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EDITORIAL

The Lancet Oncology Commission: Radiotherapy & Theranostic Services in LMICs: Minding & Mending the Gaps

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In the early 1990s, the World Bank Group (WBG) reached a consensus on classifying countries by income status.[1] The primary aim of the system developed by the WBG was to provide a framework that could be used for analytic purposes. Since then, scholars across various disciplines have skillfully adopted the classification to enable improvements that have benefitted a wide swath of society, including the healthcare sector.[2] This approach's foundational — and aspirational — premise was that the taxonomy (e.g., "High-, Middle-, and Low-income countries") would be dynamic. Indeed, over the years, several nations have liberated themselves from the shackles of limited financial means, though far too many remain mired in the low- or middle-income ranks.[3]

In 2015, Atun et al[4] — on behalf of the Global Task Force on Radiotherapy for Cancer Control (GTFRCC) — published a seminal paper in *The Lancet Oncology* which endeavored to provide a cross-sectional picture of radiotherapy around the world and direct attention to radiotherapy (RT) as a ". . .neglected and necessary facet of global cancer control." These authors acknowledged that closing the gaps to achieve equitable delivery of radiotherapy constituted a complex undertaking requiring at least two decades of remedial work.[5] Today, another major article has been published

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in *The Lancet Oncology* by Abdel-Wahab et al,[6] which extends the efforts of the GTFRCC and underscores the needs that persist in low- and middle-income countries. With this editorial, we wish to contextualize the findings of this noble task force for the readership of The Red Journal. Several professional bodies, including the American Society for Radiation Oncology (ASTRO) − the society that houses The Red Journal as its official publication − and the IAEA (International Atomic Energy Agency) have endorsed the report by Abdel-Wahab et al. However, the opinions expressed herein reflect only our views as editorialists practicing in various countries, not as representatives of these professional bodies.

At the outset, we wish to make several laudatory observations. First, we salute *The Lancet Oncology*, which became immediately engaged when contacted by the GTFRCC and now demonstrates sustained interest by, once again, devoting a significant number of its prestigious pages to this topic. Second, the experts recruited to compose the report by Abdel-Wahab et al reflect authentic diversity in terms of geography (i.e., all continents except Antarctica are represented), occupation (e.g., radiation oncologists, nuclear medicine specialists, medical physicists, healthcare economists, etc.), and WBG status (a substantial percentage of the 52 authors reside in LMICs). Moreover, the authors are kindred spirits in that they have selflessly volunteered to channel their expertise in global cancer control toward improving lives at the collective level. Third, the manuscript itself is comprehensive, extensively referenced, and − relative to most policy papers − readable. Finally, we appreciate Abdel-Wahab et al's decision to compose an interim report as well as an updated document. The former manifests in the dire data we summarize in the ensuing paragraph; the latter is evinced by the focus of significant sections of the paper on the burgeoning field of "Theranostics."

From the evidence presented, we learn that severe disparities in capital equipment and shortages of skilled human resources still characterize the state of radiotherapy in LMICs (compared to high-income countries). Such problems are compounded given the reality that more than half of patients diagnosed with cancer reside in low- and middle-income countries, where over 90% of patients with cancer lack access to radiotherapy. It is essential to amplify the distinction between availability and accessibility.[7] Whereas availability implies a presence (e.g., of specialized machinery) that is potentially usable, accessibility connotes the capability of being quickly, if not immediately, put to use. Accordingly, while it is encouraging to learn that there is a greater availability of linear accelerators in LMICs when examining data from 2023 as opposed to 2013 (Figure 3 of Abdel-Wahab et al) and that a substantial percentage of these linear accelerators (LINACS) are suitable for image-guided radiotherapy (Figure 6 of Abdel-Wahab et al), it is commensurately frustrating to apprehend the extent of LINAC downtime (Panel 1 and Figure 5 of Abdel-Wahab et al) − in some measure due to a lack of available replacement parts − and sheer impedance caused by inadequate transportation means or systems coupled with exorbitant costs of travel. In the spirit of being solution-oriented, Abdel-Wahab et al proceed to present encouraging models justifying the implementation of stereotactic body radiotherapy (SBRT) (e.g., Panel 2 of Abdel-Wahab et al) and describe the advantages inherent to hypofractionation (Figure 12 and Table 4 of Abdel-Wahab et al). Simultaneously, though, there is a dearth of appropriately trained/credentialed professionals to oversee these sophisticated RT procedures, and requisite quality assurance standards are not consistently deployed. Moreover, even though Abdel-Wahab et al articulate the economic upside in extending the work-day, one wonders if a price will be paid vis-à-vis staff burnout,[8] which could have a self-defeating effect, coupled with the already alarming attrition rate[9,10] of radiation therapy technologists (RTTs) and medical physicists (MPs) in LMICs who seek to depart for HICs in search of "greener pastures," thereby increasing the workforce in countries they migrate to, to the detriment of countries from which they emigrate. This regrettable attrition, which has rapidly engulfed LMICs in recent years, nullifies the aim of augmenting the human resource pools in these resource-constrained countries. In other words, we are thrust into an undulating narrative of highs and lows: just as we are on the verge of breathing a sigh of relief on behalf of our fellow human beings living in resource-constrained regions, it is unsettling to confront the *de facto* crisis that continues to exist. Thus, it is not surprising when we read the projection that by 2030, approximately three-quarters of all cancer deaths worldwide will still occur in LMICs.

