Chapter

Proton Therapy in Lower-Middle-Income Countries: From Facts and Reality to Desire, Challenges and Limitations

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Abstract

Around 50% of cancer patients will require radiotherapy (RT) and 10–15% of these patients could be eligible for proton beam radiotherapy (PBT). Dosimetric advantages are undeniable, mainly in pediatric and reirradiation scenarios. Though, PBT facilities are scarce worldwide and the IAEA has reported 116 functional particle facilities, of which 98 are PBT, virtually absent in low- and middle-income countries (LMIC). The Latin America and Caribbean region represent a unique opportunity for a PBT center, as there are currently no functional facilities and current RT needs are significant. The challenges can be summarized as high initial investment and maintenance, geographic coverage, required baseline technology and certification, over-optimistic workload, unclear rates and reimbursement, unmet business plan and revenue expectations, and lack of trained human resources. Investment costs for a PBT facility are estimated to be at around 140 million euros; therefore, this seems unsuitable for LMIC. Mexico's geographical advantage, GDP, baseline technologies and high demand for RT makes it an ideal candidate. Nevertheless, a PBT center would account for a third of Mexico's annual health expenditure for 2020. Enormous efforts must be made by both the private sector and governmental authorities to provide funding.

Keywords: proton therapy, cost-effectiveness, low-to-middle-income countries, infrastructure

1. Introduction

Radiotherapy (RT) is an integral component of contemporary cancer treatment, both as curative and palliative therapy. Around 50% of patients will, at some point during their cancer history, require RT. Its contribution to cancer survival is estimated at around 40% versus 49% for surgery and 11% for systemic treatment modalities. [1] In the past decade, ongoing research in systemic therapies has broadened the indications for RT, since as long-term survival increases so does the prevalence of the disease. Oligometastatic cancer recurrence is increasingly managed with RT, as well as oligoprogressive disease. This in addition to its more common applications, such as local control in curable or metastatic settings. However, dose-limiting toxicity remains the main problem for RT, especially for in-field recurrences where reirradiation is a bigger concern.

Proton beam radiotherapy (PBT) is a novel technique with endless possibilities. Different simulation models have estimated that 10–15% of all radiated patients from various European countries could be eligible for PBT, but only less than 1% receive it. [2] Since toxicity and dosimetry advantages are undeniable, and although there is still scarce clinical practice, indications and applications are on the rise mainly in pediatric and reirradiation scenarios, without excluding common indications for radiation treatments, especially when dose constraints are an issue. Still, PBT remains non-existent in Latin America and virtually absent in low- and middle-income countries (LMIC). The following chapter will focus on how a PBT can be suitable for proven clinical indications in LMIC, particularly in Latin America and Mexico, where cancer and epidemiology registries—although insufficient—present a broader view of current RT needs when compared to other LMIC across Africa and Asia. A general overview of the facts and realities of RT, as well as the challenges and limitations expected for a proton facility in these countries, will be presented.

The Latin America and Caribbean (LAC) region represents a unique clinical opportunity for a proton radiation therapy center, as there are currently no functional facilities and because current radiotherapy needs are significant. Nevertheless, auxiliary diagnostic facilities required for a functional PBT center, such as computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI) and pathology departments, although insufficient, are found in some LAC cities, meeting the highest quality requirements and the most rigorous international certifications. There is an upcoming PBT center in Buenos Aires, Argentina with operations due to start in 2022. Even with this center, availability for this type of treatment is evidently not enough for the 629 million inhabitants living/distributed in the 192 million km^2 of Latin American territory. [3]

2. Proton therapy in low- and middle-income countries

2.1 Facts and reality

According to the IAEA Directory of Radiotherapy Centres, there are 116 functional proton/ion facilities (107 in high-income countries, 8 in upper-middle-income countries and 1 in LMIC) around the world, out of which 98 are PBT. Most are located in high-income countries in North America, Europe and Asia, countries that coincidentally have the highest number of photon radiotherapy equipment, and none in LAC. [4] **Figure 1** shows available PBT facilities according to their operation status. Even LAC has RT available only in 70% of its countries, with approximately 1 megavoltage machine per 650,000 inhabitants. Distribution varies according to income groups, creating an unequal environment for adequate cancer care, particularly from a radiotherapy standpoint. [5]

Cancer accounts for 10% of the global healthcare budget, out of which RT takes up only about 5%; therefore, RT expenditure is about 0.25–1% of the total healthcare budget. [6] This represents a very small fraction of the total healthcare budget if we consider that up to 25% of the population is expected to go through radiation treatment at some point in their life. [7] Although RT is regarded as the cheapest cancer treatment modality, limited resources are available in Latin America due to absence of domestic and international funding. Approximately 90% of the population in these countries will lack access to RT.

