiation oncologists, 3000 medical physicists, and 10,000 RT technologists in Europe.[22] Country-to-country variation in licensing requirements and clinical responsibilities delegated to each discipline exists.

Africa

Infrastructure. According to DIRAC, only 23 of 52 countries in Africa have RT centers, with a total of 160 RT centers for the continent.[26,27] The 29 countries with no machines account for 20% of the total African population.[27] The small number of centers in such a large continent contributes significantly to lack of access and awareness.

Equipment. Of the 277 megavoltage machines in total, 32% (88 machines) are cobalt-60 units and 68% (189 machines) are linear accelerators.[27] The distribution of RT equipment is heavily weighted toward southern and northern Africa, with 33% of the machines in South Africa and 27% in Egypt alone. Despite the gradual increase in RT centers and numbers of machines, waiting times for these machines continue to be long. Among the megavoltage machines, little is known regarding the types of plans delivered (i.e. IMRT versus 3D-CRT).

Human Resources. The available information on the number of professionals able to deliver RT in Africa and available training programs is limited. The information that does exist dates back to 1994, when South Africa reported a total of 58 practicing radiation oncologists, 190 therapy radiographers, and 30 medical physicists.[28] In 2011, a review article noted that "training facilities in cancer diagnosis and management" in Africa were few and found only in Algeria, Egypt, Libya, Morocco, Nigeria, South Africa, and Zimbabwe.[29]

Asia

Infrastructure. The most recent review of RT capacity in the Asia and Pacific region was published in 2001 by the International Atomic Energy Agency (IAEA).[30] The 17 countries included in the review hosted a total of 1462 RT centers. The highest numbers of RT centers were found in Japan (611), China (453), and India (188). Despite rapid increases in RT centers and machines in China and India, both countries are still in need of further treatment capacity.[21,30,31]

Equipment. A total of 3051 megavoltage machines were identified among 17 countries included in the 2001 IAEA review.[30] Little is known regarding the types of RT plans that are run on these machines. At the time of the review, New Zealand had the greatest number of machines per million people (7.39); in contrast, the rates in under-equipped countries were much lower: Bangladesh (0.09), Indonesia (0.12), and Vietnam (0.14). Even among countries with significant numbers of megavoltage machines, such as Turkey, linear accelerators have been found to be concentrated in urban areas, with large underserved regions in between.[32] Since the 2001 review, many countries have had rapid increases in numbers of megavoltage machines. India, which had only 35 linear accelerators in 2001, was found to have 232 in 2010.[33]

Human Resources. Although marked increases in the RT workforce have been seen in many countries such as India,[33] radiation oncologists and therapists are limited in most countries and frequently perform multiple roles in RT delivery that would otherwise be divided among many specialties in developed countries.[30] Several training programs are available or launching in Cambodia, Indonesia, Turkey, and more human resources are needed throughout the Asia and Pacific Region.[32,34,35]

Latin America and the Caribbean

Infrastructure. In this large region encompassing Central America, South America, and the Caribbean countries, 589 million people live in primarily LMICs. A 2004 survey of 19 Latin American countries identified 470 RT centers in total.[36] Only five countries—Argentina, Chile, Panama, Uruguay, and Venezuela—had more than one center per million people, whereas some countries (e.g., Haiti) had no centers whatsoever.[21]

Equipment. In 2004, there were 710 megavoltage machines among 19 Latin American countries surveyed: 314 machines (44%) were linear accelerators and 396 machines (56%) were cobalt-60 units.[36] The number of machines remains insufficient, with an estimated 100 more teletherapy machines required to meet the IAEA guidelines.[36] Only approximately 3% of the centers have the ability to generate and deliver more advanced IMRT plans.[36] Some countries are actively investing in RT resources. In 2013, Brazil's Ministry of Health pledged to purchase 80 new linear accelerators.[37]

Human Resources. In 2004, the 19 countries studied had 933 radiation oncologists, 357 medical physicists, and 2300 radiation technologists.[36] Only 25% of the RT centers had a full-time physicist, a functional simulator, and the ability to create blocks. Training programs for radiation oncology are on the rise, however. In 2004, 12 of 18 countries offered radiation oncology training through a total of 35 institutions.[36] Only 7 of 18 countries have a formal medical physics training program at 22 centers.