The frustrations mentioned above intensify when beholding the accomplishments that radiation oncology has achieved as a field during the intervening ten years since the publication of the initial Lancet Commission by Atun et al.[4] Some of the triumphs reflect the rewards of systematic, rational scientific and technological inquiry. For instance, intensity-modulated radiation therapy (IMRT) is demonstrated to be associated with less toxicity than its conventional and even 3D-conformal predecessors.[11] So too, adaptive radiation therapy (ART), stereotactic radiosurgery (SRS) for brain metastases, and SBRT for spinal metastases have all gained momentum for their compelling efficacy.[12-14] Moreover, the oligometastatic state for various malignancies is no longer a theoretical concept[15] but a recognized entity incorporated into clinical trials where radiotherapy is an oft-preferred local control modality.[16] During the same period, unparalleled innovations have also occurred in radiotherapy and the partner domains of surgical and systemic therapy with which we integrate. Furthermore, the careful combination of immunotherapy with RT, which has proven successful in only some body sites using specific sequencing arrangements, has mandated a more profound understanding of the relationship between RT and the immune system.[17,18] No less impressive is the courage demonstrated by young investigators to explore complex molecular profiles that enable optimized patient selection for RT, which could, in turn, expand or narrow

indications for the modality.[19] This exciting array of practice-changing developments in such a short period is extraordinary. Yet, we wonder: when will the rest of us who work and live in LMICs be equal beneficiaries of this exceptional scientific progress? With competing demands of communicable diseases,[20] a dearth of and slow implementation of existing national cancer control plans,[21,22] and incomplete - if not absent - national cancer registries in many countries, it is nearly impossible for the actual burden of cancer in most of these LMICs to be realized on an individual country level with resultant information to drive change. Tackling these fundamental issues would improve government buy-in and support for the institution of basic RT facilities where deficiencies persist, and then, with time, advanced RT technologies would be introduced.

Meanwhile, considerable activity in Theranostics has also transpired. The groundbreaking work of Dr. Saul Hertz led to the first therapeutic use of radioactive iodine (RAI) in the 1940s, which was deemed by most to be the earliest precedent for targeted therapy and the foundation of theranostics.[23] Although RAI has been part of the standard of care for thyrotoxicosis and differentiated thyroid cancer for several decades in HICs, there is still a significant disparity in access and utilization between HICs and LMICs (Abdel-Wahab et al, Figure 7). During the past two decades, the growing availability of novel positron emission tomographic (PET) tracers and imaging systems in HICs has revolutionized the detection, staging, and follow-up of patients with several types of cancer. In these countries, nuclear chemists and nuclear medicine physicians have developed a wide range of molecularly targeted systemic radiotherapeutic agents, which are being studied in clinical trials. However, as demonstrated by Abdel-Wahab et al (Figures 8-10), the disparity of limited RT accessibility and utilization outside of these contexts is even more marked for some of the most novel theranostic agents such as bone-specific therapies as well as Ra-223, Lu-177, and Ac-225-based therapies. While several ongoing trials mature and as new radionuclide therapies receive regulatory approval, it appears that LMICs are still playing catch-up in the more fundamental realms of cancer diagnosis and management. Limited production capacity of radioisotopes, unreliable supply chains, regulatory issues, and a scarcity of trained workforce have all been highlighted as reasons for the relatively low utilization of theranostics in LMICs. In addition, the relatively short lifespan of many radiopharmaceuticals highlights the need to cut logistical red tape and ensure timely clearance of these imported materials at the port of entry. Furthermore, limited health insurance coverage means that patients have to bear the high costs of these treatments. Another critical challenge is the limited availability of SPECT and PET imaging equipment, which are indispensable for standard theranostic care.[24]