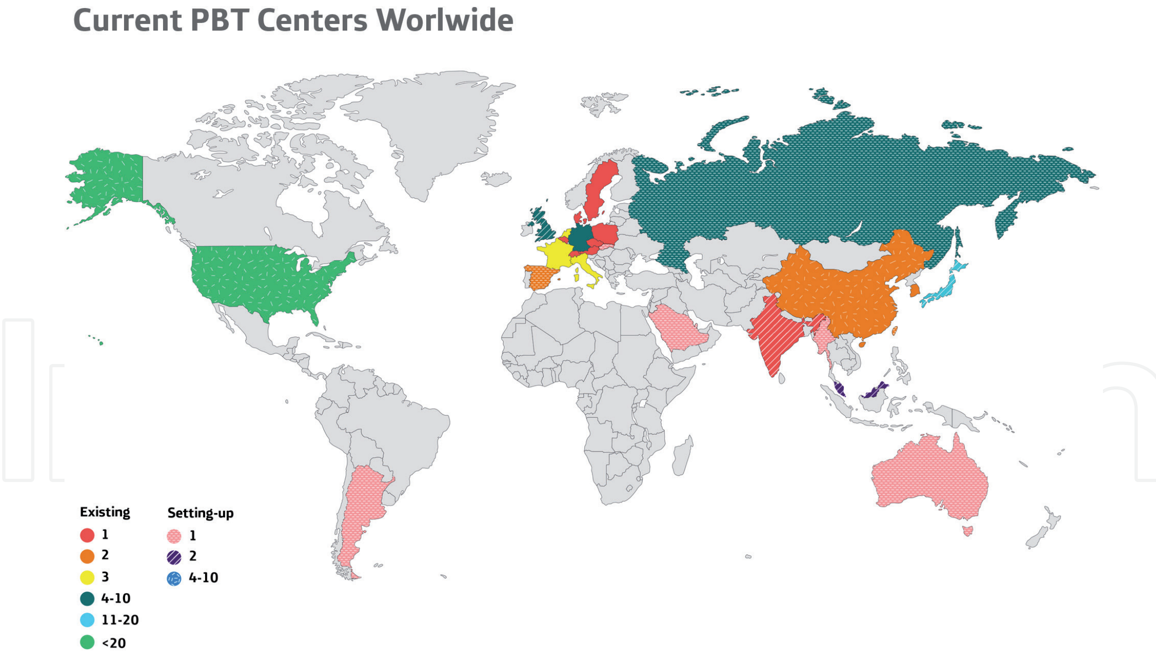

Figure 1.
Available proton therapy facilities in clinical operation and under construction.

Insufficient detailed information about attainability for radiotherapy and auxiliary diagnostic tools in LMIC is a constant. Currently very few countries in LAC have submitted recent data. Thus, planning for a PBT center requires data regarding general availability, not only for radiotherapy but also for auxiliary diagnostic tools, such as PET, MRI, CT scans and pathology laboratories, many of which are either partially or completely unavailable across the LAC region. Developing a PBT center with full access to all therapeutic and diagnostic tools involved in proton therapy must therefore be contemplated in at least one of the main cities of the region; otherwise, PBT center usage could be suboptimal. LAC presents a complex paradox, where most of childhood cancer and reirradiation scenario candidates for PBT are much more frequent than in developed countries—where most PBT centers exist—but is simultaneously the region facing the most difficulties for a functional PBT center, not due to the obvious economic challenges, but because of the lack of complementary and auxiliary tools required for it.

Another issue is that currently around 8% of LAC residents are 65 years or older, which represents the population with the highest risk for malignant neoplasms. By 2050, this figure is expected to double to 17.5% and to exceed 30% by the end of the century. In 2018, this represented over 1.3 million new cancer cases and over 660,000 cancer-related deaths; therefore, at least twice this number will reflect cancer deaths by 2050 unless international efforts to reduce mortality are effectively implemented. [8]

2.1.1 Adult tumors suitable for PBT in Latin America and their relevance for a proton facility

The LAC region encompasses 33 countries and 15 dependencies or territories with a total population of 646 million in 2019. [9] With a combined gross domestic product (GDP) of United States dollars (USD) 5.7 trillion, LAC is a region of growing importance to the world economy. [10, 11] GDP per capita ranges from USD 754 in Haiti to USD 85,477 in the Cayman Islands. Haiti is considered the only low-income country in the region; 7%, 49% and 41% are considered lower-middle-, upper-middle- and high-income countries, respectively. [12] According to Bishr et al., there is a total of 593 RT centers in 28 countries, with up to 983 megavoltage machines, of which 23.9% are telecobalt machines. Twelve countries (30%), containing 2% of the LAC population (estimated population of 12.5 million), lack RT facilities. [13]

Although the number of needed radiotherapy machines varies between reports and despite underestimation due to lack of cancer registries, the overall conclusion is that around 50% of cases requiring radiotherapy in LMIC never receive treatment, and this goes up to 90% in low-income countries. [7] Additionally, the economic burden of lost productivity due to morbidity and premature death from cancer accounts for nearly 60% of the total economic burden associated with cancer in European Union countries. [14]

