RADIATION ONCOLOGY

Proton Therapy in LMICs: Is the Need Justified?

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JCO Global Oncol 8:e2100268. © 2022 by American Society of Clinical Oncology

Proton beam therapy (PBT), because of its unique physical and biologic properties, delivers highly conformal dose distributions compared with available conventional radiation therapy (RT) techniques. It has shown potential to minimize acute and late effects of radiation including radiation-induced second malignancies. Radiation oncologists routinely select plans on the basis of the doses to target, organs at risk, and integral dose (cumulative dose to the body). On the basis of the above, PBT plans would be chosen over the best photon plans on most occasions. However, PBT facilities are resource-intensive to set-up and maintain compared with even the most modern linear accelerators (linac). They require immense infrastructure and have a lower throughput compared with a linac facility. Given the higher costs and relatively limited access, it has been argued whether it is worth investing in PBT technology for an incremental improvement in dosimetry.

At present, universal consensus exists regarding the clinical superiority of PBT in treating pediatric and/or adolescent and young adult cancers, tumors near skull base and spine, and tumors requiring reirradiation, and the same is endorsed by professional societies. The American Society for Radiation Oncology model policies have suggested many other potential indications as part of coverage with evidence development that can be treated with PBT when patients are enrolled in a suitably designed clinical trials.[1]

Retrospective and prospective studies have shown promising outcomes with PBT for other sites such as CNS tumors, head neck, esophageal, hepatocellular, and thoracic cancers.[2-6] Studies using various models such as the Markov model for cost-effectiveness have also shown promising cost-effectiveness of PBT over conventional RT for pediatric brain tumors, certain head and neck, locoregionally advanced lung, and well-selected breast cancers.[7] However, because of the paucity of definitive level-1 evidence in the form of randomized control trials, PBT is still struggling for a wider scope of clinical application and acceptance among clinicians. Past few years have seen a noticeable spurt in prospective studies being conducted involving PBT including randomized control trials for several sites such as breast, prostate, lung, head and neck, hepatocellular, esophageal, and brain cancers.[8]

PBT too has rapidly evolved in the past decade with the incorporation of pencil beam scanning, image guidance, dose optimization, and calculation algorithms, among others thereby considerably increasing its throughput and versatility. Reduction in the footprint of this equipment also has resulted in a downward trend of its cost of acquisition and maintenance. Amid all these developments and availability of newer clinical and dosimetric evidence, several high-income countries (HICs) such as the United States, the United Kingdom, Japan, Germany, Italy, France, the Netherlands, Denmark, and Austria have already invested in PBT facilities, whereas several others like Singapore, Belgium, Saudi Arabia, Switzerland, Canada, Australia, Israel, and Norway are following suit. This brings about a major question—should low- and middle-income countries (LMICs), where even basic health care necessities are not met universally, look at investing in PBT facilities?

Why PBT in LMICs?

LMIC is a very diverse group of regions with significant variability in terms of population, resources, demography, health care infrastructure, disease presentation, and outcomes. Radiation oncology access has been a persistent key gap area in LMICs where an alarming 80% increase in cancer incidence is predicted by 2030 compared with that in 2008.[9] Fortunately, accessibility, both in quantity and quality, is rapidly improving in several pockets spanning modalities like minimally invasive surgery, genomics, immunotherapy including chimeric antigen receptor-T-cell therapy, and RT is no exception. For example, in India, despite a low national average of linear accelerator (linac) density, several cities now have multiple high-end linacs and advanced therapeutics comparable with HICs. Emerging economies such as China, Egypt, Thailand, Turkey, Brazil, Mexico, and many more show similar trends of investment in world-class infrastructure, personnel, and vibrant peer-review culture, producing oncologic outcomes echoing the best global standards. With the improvement in purchasing power of the burgeoning middle class, a large section of the population is now aspiring for world-class health care within their reach. Corollary, sophisticated RT techniques such as PBT have garnered significant interest among the health care planners and investors.

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on November 22, 2021 and published at ascopubs.org/journal/go on January 13, 2022: DOI https://doi.org/10.1200/GO.21.00268

The sheer number of the deserving patients in LMICs is a straightforward reason for investing in PBT. For example, 80% of pediatric medulloblastomas in the world are diagnosed in LMICs.[10] In the United States, the use of PBT for such tumors in the pediatric age group has increased 10-fold in the past 15 years.[11] This is because of the fact that PBT in medulloblastomas has shown to minimize several late effects such as neurocognitive impairment, hearing loss, endocrinopathies, osteoporosis, cardiovascular mortality; improve scholastic performance and health-related quality of life; and minimize the probability of second malignancies.[12-14] For medulloblastomas, it has also shown to be more cost -effective than conventional RT techniques with an approximate long-term gain of 0.68 quality-adjusted life-years per child.[14] PBT in LMICs, while serving such patients with established indications with proven cost-effectiveness (albeit in HIC setting), would also enable its evaluation in several LMIC-specific indications (oral cavity, thoracic esophageal, pancreaticobiliary, and high-risk prostate cancers) that are currently relatively understudied in HICs. Theoretically, larger tumor volumes, poor nourishment, and younger age at presentation encountered in LMICs translate to a greater potential for toxicity reduction with conformal RT techniques, and hence, larger expected benefit. The potential for relatively quicker accrual of larger patient numbers, superimposed with overall lower trial costs, means higher and faster trial output per dollar spent, transcribing to a higher clinical trial cost-effectiveness.[15,16] Although, there are limited data on cost-effectiveness of PBT in the context of LMICs, a UK-based modeling study on the basis of a certain case mix showed a significant cost-saving with PBT over conventional RT grossing to one billion pounds over the lifetime of the treated patients.[17] Similar results can be conjectured in the LMIC setting, especially considering the most likely scenario of a significantly lower cost of PBT treatments in LMICs.

