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Authors
Bhatia, Rohini
Lichter, Katie E
Gurram, Lavanya
et al.

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The state of gynecologic radiation therapy in low-and middle-income countries

Rohini Bhatia[1], **Katie E Lichter**[2], **Lavanya Gurram**[3], **Emily MacDuffie**[4], **Dorothy Lombe**[5], **Gustavo R Sarria**[6], **Surbhi Grover**[7,8]

[1]Department of Radiation Oncology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

[2]Department of Radiation Oncology, University of California San Francisco, San Francisco, California, USA

[3]Department of Radiation Oncology, Tata Memorial Hospital, Mumbai, Maharashtra, India

[4]Department of Radiation Oncology, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[5]Department of Oncology, Cancer Diseases Hospital, Lusaka, Zambia

[6]Department of Radiation Oncology, University Hospital Bonn, Bonn, Nordrhein-Westfalen, Germany

[7]Department of Radiation Oncology, Botswana-University of Pennsylvania Partnership, Philadelphia, Pennsylvania, USA

[8]University of Pennsylvania, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA

Abstract

A disproportionate burden of gynecologic malignancies occurs in low- and middle-income countries. Radiation therapy is an integral component of treatment for gynecologic malignancies both from a curative (locally advanced cervical cancer) and palliative (bleeding cervical or pelvic mass) standpoint. Critical to understanding how better to serve patients in this regard is understanding both the extent of disease epidemiology and the radiotherapy infrastructure to treat these diseases. In this review, we explore various geographic regions and how they address a

Correspondence to Dr Surbhi Grover, Department of Radiation Oncology, Botswana-University of Pennsylvania Partnership, Philadelphia, PA 19104, USA; surbhigrover@gmail.com, **Twitter** Rohini Bhatia @rohinikbhatia and Dorothy Lombe @lombe_dorothy.

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unique set of challenges specific to the peoples and culture of the region. We identify common threads across regions, including sparse distribution of radiation equipment, geographic access, and specialized training. We also highlight examples of success in the use of telemedicine and cross-cultural partnerships to help bolster access to training to ensure increased access to adequate and appropriate treatment of gynecologic malignancies.

INTRODUCTION

Cancer and radiation therapy are no exception to the growing inequalities in healthcare highlighted by the recent pandemic. It is estimated that as many as 70% of cancer deaths worldwide occur in low- and middle-income countries, a classification of countries given by the World Bank based on gross national income. Further, more than 50% of patients requiring radiotherapy for treatment of their cancer in low- and middle-income countries do not have access to treatment; a situation that is exacerbated in low-income countries, where that proportion is closer to 90%.[1] Even as the world continues to grapple with coronavirus, health systems, especially those in low- and middle-income countries, are challenged to provide appropriate cancer screening and treatment. Many of these countries do not have the necessary infrastructure, personnel, and resources to deliver standard-of-care therapies.

The International Atomic Energy Agency (IAEA) is a global regulatory body for radiotherapy. The IAEA recommends a teletherapy unit, a radiation oncologist, a medical physicist, and two radiotherapists per 250 000 people.[1 2] However, in many parts of Africa, there is only one teletherapy unit per 10 million people.[1] In 2016, an analysis that employed a radiotherapy utilization rate model was used to estimate the number of patients in each country for whom radiation was indicated based on cancer diagnosis. This analysis demonstrated that although 4300 machines were available in low- and middle-income countries, an additional 7000 units would be needed to match demand.[3] Previous models have demonstrated that due to the difference in tumor distribution, types, and stage of presentation, the demand for radiation therapy in low-and middle-income countries is prob ably greater than that in high-income countries. One such model estimated the need for radiation therapy for all cancer types in Africa using GLOBOCAN data as between 47% and 61%. The authors note that these figures may underestimate the *actual* demand for radiation, given that definitions for radiotherapy indications were used based on the incidence of advanced disease. However, in areas without specialized surgery (ie, for early-stage cervical cancer) or palliative chemotherapy, radiation may play a larger role.[4]