2.1.2 Pediatric tumors in Latin America and their relevance for a proton facility

Although pediatric cancers represent 10–13% of patients treated with PBT in the US, PBT has proven clinical applications, especially for pediatric brain tumors since important toxicities such as growth deficiencies, hearing loss, intelligence quotient impairment, learning disabilities and secondary malignant neoplasms will potentially be avoided in childhood survivors. Among potential tumors treated with PBT, medulloblastoma and other pediatric central nervous system (CNS) malignancies in people under 21 are highly prevalent in LAC. LMIC countries have younger populations; for example, according to UNICEF, there are over 193 million minors registered in LAC. [15] Therefore, the expected number of children with cancer is larger. It is estimated that around 84% of childhood cancer occurs in these countries, simply because nearly 90% of the world's children population lives in LMIC. Moreover, 45% suffer from child poverty, which limits their access to RT.

GLOBOCAN estimates the incidence of childhood cancer varies between 50 and 200 cases per million children each year in different LMIC. However, this data is not reliable due to many undiagnosed childhood cancers, especially in rural areas of LAC, where diagnostic tools, such as MRI or even CT scanning, are not available [16]. Under-recording is another main issue since LMIC have weaker epidemiology networks and death certificates may be incomplete or absent. All of these factors contribute to inaccurate data.

Childhood cancer survival rates vary widely by region, particularly in LMIC, where lack of access to diagnoses is just the tip of the iceberg. Access to optimal treatments is often limited to private and selected tertiary public institutions. These out-of-pocket expenditures are often prohibitive for most of the LMIC population and, among many other factors, are essential components for this foreboding result. A simulation-based analysis for global childhood cancer survival estimates shows large variation by region, ranging from 8.1% (4.4–13.7) in low-income countries in Eastern Africa to 83% in high-income countries in North America, placing Latin America central nervous system cancer survival estimates at around 50%. [17]

2.1.3 Advantages and limitations of PBT

PBT has been used for almost seven decades. Even so, indications of PBT for cancer treatment have had an alarmingly slow development, often being displaced by other radiotherapy techniques, such as stereotactic body RT (SBRT) or intensity-modulated RT (IMRT) /volumetric arc therapy (VMAT). PBT has an important and undeniable radiobiological advantage over SBRT and VMAT techniques, [18] since it significantly reduces the absorbed dose by normal tissue and lowers whole body integral radiation doses due to the requirement of fewer treatment fields, [14, 19] which means there is overall less acute and late toxicity. This has been proven in multiple clinical trials, particularly in pediatric cancer and specific adult malignancies (skull base, head and neck, hepatocellular, central nervous system, breast, lung, prostate, testicular and ocular tumors), among other fewer common scenarios, such as reirradiation, where it allows for dose escalation in patients who otherwise would not be optimal candidates for photon therapy. [2]

Challenges for investment in particle therapy treatment centers reported by the European Investment Bank can be summarized in a) PBT is currently indicated for only a small number of cancers; b) treatment is very costly and time consuming; c) geographic coverage; d) limited research activity. Main issues for project implementation include a) delays and problems with technology specifications and certification; b) overflow of patients seeking treatment and over-optimistic workload; c) unclear rates and reimbursement schemes; d) unmet business plan and revenue expectations; e) limited number of trained human resources. Surprisingly, limitations for PBT are mainly economical, not only because of the high initial investment but also due to the yearly increases in the cost of cancer care, often above inflation rates. This raises the concern that a PBT facility that was once sustainable will not be so in the future due to operational costs, quality assurance, maintenance and continuous training and/or medical education. Lack of high-quality clinical data on outcome and long-term toxicity for PBT contributes to mistrust, but this is a symptom that reflects lack of investment, not a limitation of PBT per se. [20]

2.1.4 Realities of radiotherapy attainability in Latin America and/or Mexico

Starting a PBT center is an enormous challenge and many variables should be accounted for, not only the obvious limitations such as economic capabilities and preexisting infrastructure. But also more subjective and complex variables, such as amenable workforce, solid governmental facilities for diagnosis and oncologic treatment like a national cancer institute, national and international private sector funding, and an organized radiation oncologist society committed to and involved in providing all necessary means for a comprehensive workforce network across the country or the whole LAC region for patient recruitment and referral.

Viability of a PBT center is only possible if a continuous flow of patients is guaranteed, either from locoregional cases or from a referral-based system, and this can only be done by few LAC countries. Based on published information about current demographics, radiotherapy capabilities and diagnostic workup auxiliaries, this might only be possible in few countries. Economic capabilities are fundamental for such type of investment. Even with international support, only cities with a high population and GDP should be considered. **Table 1** ranks the 5 top cities by population and GDP amenable for any PBT projects. As stated before, there is already an ongoing PBT project running in Buenos Aires, Argentina.