What Is the Magnitude of the Need?

The benefit and requirement of PBT has been estimated as a percentage of total patients receiving RT. These varying estimates, ranging from 1.5% in the United Kingdom to much higher values in other European countries, for example, the Netherlands (10%), France (14.5%), Sweden (15%), and Italy (16%), have been used to plan the infrastructure requirements by the respective countries.[17-19] Despite similarities in cancer incidence, sociodemographic, and economic factors among these nations, such a significant difference in estimated requirement illustrates a difference in philosophy of approach toward newer technologies—one conservative (to cater to the ones with the highest need only), the other relatively generous. Before extrapolating this to LMICs, it should be borne in mind the differences in the age and stage distribution of patients and the types of cancers requiring RT between HICs and LMICs. The estimated PBT requirements must also incorporate the numbers for prospective studies to generate LMIC-specific evidence while keeping pace with changing trends in PBT usage that are likely to emerge in the future. On the basis of the above, our conservative and generous estimates for LMICs, respectively, are at least 1% and 7.5% of the total patients treated with RT. For example, in India, with nearly 300,000 patients treated with RT each year (on 545 teletherapy machines),[20] 3,000-22,500 patients could benefit from PBT. Assuming 250 patients treated per proton room per year on an average, even on a conservative estimate, 12 proton rooms would be required to fulfill the country's current requirement. In India, three rooms are currently operational[21] and three more are being commissioned. These calculations can be extrapolated to any other emerging economy that has financial means and appropriately trained human resources.

What Needs to Be Done to Fulfill the Need?

Setting up of a greenfield PBT facility in majority of regions that lack the appropriate infrastructure and human resource is imprudent. Initiating such a resource-intense endeavor is only possible through collaboration between professional societies, governments, private sector, machine manufacturers, medical insurance companies, patient advocacy groups, and other stakeholders.[22] Countries would qualify to acquire PBT facilities, only if there is already a robust conventional RT infrastructure in place with availability of large pool of clinical and technical staff. Also, the PBT facilities ideally should not come at the cost of other important health care priorities both for the government as well as for private sector. The countries also ideally must have a track record for research and innovation, although importance of providing good-quality clinical services cannot be undermined. But in LMICs, which is home to 4/5th of the world population, need many more.

Hence, we propose a tier-based system among LMIC regions/centers providing or planning to provide PBT facility to patients as per the available RT infrastructure and resources.

The first tier should consist of regions/centers in LMICs that have already invested in their first few PBT facilities. Some of these centers have already shown through their preliminary experience that PBT implementation is safe and feasible in the LMIC setting.[21] These centers must focus toward maximizing clinical accessibility within their own geographies and also expedite evidence generation for PBT. These centers will need to collaborate with professional societies, government agencies, health care planners, and patient groups to realize these goals. The second tier should include countries and/or centers in LMICs who already have a robust conventional RT infrastructure and are planning to invest in a PBT facility. Those in this tier should engage with the already established LMIC PBT facilities to learn from the best practices to optimize resources and manpower to mitigate the initial challenges, ensure shorter learning curves, higher treatment efficiency, and faster implementation of clinical trials. The third tier will include countries and/or centers that do not have the

necessary resources or adequate RT infrastructure to set up a greenfield PBT facility. Deserving patients belonging to these regions should be offered access to this technology. To realize this, we propose setting up of an LMIC proton consortium on the basis of the principles of clinical services and academic/research collaboration.

This consortium can potentially mitigate the issue of lower accessibility of PBT facilities in LMICs by allowing deserving patients from member countries to avail PBT facilities in countries already providing such facilities in the region. Professional societies and physician groups especially those working in PBT centers in LMICs can collaborate with the proposed consortium and help generate good-quality prospective data including LMIC-centric cost-effectiveness data and encourage clinical trial participation. The data and clinical evidence generated will help guide public funding and help the private sector understand the scope of this technology in their respective communities and evaluate its financial feasibility. The insurance companies and local governments must support the judicious use of PBT and encourage clinical trial participation. Fortunately, because of much lower personnel cost, lower overall construction cost, and other expenses such as electricity, the cost of PBT treatments can be significantly lower compared with HICs. LMICs with technological know-how also must invest in innovative home-grown technologies to bring the costs further down.

The industry, in its own self-interest, must also actively engage with hospitals, physicians, and patient groups in LMICs and provide additional support such as providing machine part banks locally to ensure low machine downtimes. International regulatory authorities (such as International Atomic Energy Agency), must provide guidance to the PBT facilities and national along with local regulatory authorities on standardization of safety and quality assurance protocols in these regions.[23] Leveraging strengths of various stakeholders at every level is essential to ensure safe PBT implementation.

Finally, PBT technology is an engineering marvel which is certainly of great benefit for a few, incremental benefit for some, and may be of not much benefit for many. Medical science will continue to evaluate this technology to unravel this mix of patients with varying benefit. Patients who are likely to benefit with this technology irrespective of their country of residence must be able to access this relatively easily and at a reasonable cost. Optimal balance with respect to improving cancer care accessibility while encouraging timely adoption of modern technology should be considered as parallel goals across all regions.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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No other potential conflicts of interest were reported.

ACKNOWLEDGMENT

The authors acknowledge Dr Anindita Das and Dr Sujith Kumar Mullapally for their help during the course of this work.

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