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Radiotherapeutic Management of Oligometastatic Disease in Low- and Middle-Income Countries: The Current State of Affairs and Perspectives on Future Implementation

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In 2018, there were an estimated 18.1 million new cancer cases and 9.6 million cancer deaths based on data from 185 countries.[1] Radiation therapy (RT) is required in 45% to 55% of all new cancer diagnoses[2] and 5-year overall survival (OS) benefits from RT can reach as high as 16% in head and neck and 18% in cervix populations.[3] Historically, curative-intent therapy was applied only to locally confined primary disease, but with improvements in detection, systemic therapies, surgical techniques, and conformal radiation, we can now identify and intervene upon oligometastatic disease (OMD) with the goal of changing patterns of recurrence, delaying progression, and improving quality of life as well as survival. Drs. Hellman and Weichselbaum[4] were early proponents of this counterpoint to an all-or-nothing dichotomous theory of cancer spread, wherein early metastases, limited in number and location, may still be curable through local intervention.

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Definition and Management of OMD

There is no single universally accepted definition of OMD, but current clinical practice and trial designs most commonly use a numerical threshold of 3 to 5 lesions. While exciting work is ongoing, there have been, to date, no prospectively validated OMD-specific biomarkers.[5] The European Society for Radiotherapy and Oncology (ESTRO) and European Organization for Research and Treatment of Cancer (EORTC) recently outlined nomenclature to categorize states of OMD as a reflection of metastatic capacity.[6] In this classification, they proposed 5 characteristics of metastatic progression (history of polymetastatic disease, prior OMD, interval between diagnosis of primary cancer and diagnosis of OMD, prior active systemic therapy, and any OMD progression by imaging) and define 9 distinct states of OMD. This paradigm allows tailoring treatment aims to the OMD state, which can be dynamic, with the overall goal of preventing or delaying polymetastatic progression.

The principles of treating OMD include primary tumor control, local consolidation of all metastatic sites, and minimizing treatment duration of metastasis-directed therapy (MTD) to allow cure for a minority of cases or a quick initiation of or return to systemic therapy for most.[7] Recent randomized data support MTD using stereotactic ablative radiation (SABR), which allows the precise delivery of high doses of radiation under image guidance. The SABR-COMET trial reported that, when added to standard systemic therapy, MTD with SABR in patients with a controlled primary cancer of any histology and up to 5 metastatic lesions was associated with a median survival of 41 months compared to 28 months in the standard palliative therapy arm.[8] Secondary analyses have also shown SABR to be cost-effective and not associated with greater decline in quality of life compared to standard of care.[9,10] Two phase II oligometastatic non-small cell lung cancer (NSCLC) trials demonstrated significant progression-free survival benefit following upfront systemic therapy with the use of local consolidative SABR to sites of metastatic disease consisting of 3 to 5 lesions; the absolute PFS benefit ranged from 6.2 months[11] to 9.8 months.[12] Furthermore, the Gomez trial[12] showed an absolute median OS benefit of 24.2 months associated with SABR and also highlighted the importance of the window of treatment, suggesting that early local consolidative therapy (LCT) was favorable to LCT at time of progression. The Surveillance or Metastasis-directed Therapy for Oligometastatic Prostate Cancer Recurrence (STOMP) trial demonstrated that for prostate cancer with up to 3 metastatic lesions the use of MDT (primarily SABR) significantly prolonged median androgen-deprivation therapy (ADT) free survival from 12 months (surveillance) to 21 months (LCT) with no grade 2 or higher toxicity.[13] Similarly, in the Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer (ORIOLE) trial,[14] SABR resulted in significantly reduced risk of progressive disease in men with oligorecurrent prostate cancer and 1 to 3 metastases detectable by conventional imaging, with a median PFS not reached (median follow-up: 18.8 months) in the SABR arm compared to 5.8 months with observation alone. These trials demonstrate that SABR can improve PFS, OS, and may in some cases permit a safe delay in initiating systemic therapy.