It is estimated that two thirds of cancer-related deaths will occur in LMIC and treatment related-morbidity and mortality cause an enormous economic burden, especially in developing countries. Taking into account a PBT center is projected to start soon in Argentina, geographic location, gross domestic income, RT capabilities and diagnostic auxiliary tools available, a following PBT center could be feasible in Mexico. Particularly in the metropolitan area, where most oncology centers in the country are located. Mexico is currently the 14th most powerful world economy and 11th in purchasing power parity, second biggest economy in LAC and 4th in the continent, and is currently classified as an upper-middle-income country with a median age of 28 years old, 7.3% of its population being 65 years or older. [12, 21] Mexico is an exceptionally young country for its economic capabilities, with an incidence of childhood and teenage cancer of 89.6 per million inhabitants (111.4 in children aged 0–9 and 68.1 for teenagers aged 10–18) in 2017 and a prevalence of 18,000 annual

Rank	Country	GDP (PPP) in millions	GDP (PPP) per capita	Highest GDP (city)	Highest population (city)
1	Brazil	3,078,901	14,562	Sao Paulo US$ 699.2 B (2017)	Sao Paulo 21.3 M (2015)
2	Mexico	2,424,511	18,804	Mexico city US$ 411 B (2011)	Mexico city 8.85 M (2015)
3	Argentina	924,539	20,369	Buenos Aires US$ 118 B (2008)	Buenos Aires 2.8 M (2010)
4	Colombia	719,251	14,136	Bogota US$ 221.7 B (2016)	Bogota 8.08 M (2017)
5	Chile	456,394	23,454	Santiago US$ 175 B (2014)	Santiago 7.3 M (2015)

Abbreviations: B: billion; GDP: gross domestic product; M: million; PPP: purchasing power parity; US$: american dollars.

Table 1.
Top 5 cities by population and GDP amenable for any PBT projects.

cases in persons under 18 years of age. [22] The estimated incidence and prevalence of all cancers was 195,499 and 530,602 in 2020, respectively. [23] A busy PBT center is feasible. Mexican radiotherapy demographics have been recently published and this information is not only crucial for any investment on PBT, but also sets a necessary precedent for adequate development.

According to the Mexican radiotherapy certification board, the country lies on an alarmingly low density of radiotherapy facilities, with a density of 1.19 linear accelerators per million inhabitants. [24] Mexico stands out because of this, since it's not only one of the few countries in LAC that could divert health expenditures to a PBT project, but it also currently has an enormous need for radiotherapy facilities. The need for RT centers is huge and will rise in the following years in conjunction with the increasing age of its population and the number of pediatric cancer patients requiring RT (due to its high pediatric population).

2.2 Challenges

2.2.1 Cost evaluation

Van Dyk (2017) evaluated the annual cost of 4 fully independent centers with two linear accelerators each. They reported that capital costs, operational costs per year and cost per treatment course in high-income countries (HIC) are approximately $41,175,000, $18,309,00 and $5,350, respectively; whereas for LMIC, it's $32,035,000, $6,911,000 and $2,020, respectively. [25] In 2003, Goiten estimated that particle therapy was about 2.4 times more expensive than most sophisticated RT techniques, and that this could be reduced to 1.7–2.1 over a decade. [26] The investment costs are estimated to be about 140 million euros or 150–200 million dollars for a 4 to 5-room PBT facility and 40 million for a single-room center, which represent a more affordable option even for high-income countries [26, 27]. The former represents a small, but important, fraction of Mexico's health expenditure (which is approximately 31,700 million USD in 2020) [28].

Lifespan of a PBT facility should also be considered. Although the cost of a 4- or 5-room PBT center can reach several hundred million dollars, a large portion of the cost is attributable to the cyclotron or synchrotron and the huge rotational gantries with a lifespan of more than 30 years. Which is significantly longer than the 7-year average lifespan of a linear accelerator. The direct cost of a modern 4-gantry PBT center is similar to that of a linear accelerator facility with 16 machines over its 30-year lifespan (4 linear accelerators replaced 3 or 4 times over this period). [29].

Several US PBT centers had to accept a reference price as payment for PBT instead of no payment or coverage. In this case, payment is made based on the next most expensive alternative, which does not cover the real cost of delivering the treatment. [30] Additionally, some payers are complaining that they pay for a therapy with no clear evidence of benefit. [31] A focus only on direct up-front costs at the time of the treatment is inaccurate because the indirect costs of managing and surviving with the late adverse effects of radiotherapy could be reduced significantly or even completely with PBT. [29].