Illustrating the disproportionate burden of disease, 19.2% of all cancers are gynecologic malignancies that occur in low- and middle-income countries.[5] Cervical cancer itself is the third most common cancer among women globally, with striking disparities in survival.[6] In high-income countries, 50–60% of women are alive 5 years after diagnosis compared with only 10–20% in some parts of Africa.[7 8] An estimated 70% of patients with newly diagnosed disease will benefit from either a curative definitive treatment or from palliation of pain or bleeding.[9] Radiation can improve absolute 5-year sur vival of women with cervical cancer by 17% above the contribution from surgery and chemotherapy. If the radiotherapy gap is

closed in the next two decades, 10 million life years in low- and middle-income countries would be saved that would otherwise be lost to this disease.[10]

Challenges to implementation of gynecologic radiation oncology include limited epidemiologic data, limited or outdated equipment, financial challenges of both countries and patients, referral systems, infrastructure both in terms of power supply and legitimate access to cancer facilities, specialty trained personnel, and buy-in from local communities to build awareness for cancer care and radiation. To illustrate the potential success of improving access and equipment, we note Rwanda's recent progress with acquiring a linear accelerator. In January 2020, Rwanda welcomed a new radiotherapy department at the Rwanda Military Hospital (RMH) in Kigali with two linear accelerators, serving a population of 12 million inhabitants. In their first 21 months of treatment of 552 patients, 206 (37.3%) were patients with gynecologic malignancies.[11]

Unique to gynecologic radiation includes the ability to use brachytherapy in the treatment of cervical, vaginal, vulvar, and endometrial cancers. Brachytherapy is a key component in the treatment of gynecologic malignancies, specifically a part of the definitive paradigm in treating cervical cancer stage IB and above.[12] Despite evidence for the use of this treatment, large disparity exists in equipment and access to brachytherapy.[13 14] For example, a high-dose-rate brachytherapy unit is capable of treating roughly 10–12 cases per day; Ethiopia is a country of 84.1 million individuals with 60 000 new cancer cases each year and uses one high-dose-rate after-loader. One hospital in Thailand performs 1000 brachytherapy procedures in 1 year with one after-loader. In Honduras, 1000 new cases of cervical cancer are diagnosed annually, and there is no brachytherapy facility in the country.[15]

In this paper, we discuss challenges and successes in gynecologic radiation oncology in low- and middle-income countries by geographic region. We note that this is a brief overview of a nuanced topic that is region-, culture-, and people-specific. We hope that this overview provides an outline of areas for growth in improving access to radiation therapy for gynecologic cancers worldwide.

LATIN AMERICA AND THE CARIBBEAN

Overview

Latin America and the Caribbean is an extensive region that extends south of the Rio Grande and the Bahamas and includes Mexico, Central America, South America, and parts of the Caribbean. As of 2020, the area has an estimated population of 670 million people with approximately a third of the population concentrated in large cities and two-thirds living in small cities and/or rural areas. [16] Most Latin America and Caribbean countries today are middle-income countries, with heterogeneities across different development indicators, and Haiti being the only low-income country.[17] Despite recent decline in observed incidence around the world, cervical cancer continues to disproportionately affect women in this region.[18–21]

Infrastructure of Radiotherapy Across Latin America and the Caribbean— Today the Latin America and Caribbean region has approximately 628 radiation therapy

centers across 32 countries.[22] Twelve countries lack radiotherapy altogether. The IAEA's Directory of Radiotherapy Centers and Equipment has recorded 1096 megavoltage therapy and 393 brachytherapy facilities within Latin America and the Caribbean, with 50% of equipment >10 years old (Figure 1).[23] Approximately half of the radiation facilities, and a majority of brachytherapy facilities, are concentrated within two high-income countries, Brazil and Mexico, which constitute approximately 53% of the Latin American and Caribbean population. In this sense, hastening investments in the region in infrastructure and technology will be required to meet the 2030 UN Agenda for Sustainable Development Goals.[24]

Techniques and Fractionation in Latin America and the Caribbean The elevated proportion of patients to be treated at each specialized center is a common pattern across the region. Currently, an increased rate of the use of hypofractionation can be noted worldwide.[25 26] Nevertheless, Latin America and the Caribbean falls behind in its implementation due to a variety of documented contributing factors. In a recently published practitioner-based survey study, some of the barriers to implementation included concern for lack of long-term data, inferior local control, and rates of acute and late toxicity.[25] Yet, an accelerated patient rotation rate holds the potential to increase centers' capacity to treat a higher volume of patients and decrease waiting times. Several regional efforts are assessing hypofractionation for cervical cancer, including a trial assessing chemotherapy and pelvic hypofractionated radiation followed by brachytherapy (NCT04070976),[27] and chemotherapy and pelvic hypofractionated radiation followed by surgery in cervical cancer (NCT03750539).[28]