Classification and Cancer Burden in Low- and Middle-Income Countries

Currently, three-quarters of global cancer deaths are in low- and middle-income countries (LMICs)[15] and the combination of reduced death from infectious etiologies and longer life expectancies are contributing to increased cancer incidence in these countries. World Bank classifies LMICs based on gross national income (GNI) per capita. Specifically, low-income economies are defined as < $1,025, lower middle-income economies are between $1,026 and $3,995, and upper middle-income economies are between $3,996 and $12,375.[16] While incidence of cancer types is influenced by societal, economic, and lifestyle factors, the ratio of mortality to incidence is consistently elevated across all cancer types in LMICs. For instance, Asia accounts for 48.4% of total cancer cases and 57.3% of cancer deaths, and Africa accounts for 5.8% of cases and 7.3% of deaths. Despite elevated incidence of prostate cancer in high-income countries (primarily in Australia, Northern and Western Europe, and North America), the highest mortality rates are in Sub-Saharan Africa and the Caribbean. Furthermore, mortality is likely underestimated in LMICs, where most cancer registries are hospital- rather than population-based and frequently offer insufficient coverage. In 2010, only 7.5%, 6.5%, and 1% of the total population of South America, Asia, and Africa, respectively, were covered by high-quality cancer registration.[17]

Impediments to Radiation Therapy in LMICs

The Directory of Radiotherapy Centers (DIRAC) of the International Atomic Energy Agency (IAEA) is a continuous central registry and quantification of international RT capacity. Member states self-report data on teletherapy machines, sources and devices used in brachytherapy, dosimetry equipment, patient dose calculation, and quality assurance. Of the 138 countries classified as LMICs, 119 are part of the IAEA and 90 have radiation capability.[16] The number of RT machines per million people decreases from 7.7 in high-income countries to 1.5 in upper middle, 0.43 in lower middle, and 0.05 in low-income countries.[18] This is much lower than the 4 per 1 million recommended by the IAEA and only approximately 20% of LMICs have a current organization to consistently offer RT.[19,20] One of the greatest impediments to implementing RT in general is a lack of infrastructure: There is a direct correlation between gross domestic product and access to RT.[21] Equipment costs can be several million dollars[22] and LMICs often rely on donated linear accelerators, which can be more than 20 years old. In 2019, 29 of the 54 African countries listed by World Bank have photon- and electron-beam teletherapy machines and only 6 (Kenya, Tunisia, Algeria, Morocco, South Africa, and Egypt) have more than 10 machines.[18] It is no surprise that machine deficit correlates with decreased life expectancy,[21,23,24] as the contribution of RT to cancer survival is around 40%, compared to a 49% contribution from surgery and an 11% contribution from systemic therapy.[25] Additional costly infrastructure considerations include appropriate radiation shielding of treatment vaults and reliable water and power supplies. Even greater expense is tied to SABR use for oligometastatic disease due to the time-intensive nature of planning and delivery as well as more stringent engineering tolerances.

Personnel limitations also complicate availability of high-quality RT. The ESTRO - Quantification of Radiation Therapy Infrastructure and Staffing Needs (ESTRO-QUARTS) estimates RT units and staffing requirements. Based on ESTRO-QUARTS and DIRAC, Datta et al[26] estimated the percentage of additional infrastructure and personnel required in 2020 based on 2014 inventory in LMICs as follows: medical physicists (+292.3%), RT technologists (+270.3%), teletherapy units (+221.6%), and radiation oncologists (+102.9%). While the demand of these professions has risen in LMICs, the supply has not proportionally increased. For example, Lebanon has 11 radiation oncologists for a population of 5 million people.[27] Additionally, these limited staff are usually in centralized urban areas in contrast to the high percentage of rural inhabitants in LMICs. This disconnect results in patients traveling great distances for treatment, often finding limited temporary housing.[28] There are several explanations for the lack of personnel support in LMICs. Foremost are financial reasons: Annual salaries of professionals in the field are 5 times higher in developed countries, prompting considerable relocation of qualified personnel to higher income countries where the profession is better supported.[22] Second, training often necessitates travel abroad with no guarantee that trainees will return to practice in their home country. Finally, the engineering support for RT units is commonly provided by the manufacturer and availability is severely limited in LMICs where low overall supply does not make it economical for companies to provide greater levels of support.