North America

The United States and Canada are HICs with well-established RT infrastructure, equipment, and human resources. We therefore provide only a brief review of RT capacity in this region. The United States currently has 3331 RT centers registered with DIRAC, and Canada has 57 RT centers.[38] Both countries have well above the European Society for Radiotherapy and Oncology–Quantification of Radiotherapy Infrastructure and Staffing Needs guideline of 5.5 megavoltage machine per million people, although regional variations in access do exist. Many centers perform a variety of advanced RT delivery techniques (i.e., IMRT, 3D-CRT, stereotactic ablative radiotherapy). Published guidelines on quality assurance standards, such as the Technical Quality Control Guidelines, which are published by the Canadian Partnership for Quality Radiotherapy, now exist.[39]

Strategies for RT delivery in minimal-resource settings

It is evident that delivery of RT for lung cancer in LMICs, including access to care, quality of care, and economic efficiency, must be improved.[40] In addition to more RT resources, access to appropriate lung cancer care requires a functional cancer control system and health care system. This includes sufficient pathology, radiology, surgery, and internal medicine services, as well as sufficient drugs, medical supplies and equipment, primary care, and palliative care.

Access is a multidimensional issue that includes availability of RT equipment, human resources, accessibility of RT centers, affordability of services, and awareness of the importance of and appropriate use of RT.[41] Implementation of universal health coverage, coupled with a cancer registry system to understand in-country disease patterns, is an important step to address

Table 2. Resource-tiered technological guidelines

Indications	Simulation	Treatment technique	Oncology center
Palliative treatment of locally advanced primary and metastatic lung tumors	2D and CT simulation	2D treatment (rectangular portals) and 3D CRT	Tier 1[a]
Routine radical radiotherapy and chemoradiation of lung cancers	CT simulation	3D CRT	Tier 2[b]
Complex cases of radical radiotherapy and chemoradiation	CT simulation	IMRT and IGRT	Tier 3[c]
Specialized techniques such as SABR	CT simulation, including 4D techniques	IMRT, IGRT, and 4D treatment	Tier 3[c]

[a]Tier 1, basic oncology center with cobalt machine.
[b]Tier 2, intermediate oncology center with basic linear accelerator and CT-based simulation.
[c]Tier 3: advanced- level oncology center with linear accelerators, CT simulation, and image guidance.
2D, two-dimensional; CT, computed tomography; 3D CRT, three-dimensional conformal therapy; 4D, four-dimensional; IMRT, intensity-modulated radiotherapy; IGRT, image-guided radiotherapy; SABR, stereotactic ablative radiotherapy.

many of these issues.[42] It is essential that any improvements in RT capacity be made through a comprehensive quality assurance and quality control process. As RT resources for lung cancer expand, maintaining this standard will require activities ensuring quality and safety, including activities such as rigorous training, dosimetry audits, accreditation, continuing medical education, and peer review.[43]

With regard to economic efficiency, resource-tiered planning of treatment resources for lung cancer and national cancer control planning are important (Table 2). Despite the considerable variability with regard to resource capability, tiered frameworks can assist hospitals and planners in making appropriate choices. Such practice has been similarly adopted by the Breast Global Health Initiative, in which four levels of health care resources, depending on the country's resource capacity, were developed.[44] Guidance on lung cancer is already available from an IAEA task force, although some updating is required.[45] Ensuring timely diagnosis and early detection would probably also minimize required treatment resources and improve effectiveness of therapy. Scientific and technological innovations, such as the use of shorter fractionation schedules in cases in which evidence on its safety and efficacy exists, can also optimize the economics of care.[46]

Table 3. Current international initiatives to address global radiotherapy needs

Program	Region of Origin	Year Created	Purpose
Programme of Action for Cancer Therapy	France; International Atomic Energy Association	2004	Increase access to RT machines for member states
Global Task Force on Radiotherapy for Cancer Control	Geneva, Switzerland; Union for International Cancer Control	2014	Develop an investment framework to demonstrate the health and economic benefits resulting from scaling up RT capacity
International Cancer Expert Corps	United States; National Institutes of Health	2014	Create a network of cancer professionals to develop sustainable expertise for better cancer care