Brachytherapy in Latin America and the Caribbean—Use of brachytherapy for gynecologic malignancies varies across the region.[29] According to a 2011 patterns of care study surveying radiotherapy centers across 17 Latin American countries, just over half the survey respondents reported use of brachytherapy in their centers.[30] Among those performing brachytherapy, 95% of procedures were for gynecological cancers, with no other site exceeding >1%. Centers that do not perform gynecologic brachytherapy as part of curative treatment previously noted common barriers that ranged from lack of patient referrals and patient capacity to pay for treatment to infrastructure-related issues, such as the frequent radioactive source changes and limited access to reliable power sources.[13 31] Nonetheless, some experiences have reported a shifting tendency towards use of brachytherapy sources with longer half-lives, such as cobalt.[32] This particular feature may open new doors to widespread brachytherapy implementation as centers benefit logistically and financially from less frequent source replacements.[33]

Training in Latin America and the Caribbean—The breadth of radiation therapy training remains heterogeneous across Latin America and the Caribbean and was considered a subspecialty until recently. As of 2015, less than a third of Latin America and Caribbean countries have formal radiation oncology training, with few offering dedicated medical physics programs. Today the professional and resident societies, Asociación Ibero Latinoamericana de Terapia Radiante (ALATRO) and Latin American Residents in Radiation Oncology (LARRO), continue to support the development of radiotherapy throughout the Latin America and Caribbean region through educational, research,

networking, mentorship, and political advocacy efforts.[34–36] Specifically focused on gynecologic malignancies, Rayos Contra Cancer and BIO Ventures for Global Health have established a gynecologic high-dose-rate brachytherapy training program for physicians and physicists to address fundamental gaps in training required to operate their acquired equipment safely and effectively.[36 37] Furthermore, the development of such web-based curricula allows has increased providers exposure to other educational topics, including hypofractionation and stereotactic body radiation therapy.[38] An initial experience with developing a longitudinal remote program has encouraged addressing further diverse topics, including gynecological topics, currently under planning.

EAST ASIA AND THE PACIFIC AND SOUTH ASIA

Overview

Low- and middle-income countries in Asia carry one of the highest rates of cervical cancer mortality worldwide, yet have a consistently poor equitable distribution of radiotherapy resources.[39 40] Cervical cancer is the fourth most common women's cancer in the majority of Asian countries, with highest mortality rates observed in South Asia.[41] Approximately two-thirds present in locally advanced stages with the requirement of radiotherapy. However, only 40% of women requiring radiation are able to receive treatment due to problems of access.[42]

Infrastructure of Radiotherapy Across Asia

Clustering of radiotherapy and oncology centers in urban areas has led to limited access for many across Asia. Additionally, treatment is hindered by poor allocation of national budgets for oncology-directed care, heightened costs of treatment in private sectors, and lower socioeconomic strata of the afflicted.[13 43 44]

The number of linear accelerators varies across the region. In larger middle-income to upper-middle-income countries, like the Russian Federation, India, and Republic of Korea, there are several hundred linear accelerators whereas mid-sized low- and middle-income countries, like Indonesia, Philippines, and Pakistan, may have fewer than 50 machines serving the countries' populations. Availability becomes even scarcer in countries like Cambodia, Mongolia, Myanmar, and Nepal. The deficit is doubled when brachytherapy equipment is taken into consideration, with numbers as low as one (Cambodia and Mongolia; Figure 2).[22] In a report from India, it was estimated that at least 109 external beam radiation therapyand 127 brachytherapy machines would be required to address the need of cervical cancer cases in the country.[42] Due to the lack of radiation equipment and personnel, the use of neoadjuvant chemotherapy and surgery has increased in many low- and middle-income countries.[44 45] Alhough a phase III randomized controlled trial from India established the superiority of concurrent chemoradiation over radiotherapy in stage IIIB cervical cancer, the use of this approach is challenging in many centers due to lack of ancillary services.[46]