MDT Integration in LMICs

While curative-intent treatment of OMD has shown great promise, implementing such a paradigm in LMICs requires careful consideration of resource availability and allocation. In a resource-limited setting, cost-effectiveness is paramount. The argument for developing MDT capacities in LMIC begs several key questions: (1) To what degree is any treatment of metastatic cancer a feasible economic priority? (2) Is the population of patients eligible for treatment sufficient to justify the infrastructure required? (3) Is SABR inclusion into OMD management paradigms expected to add value over traditional systemic therapies? The first answer will be highly specific to the financial, cultural, and medical landscape of each nation and is beyond the scope of this discussion. Discussion regarding the second and third questions are as follows:

Understanding the eligible patient population requires knowledge of disease staging as well as ability to pay for care. As discussed above, many patients in LMICs are not covered by high-quality national cancer registries.[17] Without nation-level or, at minimum, robust hospital-level data expected to provide a representative sampling of the population, analysts and researchers can only extrapolate from nations where such data exists. While registries are critical to understanding population-level trends and needs, the other side of this coin with respect to OMD is the ability of patients to be adequately imaged. WHO recommends at least one imaging department (x-ray and ultrasound) per 50,000 people.[29] Most countries in Africa report < 1 CT unit per 1 million people, as compared to Denmark with 24 CT units per 1 million inhabitants.[30] Organizations such as RAD-AID are working to address this radiology gap through education (development of a US medical school clerkship curriculum in public health and radiology) and acquisition of technology through donation or lower-cost older machines, and lower-cost technology such as cellular phones.[31,32]

When the incidence of OMD and, in turn, the resources required to implement a modern management strategy can be satisfactorily estimated, the ability of patients to pay for sophisticated cancer care must then be assessed. Even in highly developed nations, cancer care can be prohibitively expensive to individuals and cost-sharing mechanisms are critically important. Limited public health care coverage options in LMICs result in proliferation of private, fee-for-service options causing high out-of-pocket expenses and further widening of health inequity. Universal health care coverage is essential to ensure risk pooling and protect from the destabilizing financial consequences of poor health. Mexico established a national health insurance program, Seguro Popular, in 2003 that introduced the concept of nonpersonal health-related public goods (immunization, primary prevention, early detection, epidemiological surveillance) and personal health services. Nonpersonal health services were financed through the Ministry of Health via general taxation. In contrast, personal health services were funded through prepaid contributions based on capacity to pay in addition to general taxation.[33] Mexico's implementation of universal health coverage serves as a model for other LMICs.

With adequate detection capabilities, registry management, and identification of payers, we must ask if OMD is a cost-effective component of cancer care. Currently data is limited to adequately comment on SBRT cost effectiveness in treating OMD compared with systemic therapy. It has been described, however, that the average monthly cost of targeted agents is between $12,000 for oral kinase inhibitors to $150,000 for monoclonal antibodies[34] and on average launch prices increase by approximately 10% (or $8,500) per year.[35] Furthermore, the lower expected revenues from LMICs may not justify the initial investment that companies undertake to overcome regulatory barriers.[34] In one Canadian study, SBRT was more cost-effective (expected cost per net quality-adjusted life years) than video-assisted thoracic surgery or systemic therapy in treating pulmonary metastases from melanoma or non-EGFR mutant lung adenocarcinoma.[36] An analysis of the SABR-COMET trial found that the addition of MDT was cost-effective compared with standard-of-care management alone for patients with 1 to 5 oligometastatic lesions.[9] While radiation has been shown to be a cost-effective cancer treatment – curative intent and palliation – compared with other cancer interventions in Australia,[37] it is unclear whether this translates to LMICs.