2.2.2 Cost-effectiveness analysis and limitations

Investment in high-cost RT facilities will also lead to an increase of the mean treatment cost; however, the cost-effectiveness of PBT may improve if the rate of patients with indications expected to benefit from this innovation increases. [32] PBT cost-effectiveness studies should include costs associated with intervention and secondary benefit comparisons. In summary, all potential costs saved from morbidity and/or mortality reduction versus all possible expenses should be considered. It is very difficult to include and assess every direct and indirect cost related to intervention. This should include construction of the PBT facilities, operational or procedural cost (personnel costs, electricity and maintenance, beam delivery time, number of patients treated). In addition, it should consider potential toxicities and their related costs, such as support medication and/or hospitalization related to RT-induced toxicities, both potentially more frequent in patients with a long life expectancy, close anatomical relationships to organs at risk (OAR), advanced tumor stage, histopathology and pre-existing comorbidities. Others factors that affect cost-effectiveness are treatment volume, treatment fields, treatment duration, total dose and fractionation. [2] A country's health system organization also influences economic cost. Since public (complete coverage versus adjusted-socioeconomical payment) and private services (with or without insurance company, and percentage of reimbursement) differ significantly in availability, reimbursement and cost, this must be considered in the analysis. And even more important is the availability of treatment machines.

PBT use in pediatric cancer is based on integral dose advantages of protons over photon RT. It modulates dosage to avoid OAR when the dose is high and OAR are close and with integral dose minimization. [33] Verma (2016) reported a 2.4-fold increase in initial cost of PBT versus conventional or IMRT in pediatric cancers. However, total costs of adverse effects showed an 8-fold decrease in favor of PBT. This yields a 2.6-fold reduction of overall costs in favor of PBT. [2] Currently, PBT is the most cost-effective option for several pediatric brain tumors. [34] Especially in craniospinal irradiation (CSI) with high dose boost requiring more conformation, such as in medulloblastoma, in which associated adverse effects related to radiotherapy are IQ decline, hearing loss and growth hormone deficiency. In atypical cases, such as high-grade glioma and sarcoma or retreatment of spine lesions, the doses achieved treat less normal tissue and can avoid internal OAR better. [35, 36] Other pediatric tumors suitable for PBT are intracranial and skull base tumors, spine tumors, Hodgkin Lymphoma and retreatment. As such, PBT is more cost-effective for pediatric cancer due to the decrease in long-term toxicity, long life expectancy after cancer treatment and more remaining years of economic-productive life. Therefore, although the number of cancers that are cured is generally very low, treatment of curable childhood cancer is highly cost-effective. Some issues to be considered include limited data, lack of long-term follow-up and contraindications for PBT (Wilms' tumor classic fields, whole lung classic fields and palliative RT). [2] By contrast, a Brazilian patient volume-based analysis showed that PBT was not cost-effective for pediatric medulloblastoma treatment. [37].

Other outcomes that can be measured include total life-years gained or lost, and quality-adjusted life years (QALYs). [2] For pediatric brain tumor, the incremental cost-effectiveness ratio was $21,716 to 26,419 dollars per QALY, depending on the study. [34].

In adult cases, PBT as standard treatment for breast cancer has not been shown to be cost-effective and is associated with a minimal increase in QALYs. However, specific subgroups that may benefit include patients with high-risk late cardiac toxicity, such as left-sided tumors or internal mammary node irradiation and those with double baseline risk of non-radiotherapy-related cardiac disease. [34, 38] For locoregionally advanced non-small cell lung cancer (NSCLC), PBT increased QALYs compared to conformal or IMRT, and was probably more cost-effective than for early-stage NSCLC. [34, 39, 40] In locally advanced head and neck cancer, intensity-modulated PBT (IMPT) reduces xerostomia and dysphagia rates compared to IMRT; however, cost was increased, [41] with an incremental cost-effectiveness ratio of $4,254 to 143,229 US dollars per QALY, depending on study and radiation technique. [34] In another Chinese study, IMPT was more cost-effective and provided an extra 1.65 QALYs for paranasal sinus and nasal cavity cancers compared to IMRT. [42] For prostate cancer, PBT showed increased costs without increasing QALYs compared to IMRT; in this case, life expectancy determines cost-effectiveness. [43] However, PBT is currently not considered medically necessary for the treatment of lung, prostate, breast, gastro-esophageal, hepatocellular, head and neck, gynecologic cancer or Hodgkin and non-Hodgkin Lymphoma. [44] A review of PBT concluded that no clinical data had shown superiority over advanced RT for treatment of central nervous system lesions. It is only medically necessary for cases with adjacent structures. [45] Given the excellent long-term results with PBT, it is considered medically necessary for the treatment of base skull and sacral chordomas and chondrosarcomas, [46] and uveal melanoma due to lower local recurrence rate, retinopathy and cataract formation. [47] PBT is appropriate for reirradiation where the dose tolerance of adjacent normal structures would be exceeded with conformal or IMRT. [44].