Techniques and Fractionation in Asia

There has been a shift to the use to of 3D conformal radiation therapy for external beam therapy in many tertiary centers of low-and middle-income countries across Asia. National guidelines have been developed in countries like India and Korea to consolidate the approach to treatment.[47] Despite this, there is an unmatched need in rural settings, where cobalt continues to be the mainstay of external beam treatment. The use of intensity-modulated radiation therapy is on the rise, but its use remains limited by technical and implementation problems similar to those of 3D conformal radiation therapy. Adaptation of new radiation techniques may begin to spread throughout the region, but reports of machine downtimes and impact on overall treatment times are sparse. Though the use of image-adapted brachytherapy is common in high-income countries, the same has not been the case in Asia. In a survey of practice in South East Asia, it was observed that this approach has not yet been initiated in many countries with CT scanners, and the use of MRI for treatment remains implausible.[48 49] In addition, the recent increase in replacement of brachytherapy by external beam radiation therapy techniques due to lack of brachytherapy equipment and training limitations has resulted in inferior outcomes.[50 51] In order to further research and clinical practice in the region, several centers in India have participated in the multicentric, international collaborative EMBRACE study to evaluate the effect of image-guided brachytherapy.[52] The use of single-application multifractionated brachytherapy has increased with efforts to reduce the overall treatment time and increase capacity.[53 54]

Training

Ongoing support from international agencies like IAEA, Union for International Cancer Control (UICC), and the World Health Organization (WHO) has led to an increased regional collaboration and improvements in the training of professionals.[55] The involvement of international teaching bodies such as European School of Oncology and European Society of Radiotherapy and Oncology has led to a wider dissemination of evidence-based practices. In addition, Asian societies like Federation of Asian Organizations for Radiation Oncology, Indian Brachytherapy Society, and Forum for Nuclear Cooperation in Asia have developed collaborative efforts within the continent. A collaborative initiative between the Royal Australian and New Zealand College of Radiologists (RANZCR) and Asia Pacific School on Internet Governance (APSIG) helped Mongolia in establishing linear accelerator set-up, commissioning, and training of physicists.[56] Despite these collaborations, an accurate estimate of radiation professional availability and the unmet need is lacking. In a global survey, it was estimated that in at least nine countries in Asia, one oncologist would oversee treatment of more than 500 patients, thus highlighting the urgent need to expand the availability of professionals in this area.[57]

SUB-SAHARAN AFRICA

Overview

Africa accounted for 11.6% of all new gynecological cancers globally in 2020.[58] When cervical cancer is isolated, the contribution of new cases increases to 19.4%, second only to Asia with 76 745 deaths attributed to this highly preventable and treatable disease. Most of the focus in gynecologic oncology across sub-Saharan Africa is in cervical cancer,

for which the standard of care for locally advanced disease is chemoradiotherapy with a brachytherapy boost. However, other cancers such as uterine and vulva cancer are amenable to radiotherapy, both in the adjuvant and definitive treatment settings.[59 60] Cancer care in Africa must surmount challenges brought about by the epidemiologic shift of disease that includes not just a transition from infectious to chronic disease but persistent infectious disease and chronic disease care. In sub-Saharan Africa, over 80% of new HIV infections occur among adolescent girls aged 15–19 years. AIDS-related illnesses, including cervical cancer, remain the leading cause of death among women aged 15–49 years in the region.[61] For good clinical outcomes of gynecologic malignancies, a multidisciplinary team approach in managing these women is appropriate to facilitate best treatment approaches and timely referrals along the continuum of care.[62]

Infrastructure of Radiotherapy Across Asia

Of the 187 radiotherapy machines in sub-Saharan Africa, 60% are spread over two countries, South Africa and Egypt; while 29 of 54 countries in Africa lack any radiotherapy resource (Figure 1).[14] Such sparse distribution of machines translates into the first significant patient barrier—geographical distance—hindering access to care. Radiation oncology for gynecological malignancies tends to last 6–8 weeks, meaning women who do not live close to radiotherapy centers spend considerable lengths of time away from their home causing social and economic disruption. The prospect of this migration for medical purposes may deter women from seeking timely care.[63] Additional barriers may include delayed patient presentation to a health facility due to lack of community and social support to seek out help.[64] Once a patient presents to a healthcare facility, multiple visits may be required for staging and treatment, creating a logistical barrier. A high patient-to-machine ratio also creates a long waiting time, which can complicate the geographical challenges.