Innovation

The complexity of operation and maintenance of advanced RT delivery equipment has driven researchers and vendors to investigate novel devices that may broaden access. Two main approaches to increasing access to external beam radiation units in LMICs have been proposed[47,48]: (1) development of enhanced cobalt 60 (Co-60) units capable of modern dose delivery and (2) manufacture of simpler robust linear accelerators (linacs) that can operate in locations with problematic infrastructure or in problematic environments. Each path has supporters and critics.[47–49]

During a three-decade decline of use in HICs, Co-60 delivery has acquired a reputation of being inferior and having no place in modern RT. However, some researchers have advocated that the dose delivery limitations have not resulted from the characteristics of the Co-60 beam (such as beam penetration and penumbra width), but rather from a lack of machine development.[49,50] Recent modeling studies and investigations on modified Co-60 units have shown that the improved conformal delivery expected in modern RT is achievable in a Co-60–based IMRT setting.[50–55]

Linac suppliers have been developing units that are more conducive to use in LMICs. Unfortunately, however, much of this development is proprietary and not yet described in the literature. One approach has been to develop simple low-energy units with intentional removal of components that require more careful maintenance or frequent repair. This approach may result in linac units with limitations similar to those of the more advanced Co-60 units that are now available.[47,48] The motivation to bring the number of radiation units to the level required to meet the current and projected global needs will drive the development of both Co-60 units and linacs that are more appropriate for LMICs. Analysis in the literature suggests that LMICs would likely benefit from a mixed approach using both Co-60– and linac-based devices.[47,48]

Current international initiatives

A number of international initiatives have been spearheaded by United Nations agencies and nongovernmental agencies to address the global shortfall of RT capacity (Table 3). Through its Programme of Action for Cancer Therapy, the IAEA has engaged at the country level to help member states' governments build RT services. This initiative is being undertaken in the context of local cancer control programs by providing expert technical advice on and assistance with the procurement of equipment.[56]

Unfortunately, the urgency and necessity to build RT capacity in LMICs has still not been universally recognized within the health and development community. To promote awareness and action to address this unmet need, the Union for International Cancer Control launched the Global Task Force on Radiotherapy for Cancer Control in early 2014. This task force is developing an investment framework to demonstrate the health and economic benefits that would result from the scaling up of capacity for RT in LMICs.[57] In late 2014, the International Cancer Expert Corps was established to promote the development of a high-quality sustainable workforce to improve cancer care capability and capacity within LMICs.[58,59] The goal of the International Cancer Expert Corps is to develop a global workforce that includes oncologists, pathologist, radiologists, and nurses who would be provided with training and sustainable clinical support in LMICs.

Many academic centers and national bodies are responding to the global health interest of their trainees by establishing collaborations with international institutions. The hope is that such collaborations will facilitate greater exchange of knowledge between established cancer treatment centers and limited resource settings.[58,60] One such example is the University of Pennsylvania and Massachusetts General Hospital partnership with the oncology department in Botswana.[61,62] The Canadian Association of Radiation Oncology International Communications Working Group and the American Society for Therapeutic Radiation Oncology have both launched scholarship programs to enable radiation oncology trainees to improve their knowledge on global health issues and challenges by participating in research and clinical work in low- resource settings.[63,64] The development of bilateral exchange programs with involved centers would be an important next step.

Conclusion

Treatment of NSCLC requires access to RT, surgery, systemic therapy, and a wide range of supportive and diagnostic services. This multimodal approach is available in most developed countries, but little or no access to RT exists in many LMICs. Priorities include investing in both human capacity and treatment resources, ensuring quality of care, providing guidance on priority setting with limited resources, and fostering innovation to increase the economic efficiency of RT delivery. Such technical innovation could simplify RT planning and treatment, particularly in regions that have not yet implemented basic infrastructures and systems to deliver RT. Although smoking cessation is an essential goal to prevent cancer in LMICs, such efforts will not diminish the increasing number of patients in whom development of NSCLC is expected over the next few decades and who will require treatment. Scaling up RT in these regions is urgently needed to prevent unnecessary morbidity and mortality due to NSCLC.

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