Limitations of cost-effectiveness analyses are short-term follow-up of clinical and toxicity evidence, and lack of standard indications. Therefore, a subgroup of patients that will clinically benefit and gain most QALYs may be identified for an adequate distribution of limited access and availability of PBT facilities.

2.2.3 Human resources

As currently there are no functional PBT centers in LAC, adequate training for radiation oncologists, medical physicists, dosimetrists and radiation therapy technicians is imperative. Although this topic is popular in medical conferences and webinars, the lack of clinical experience is an issue. If a PBT center is considered for LAC, training in all levels of attention will be necessary and this represents an enormous challenge by itself since long term fellowships are required, at least for physicists and radiation oncologists. Periodic supervision from experienced personal or remote assistant and continuous medical education are two alternatives if intercountry fellowships are not feasible. [48].

2.2.4 Technical needs and limitations

PBT project management requires planning (construction design, permits, functional set-up), implementation (regulatory frame, technical expertise during construction) and operation (treatment planning time, patient logistics, nuclear safety, business plan, financial sustainability). Current PBT facilities require a space the size of a football field. This space is unavailable at or near the main hospitals and could be highly expensive in many capital cities. Therefore, future PBT units that are smaller (single-room PBT), more efficient and less expensive (even as low as $30 million dollars) are expected. [49].

The margins for protons are larger due to range uncertainties, which contribute to less conformality and larger higher dose volumes that include nearest OAR. Techniques to reduce clinical-to-planning target volume (CTV-to-PTV) margin include beam-specific PTV and in-vivo range verification; however, this approach is more expensive. [50, 51] Another limitation is image guidance and adaptive radiotherapy, since this modern technology is lacking in most PBT facilities. [2] Daily reproducibility, setup and anatomical changes are important determinants of dose distribution and thus in tumor control and complications. The treatment time per fraction with proton therapy is longer than for IMRT (22 versus 14 minutes). [52] The ideal PBT facility should have daily volumetric imaging for correct patient setup and identification of anatomical changes, adaptative replanning to compensate variations and setup with respiratory motion management. [53] It is expected that advances will give rise to more compact PBT facilities (1 or 2 treatment rooms) with volumetric image guidance and with a lower cost over time. [2].

2.2.5 Initial investment

PBT has been approved for cancer treatment by the FDA since 1988. Uniform federal government regulations with rigorous evaluation of useful and vital versus inefficient and unworthy technology are necessary since uncontrolled and unregulated healthcare spending on new technology without adequate determination of its effectiveness will eat up funds that could be spent efficiently. It should be considered that private insurers have declined to reimburse PBT for common cancer with no proven benefits compared to other modern techniques.

3. Conclusions

Currently there are virtually no PBT centers in LMIC, and none in LAC. Disparities on PBT distribution around the globe go further than just the obvious—lack of appropriate oncological treatments to alleviate human suffering—but are partially responsible for the slow development of PBT worldwide. At present, most patients amenable for PBT treatments are in LMIC countries, and clinical trials has been halted at least partially because of a lack of recruitment. There is a negative paradox, wherein patients in need of PBT have no access to it and PBT centers around the world with all dosimetric advantages represent less than 1% of all RT treatments. However, a PBT center in any LMIC is economically unviable and requires extensive sociodemographic studies. Mexico could be a strong candidate, not only due to its geographical advantages and total population, but because of its exceptionally young population for its economical capabilities, detailed published data on current needed access to radiotherapy and a modest but sufficient number of the required auxiliary diagnostic tools, such as PET, MRI and pathology services. Enormous efforts must be made by the private sector (national and international alike) and governmental authorities to provide funding and a comprehensive referral system for the PBT center. As stated previously, following the ALARA principle, PBT provides a clinical benefit to certain patients that is not achievable with photons.

Conflict of interest

The authors declare no conflict of interest.

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References

[1] Levitt SH, Leer JW. The role of radiotherapy in Swedenda landmark study by the Swedish Council on Technology Assessment in Health Care. Acta Oncol 1996;35:965-966

[2] Verma V., Shah C., Rwigen J-C. M., Solberg T., Zhu X., Simone II C.B. Cost-comparativeness of proton versus photon therapy. Chin Clin Oncol 2016;5(4):56-65

[3] UBA New Technologies Cancer Treatment Center [Internet]. 2020. Available from: https://www.iba-asiapacific.com/zh-hans/node/2511

[4] IAEA DIRAC Directory of RAdiotherapy Centres. Status of Radiation Therapy Equipment [Internet]. 2020. Available from: https://dirac.iaea.org/Query/Map2?mapId=2

[5] Latin America and the Caribbean Population [Internet]. 2020. Available from: https://www.worldometers.info/world-population/latin-america-and-the-caribbean-population/

[6] Gonzales, Selena, Cox, Cynthia. What are recent trends in cancer spending and outcomes? [Internet]. 2016. Available from: https://www.healthsystemtracker.org/chart-collection/recent-trends-cancer-spending-outcomes/#item-start