In 2019, 29 centers from 12 sub-Saharan African countries were surveyed at the Cervical Cancer Research Networks (CCRN) annual symposium. Of the countries surveyed, 96% of the centers had radiation therapy available and clinical trials were open at 4% of those centers. The centers had between one and four linear accelerators and at least seven centers had cobalt machines. Brachytherapy was used by 85% of centers; 80% of these centers used high-dose-rate brachytherapy. It is important to note that the centers attending the CCRN symposium are not necessarily an adequate representation of the distribution and estimation of cancer centers across sub-Saharan Africa. However, it is encouraging that the centers that do have radiation therapy are able to provide treatment with adequate dose and within an appropriate period. The authors of this survey additionally suggest that given that radiation is a limited resource, understanding how to appropriately triage and/or include hypofractionation schedules for patients may be worthwhile.[65]

Based on current available data, brachytherapy is offered in 19 out of 52 African nations with a strong push for an increase in centers to offer brachytherapy (Figure 2). The potential treatable capacity of patients with cervical cancer given the resources was calculated to be 24 300 patients a year in 2008, with only marginal increases in equipment availability since that time. The incidence of cervical cancer in Africa was just under 120 000 in 2018.[39] There is a clear disparity between available services and need.[66]

Capital investment in radiation oncology, although significant, is a surmountable barrier if there is political will to establish oncology services. This involves robust service contracts for the radiotherapy machines and highly skilled, knowledgeable personnel, such as medical physicists. Many sub-Saharan African countries go through cycles of establishment of centers followed by a lack of maintenance, leading to frequent machine breakdowns. Complicating factors include unreliable power supply—for example, only 40% of Nigerians have access to an energy supply and attempts to revive the power sector have been impeded by corruption in public office.

Therefore, a more high-level multi-pronged approach is needed to ensure sustainable radiation oncology services for the region, including developing opportunistic infrastructure and human resources in parallel with, rather than sequentially after, initial investment by donors with specific agendas.[67 68]

Training and Human Resources Across Africa

Unfortunately, ample training programs across the region are sparse and inadequate. Based on recent data, only 12 African countries have established training programs for radiation (Algeria, Egypt, Libya, Tunisia, Morocco, Sudan, Nigeria, South Africa, Zimbabwe, Zambia, Ghana, and Tanzania), with many countries relying on external training.[69–71] The risk with external training is that trained professionals might not return to the country of origin, due in part to ineffective staff retention and poorly equipped treatment centers that are not in line with the training they receive. For example, IAEA recommends two radiation oncologists per center and an additional radiation oncologist for each 200–250 new patient with cancer treated annually. Nigeria is thus estimated to require 420 radiation oncologists —probably, the need is greater because many function as clinical medical oncologists as well. As of January 2016, 10 of Nigeria's 51 radiation oncologists were not serving the nation within their trained specialty. Eight worked as medical oncologists in hospitals with no radiation therapy departments.[72]

Rayos Contra Cancer (RCC) conducted a pilot study that administered high-dose-rate brachytherapy training via videoconferencing to radiation oncology clinicians, including those in Africa and the Middle East to be followed by site visits with in-person training. This feasible model could broaden the use of brachytherapy for cervical cancer cases globally.[37]

Additionally, there are presently nine documented medical physics programs in all of Africa, in Algeria, Egypt, Ghana, Libya, Morocco, Nigeria, South Africa, Sudan, and Tunisia. Medical physics specifically is affected by shortages of staff in Africa, as some African countries may not recognize the medical physics profession. The African Radiation Oncology network is an initiative that has been established to help with peer-to-peer interactions, and to offer a space for discussion and education through telemedicine.[73]

EASTERN EUROPE

Overview

Eastern Europe is a region loosely described as encompassing the European portion of the former Soviet Union, but there is no universally agreed definition. Since World War