Lessons From Existing Efforts, Potential Future Directions

Fostering the development of RT capabilities in any LMIC will no doubt require addressing specific local considerations and no template will provide a single best approach. With that said, valuable lessons can be learned from the published experience in Botswana, classified as lower income, including the necessity of obtaining government support and establishment of quality cancer registries for diagnosis, care, and evaluating patient outcome. While the private sector identified the oncology market and constructed the radiation bunker to house a donated linear accelerator,[28] the public sector was instrumental in the delivery of radiation through financial compensation of personnel, infrastructure support, and coordination with neighboring South Africa (from whom Botswana initially obtained its electrical power).

Another valuable example is the development of RT capabilities in the Dominican Republic (DR). DR is an upper-middle income country where most physicians are trained abroad. A radiation oncology residency program was established in 2010; however, there is no formal training program for radiation therapists, dosimetrists, or medical physicists. While radiation was established in 1945, 76% of the existing machines were installed from 2010 onward. For DR, three key events led to the increase in RT units: In 2004, IAEA analysis of DR noted a severe deficiency in radiation capability with only three centers housing four machines.[38] In 2007, a publicly financed health insurance scheme was established. In 2009, the Ministry of Public Health recognized cancer and noncommunicable diseases as a priority, which allowed cancer care to be covered under the public health insurance. Now with 12 radiation centers housing 21 machines, DR contains the highest number of RT centers in the Caribbean. They have both a public sector and private sector offering radiation, and 95% of patients have health insurance.[38] Despite these successes, however, challenges remain in DR with respect to treatment of OMD. While SBRT technology is available, it is used infrequently due to limitations of availability and lower reimbursement rates. Also, most patients in DR still present with advanced stage disease. This is thought to be attributable to limited patient education, cultural taboos regarding cancer, and reliance on natural remedies. This highlights the importance of community engagement in the coordinated effort to manage cancer.

Technological advancements might also someday help to develop and increase access to RT in LMICs. Mobile linear accelerators are now feasible[39] and may help bring RT to underserved parts of high-income countries as well as patients in LMICs. While likely not a permanent solution, it might act as an impetus to support the growing expansion of RT in underserved parts of the world, especially if combined with hypofractionation or ultrafractionation approaches, which significantly decrease the number of treatments for an RT course.

A noteworthy disadvantage of current SBRT approaches in resource-limited settings such as LMICs is the increased treatment times required, meaning fewer patients can be treated each day. One solution may be to extend practice hours, which has been shown to be feasible in Zambia.[40] However, Yahya et al[23] found the extended working hours model was able to fulfill RT needs in high- and upper-middle income countries in Southeast Asia but not in LMICs. The natural alternative to increased working hours would be some combination of decreased treatment duration and/or decreased total treatments per patient. FLASH RT, in which ultrahigh dose rate radiation is delivered in milliseconds, appears to be less toxic to healthy tissues and may broaden the applicability of single-fraction regimens.[41,42] This is beneficial in situations where patients travel long distances, often from other countries, to receive treatment and will reduce time burden for the patient. Additionally, compressing treatment into one session allows for high efficiency use of the linear accelerator.[43]

As discussed, a major limitation to RT delivery in LMICs is lack of personnel, often driven by emigration to seek training. The increasingly interconnected global environment offers the opportunity for remote collaboration in the RT process. Remote planning[44-45] and quality assurance are feasible[46] and may help increase access to radiation. A commitment to greater remote collaboration might someday permit remote training to reduce the need for physicians, physicists, and dosimetrists from LMICs to emigrate to obtain the necessary knowledge to practice. These types of efforts can and should be coordinated with international agencies such as IAEA and professional societies in radiation oncology to facilitate increased access to radiation around the globe.

Conclusions

Without adequate cancer registries, it is difficult to estimate at what cancer stage patients from LMICs typically present. The high mortality-to-incidence ratio is likely a combination of presenting at a more advanced stage, due to lack of screening and access to health care, and lack of treatment options. Implementing RT and MDT in LMICs has many barriers; however, with technological advances, some of these may be overcome. With scarce resources available to many LMICs, it may be difficult to adequately treat patients presenting with metastatic disease. However, an approach to OMD that includes RT-based MDT would likely benefit patients in LMICs, providing a possibility of cure in a patient subset and survival improvements in others, all with a low risk of serious toxicity. Continued efforts to integrate MDT in LMICs are needed.

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