[7] Zubizarreta E., Van Dyk J., Lievens Y. Analysis of Global Radiotherapy Needs and Costs by Geographic Region and Income Level. Clin Oncol (R Coll Radiol) 2017;29(2):84-92. DOI: 10.1016/j.clon.2016.11.011

[8] Álvarez F., Brassiolo P., Toledo M., Allub L., Alves G., De la Mata D. [Internet]. 2020. RED 2020: Los sistemas de pensiones y salud en América Latina. Los desafíos del envejecimiento, el cambio tecnológico y la informalidad. Caracas: CAF. Available from http://scioteca.caf.com/handle/123456789/1652

[9] United Nations Industrial Development Organization [Internet]. 2015. Inclusive and Sustainable Industrial Development in Latin America and Caribbean Region. Available from: https://www.unido.org/sites/default/files/2015-07/UNIDO_in_LAC_Region_0.pdf

[10] Organisation for the Economic Co-operation and Development. OECD [Internet]. 2017. Active with Latin America and the Caribbean. Available from: http://www.oecd.org/latin-america/Active-with-Latin-America-and-the-Caribbean.pdf

[11] The World Bank Group [Internet]. 2020. World Development Indicators. Available from: https://databank.worldbank.org/reports.aspx?source=2&country=LCN

[12] The World Bank Group [Internet]. 2020. World Bank Country and Lending Groups. Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups

[13] Bishr, M. K., Zaghloul, M. S. (2018) Radiation Therapy Availability in Africa andLatin America: Two Models of Low and Middle-Income Countries. Int J Radiat Oncol Bio Phys;102(3):490-498

[14] The economic burden of cancer [Internet]. 2020. Available from: https://canceratlas.cancer.org/taking-action/economic-burden/

[15] Children in Latin America and the Caribbean. Overview 2019 [Internet]. 2019. Available from: https://www.unicef.org/lac/media/7131/file/PDF%20Children%20in%20Latin%20America%20and%20the%20

Caribbean%20-%20Overview%20 2019.pdf

[16] Howard SC, Metzger ML, Wilimas JA, et al. Childhood cancer epidemiology in low-income countries. Cancer 2008; 112: 461-72.

[17] Ward ZJ, Yeh JM, Bhakta N, Frazier AL, Girardi F, Atun R. Global childhood cancer survival estimates and priority-setting: a simulation-based analysis. Lancet Oncol 2019;20(7):972-983.

[18] Uhl M, Herfarth K, Debus J. Comparing the use of protons and carbon ions for treatment. Cancer J 2014;20:433-9.

[19] Jones B. (2017). Proton radiobiology and its clinical implications. ecancer 11;777

[20] Goossens M. E., Van den Bulcke M., Gevaert T., Meheus L., Verellen D., et al. (2019). Is there any benefit to particles over photon radiotherapy? ecancer; 13:982.

[21] INEGI. Datos epidemiológicos [Internet]. 2019. Available from: https://www.gob.mx/cms/uploads/attachment/file/520501/LSDM2019_OK_23DIC19.pdf

[22] Programa sectorial de salud [Internet]. 2014. Programa de acción específico. Cáncer en la infancia y la adolescencia 2013-2018. Available from http://www.censia.salud.gob.mx/contenidos/descargas/transparencia/especiales/PAE_Cancer.pdf

[23] World Health Organization [Internet]. 2020. Cancer today. International Atomy for Research on Cancer. Available from https://gco.iarc.fr/today/home

[24] Maldonado Magos F., Lozano Ruiz F. J., Pérez Álvarez S. I., Garay Villar O., Cárdenas Pérez C, et al. (2020). Radiation oncology in Mexico: Current status according to Mexico's Radiation Oncology Certification Board. Reports of Radiation Oncology & Radiotherapy;25(5):840-845

[25] Van Dyk J., Zubizarreta E., Lievens Y. (2017). Cost evaluation to optimise radiation therapy implementation in different income settings: A time-driven activity-based analysis. Radiother Oncol 125:178-185.

[26] Goiten M. Jermann M. (2003) The relative costs of proton and X-ray radiation therapy. Clinical Oncol 15:S37-S50

[27] Kerstiens J., Johnstone G. P., Johnstone P. A. (2018). Proton Facility Economics: Single-Room Centers. J Am Coll Radiol

[28] Dirección General de Finanzas [Internet]. 2019. Recursos destinados al Sector Salud en el Proyecto de Presupuesto de Egresos de la Federación 2020. Available from: http://bibliodigitalibd.senado.gob.mx/bitstream/handle/123456789/4685/1%20Publicación%20Sector%20Salud_2020.pdf?sequence=1&isAllowed=y

[29] Salama J. K., Willet C. G. (2014). Is proton beam theray better than standard radiation therapy? A paucity of practicality puts photons ahead of protons. Clinical Advances in Hematology & Oncology 12(2):861-868.