I and the political isolation of the Soviet era, this region has experienced considerably less economic growth and subsequent lag in healthcare delivery than their Western counterparts.[74] A majority of the countries are classified as low or middle income, despite half of the countries joining the European Union in the early 2000s. Cancer has risen to the second most common cause of death, with more than 50% of all cancer cases diagnosed at an advanced stage (III or IV).[6] The age-standardized incidence of cervical cancer and endometrial cancer in Eastern Europe is 10–28% and 15% per 100 000 people per year, respectively.[75 76]

Radiotherapy Infrastructure in Eastern Europe

There are a number of barriers to obtaining radiotherapy for treatment of gynecological malignancies in this region. Investment in technology and infrastructure to provide radiation therapy has been limited, resulting in 85% of equipment being more than 15 years old.[77] Data collected between 2017 and 2021 and recorded by the IAEA reported 488 radiation centers across 28 nations encompassing Eastern Europe and Northern Asia, although notably 156 (32%) of these centers are located in Russia alone (Figure 1). The average distribution of radiation equipment is 2.6 per million people. All countries have at least one modality for radiation delivery with a cobalt-60 predominance of 70%, although a majority of countries have at least one linear accelerator and cobalt-60 machine. All but Albania have at least one high-dose-rate brachytherapy unit, which is predominantly used to treat gynecological (59%), prostate (17%), and breast (9%) cancers.[78]

Barriers to radiotherapy also include geographic concentration of centers in urban areas, complicating treatment for patients in rural areas who must travel for daily treatment.[75] While the supply of Eastern European radiation oncologists is lower than desired at 9.3 per million people, there is a particularly marked shortage of physicists (6.1 per million) and radiation therapists (21.9 per million) as compared with Western European nations, where staffing numbers are roughly double these values.[79]

Training in Eastern Europe

Some countries offer specialty training, but programs often lack standardization, and the lure of higher salaries in the West results in substantial brain drain from the region.[77] Recent expansion of specialized training bodies such as the European School of Oncology, which notably now has sites in Croatia, Hungary, and Bosnia and Herzegovina, may provide a mechanism to reduce chronic understaffing at many centers. Continued efforts to support the requisition of updated technology, training of healthcare professionals, and outreach to the rural populace will be required to bring Eastern European nations closer to the gains experienced by their Western neighbors.

CONCLUSION

Gynecologic malignancies make up a significant portion of morbidity and mortality in women worldwide. An integral part of their treatment regimen is radiation therapy. However, access to specialists, including gynecologic oncologists, radiation oncologists, medical physicists, radiation therapists, is varied but universally limited across regions. Each region

explored above addresses a unique set of challenges specific to the peoples and culture of the region. However, there are common threads that can be identified. First, as has been previously explored, the availability of radiation equipment is sparse. In a field where daily treatment is important to kill a biological tumor and enable normal tissue recovery, geographic access to a linear accelerator is a critical component of accurate and comprehensive delivery of cancer care. Second, buy-in from local community leaders to help increase awareness of symptoms and promote presentation to a healthcare facility are important. Symptoms like vaginal bleeding may be embarrassing, difficult to discuss, or not talked about at all, leading to delayed and advanced-stage presentation. Further, a brief comment should also be made about access to palliative radiotherapy in this setting. There are scarce data on the proportion of patients treated with curative versus palliative intent in low-and middle-income countries. Recent work by Krakauer et al[80] has looked at the global need for palliative care for patients with cervical cancer, and provided a quantitative estimate of the need for palliation in this population. The authors estimated that one million women with cervical cancer had moderate or severe pain, 85% of whom were in low- and middle-income countries. Further understanding of the extent to which palliative therapy is offered and at what stage of disease it is offered is needed. Third, an emphasis on brachytherapy training globally will strengthen improved access to this critical therapy for women. Finally, partnerships between academic institutions, government organizations, and hospitals can foster areas of growth, bidirectional learning as has been demonstrated by Rayos Contra Cancer, and sharing of resources.

We recognize and applaud the work done by all healthcare practitioners in low- and middle-income countries towards addressing disparities in access to radiation. The task at hand includes prioritizing actions specific to each country and the needs they require. Partnerships designed to assist in training personnel with contouring, brachytherapy technique and planning, or the use of newer technologies; addressing governmental and policy stakeholders in investing in healthcare infrastructure; and finally, increasing community awareness about screening and the potential for treatment if diagnosed with cancer can all advance delivery of high-quality care to patients with gynecologic cancer worldwide.