Abdel-Wahab et al present multiple worthwhile suggestions (e.g., the use of external audits and instilling a culture of radiation safety) to bring "the ideal and the real" into alignment. Particular emphasis is placed on the disruptive value of artificial intelligence, such as AI-based predictive maintenance models. At an even more rudimentary level, demands could be made on vendors to extend product life cycles to optimize machine durability.[25] At the other end of the spectrum, an intriguing recommendation made by Abdel-Wahab et al is a call for research and innovation. At first blush, this may seem naive; however, the involvement of radiation professionals in scientific investigations that are titrated to homegrown curiosities would not only yield vital information to propel our field forward but would also have spillover benefits such as elevating standards of care outside the research question being posed and nurturing of staff morale as colleagues rally around pursuits that interest them.[26] Acceptance of high-quality research from LMICs for publication in high-impact journals would improve the visibility of these intrepid institutions and foster greater interest in collaborations with institutions in HICs.

By way of illustration, partnership with The African Organization for Research and Training in Cancer (AORTIC) could be highly strategic in bridging the education and research gaps realized by the Lancet Commission report. AORTIC is able to play a pivotal role with members from a large number of countries within Africa, some of whom influence policy within their respective countries.[27] In addition, cooperation between national ministries of health, policy stakeholders and patient advocacy groups in their respective countries will be crucial in maintaining the discussion on availability of RT facilities.[28] Sustained engagement between national stakeholders and relevant Centers for Disease Control, as well as strong public/private sector partnerships can play a crucial role in expanding access to cancer therapies and addressing human resource constraints in LMICs.

Engagement with the IAEA as well as other renowned organizations (e.g., ASTRO, ESTRO), and leveraging the existing expertise of these organizations would foster collaborations with a higher probability of achieving the outlined action points at a global level. Our group would humbly suggest that yet another technique that could provide a valuable bridge for some of the goals proposed is the "twinning" mechanism.[29] In this approach, professionals are brought together across cultures to reciprocally bolster each other. For the arrangement to be sustainable, the partners embrace the principles of "social exchange theory," which posits that each party has goods that the other party values.[30] Within this mechanism, healthcare professionals from HICs might employ telemedicine techniques to provide regular mentoring on technical advances while counterparts from LMICs − drawing from historical needs to be nimble − propose efficiencies based on resourcefulness derived from navigating high numbers of challenging cases that may not be as frequent in HICs. This approach has already helped a public cancer clinic in Guatemala to upgrade its program from Cobalt teletherapy to Image-Guided IMRT.[31]

These changes will all take time. Understandably, many readers will feel impatience, borne out of a desire to restore fundamental rights to our fellow human beings who bear the

coinciding misfortunes of being diagnosed with a malignant disease while living in a place that is resource-constrained. The 20-year commitment of the Lancet Commission reminds us of the importance of long-term goals, setting realistic, measurable, and achievable targets while maintaining effective monitoring and evaluation plans.

The thoroughness of the report by Abdel-Wahab et al is unparalleled. The authors' commitment to the greater good of individuals and communities of low- and middle-income countries is unassailable. All of the tasks proposed are eminently reasonable and will indeed be pursued in earnest before the next formal assessment by the Commission in 2034. Our group hopes it might be possible, as dictated by the principles of "implementation science",[32] to integrate these overarching goals with quantitative benchmarks, so that efforts could be coordinated around well-defined and specific objectives. For instance, one low-hanging fruit includes reducing the attrition rate of the already low numbers of healthcare professionals in LMICs by encouraging the recognition of additional professionals such as MPs and RTTs, allowing them the opportunity for career development and placing them suitably on a national salary structure. HICs that have inadvertently recruited professionals from LMICs could be encouraged, in a collaborative effort, to give back by aiding with education, training of additional professionals, and partnering to finance necessary equipment that is lacking to achieve desired goals.

In summary, we applaud the Commission's cognitively oriented approach towards remedying the long-standing deficiencies of radiotherapy and theranostics that persist in the LMICs. On this point, we recall that when epidemiologist Dr. Leonard Sagan summarized manifold factors that influence illness and well-being in his book, *The Health of Nations*, he concluded that "it is the brain that is the true health provider."[33] In this spirit, we would do well to mind the gaps highlighted in the report of the Lancet Oncology Commission in order to mend them.

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