[30] Bekelman JE, Hahn SM. (2014). Reference pricing with evidence development: a way forward for proton therapy. J Clin Oncol;32:1540-1542.

[31] Zietman A. L. (2018). Too Big to Fail? The Current Status of Proton Therapy in the USA. Clinical Oncol 30:271-273.

[32] Pommier P., Lievens Y., Feschet F., Borras J. M., Baron M. H., et al. (2010) Simulating demand for innovative

radiotherapies: an illustrative model based on carbon ion and proton radiotherapy. Radiother Oncol 96(2):243-249.

[33] Buchsbaum J. C. (2015). Pediatric proton therapy in 2015: Indications, applications and considerations. Applied Radiation Oncology:4-11

[34] Verma V., Mishra M. V., Mehta M. P. (2016) A Systematic Review of the Cost and Cost-Effectiveness Studies of Proton Radiotherapy. Cancer;122(10):1483-501.

[35] Pediatric proton therapy in 2015: Indications, applications and considerations. Applied Radiation Oncology:4-11.

[36] Hirano E, Fuji H, Onoe T, Kumar V, Shirato H, Kawabuchi K. Cost-effectiveness analysis of cochlear dose reduction by proton beam therapy for medulloblastoma in childhood. J Radiat Res (Tokyo). 2014;55(2):320-327.

[37] Alves Fernandes R. R., de Mello Vianna C. M., Leborato Guerra R., de Camargo Cancela M., de Almeida L. M. (2019). Cost-Effectiveness of Proton Versus Photon Therapy in Pediatric Medulloblastoma Treatment: A Patient Volume-Based Analysis. Value in Health Regional;20:122-128.

[38] Lundkvist J, Ekman M, Ericsson SR, et al. Economic evaluation of proton radiation therapy in the treatment of breast cancer. Radiother Oncol 2005;75:179-85.

[39] Grutters JP, Pijls-Johannesma M, Ruysscher DD, et al. The cost-effectiveness of particle therapy in non-small cell lung cancer: exploring decision uncertainty and areas for future research. Cancer Treat Rev 2010;36:468-76.

[40] Lievens Y, Verhaeghe N, De Neve W, et al. Proton radiotherapy for locally-advanced non-small cell lung cancer, a cost-effective alternative to photon radiotherapy in Belgium? J Thorac Oncol 2013;8:S839-40.

[41] Ramaekers BL, Grutters JP, Pijls-Johannesma M, et al. Protons in head-and-neck cancer: bridging the gap of evidence. Int J Radiat Oncol Biol Phys 2013;85:1282-8.

[42] Li G., Qiu B., Huang Y-X, Doyen J., Bondiau P-Y, et al. Bekelman JE, Hahn SM. (2014). Reference pricing with evidence development: a way forward for proton therapy. J Clin Oncol;32:1540-1542.

[43] Yu JB, Soulos PR, Herrin J, et al. Proton versus intensity- modulated radiotherapy for prostate cancer: patterns of care and early toxicity. J Natl Cancer Inst 2013;105:25-32.

[44] AIM Specialty Health. (2018). Clinical Appropriateness Guidelines: Radiation Oncology. Proton Beam Therapy Guidelines.

[45] Combs SE. Does proton therapy have a future in CNS tumors? Curr Treat Options Neurol. 2017;19(3):12.

[46] DeLaney TF, Liebsch NJ, Pedlow FX, et al. Long-term results of Phase II study of high dose photon/proton radiotherapy in the management of spine chordomas, chondrosarcomas, and other sarcomas. J Surg Oncol. 2014;110(2):115-22.

[47] Wang Z, Nabhan M, Schild SE, et al. Charged particle radiation therapy for uveal melanoma: a systematic review and meta-analysis. Int J Radiat Oncol Biol Phys. 2013;86(1):18-26.

[48] Subgroup on Proton Therapy. (2018). EIB support to investments in proton therapy: Key issues and proposed action. Luxembourg.

[49] Klein AA, Bradley J. (2016). Single-room proton radiation therapy systems:

no small change. Int J Radiat Oncol Biol Phys;95:147-148.

[50] Park PC, Zhu XR, Lee AK, et al. A beam-specific planning target volume (PTV) design for proton therapy to account for setup and range uncertainties. Int J Radiat Oncol Biol Phys 2012;82:e329-36.

[51] Li Y, Niemela P, Liao L, et al. Selective robust optimization: A new intensity-modulated proton therapy optimization strategy. Med Phys 2015;42:4840-7.

[52] *Goiten M. Jermann M. (2003) The relative costs of proton and X-ray radiation therapy. Clinical Oncol 15:S37-S50.*

[53] Liu W, Liao Z, Schild SE, et al. Impact of respiratory motion on worst-case scenario optimized intensity modulated proton therapy for lung cancers. Pract Radiat Oncol 2015;5:e77-86.