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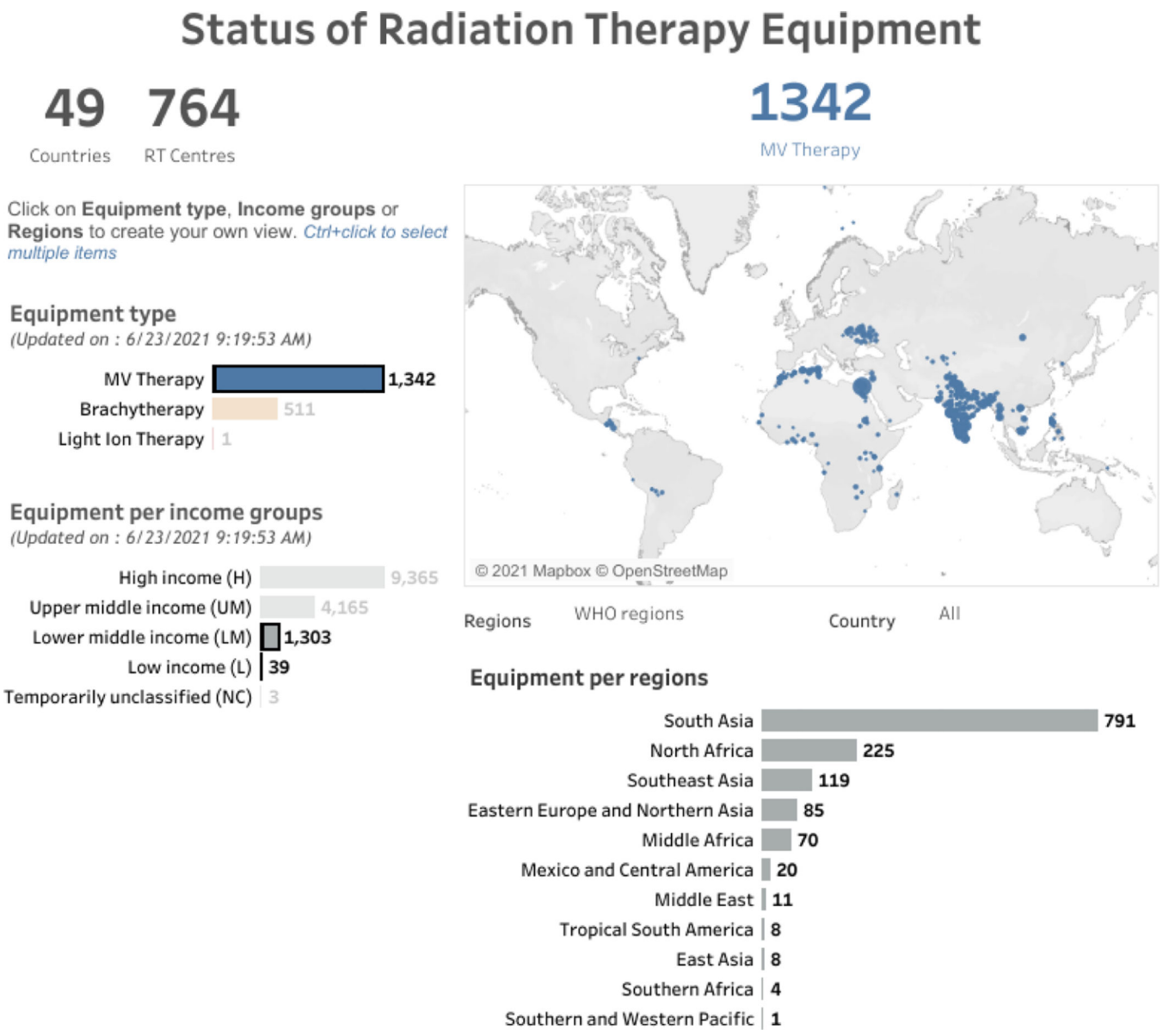

Figure 1.

MV (mega voltage) therapy availability across all low- and middle-income countries. IAEA (Directory of Radiotherapy Centers, DIRAC). http://www.dirac.iaea.org.

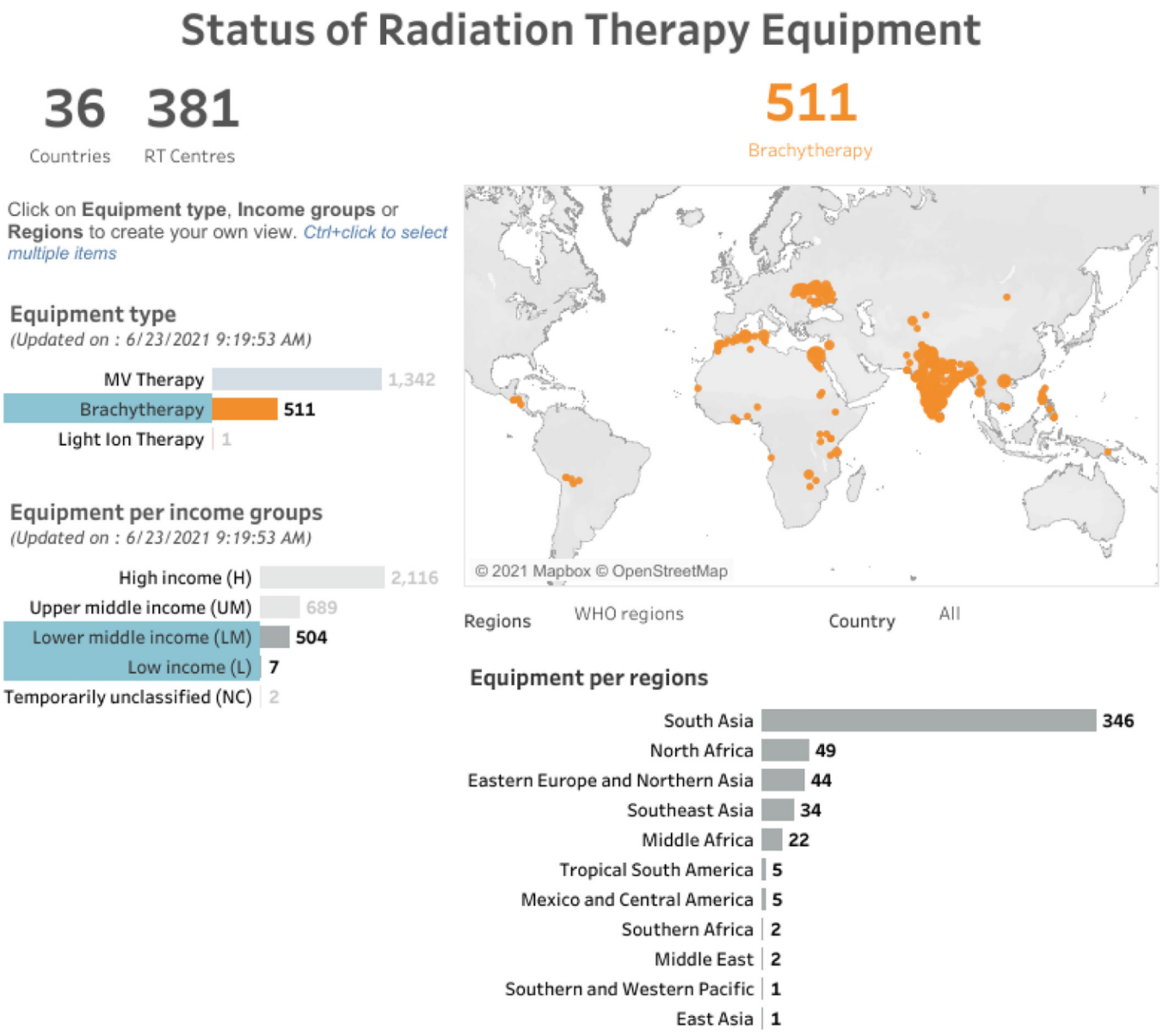

Figure 2.

Brachytherapy availability across all low- and middle-income countries. IAEA (Directory of Radiotherapy Centers, DIRAC). http://www.dirac.iaea.org.