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Proton therapy for pediatric malignancies: Fact, figures and costs. A joint consensus statement from the pediatric subcommittee of PTCOG, PROS and EPTN

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ABSTRACT

Radiotherapy plays an important role in the management of childhood cancer, with the primary aim of achieving the highest likelihood of cure with the lowest risk of radiation-induced morbidity. Proton therapy (PT) provides an undisputable advantage by reducing the radiation 'bath' dose delivered to non-target structures/volume while optimally covering the tumor with tumoricidal dose. This treatment modality comes, however, with an additional costs compared to conventional radiotherapy that could put substantial financial pressure to the health care systems with societal implications.

In this review we assess the data available to the oncology community of PT delivered to children with cancer, discuss on the urgency to develop high-quality data. Additionally, we look at the advantage of combining systemic agents with protons and look at the cost-effectiveness data published so far.

Over 300,000 new cancers are diagnosed annually in patients younger than 19 (156/10^6 person-years) worldwide [1]. The specific cancer diagnoses vary greatly by age, race, sex and country (Fig. 1); however, the most common are CNS tumors, Hodgkin lymphoma, and sarcomas (Fig. 2). Through strong cooperative group structures, overall survival (OS) rates have improved over the past 50 years and now long-term survivorship and quality of life (QOL) have become relevant.

Radiotherapy (RT) is effective for local control (LC), progression-free survival (PFS) and OS for most pediatric solid tumors; however, children are vulnerable to RT related late-effects affecting normal organ function, growth, development and the development of second malignant neoplasms (SMNs). Technological advances in imaging and RT delivery have resulted in better tumor delineation, smaller target volumes and more conformal RT but, surrounding normal tissues remain at risk due to non-target radiation dose. Proton therapy (PT), by elimination and reduction of exit and entry dose, reduces the low and intermediate dose volumes without compromising tumoricidal dose. Further advances such as pencil beam scanning (PBS) and intensity modulated proton therapy can allows usually better dose conformality, lower normal tissue dose and lower neutron dose contamination. Strategic use of PT is projected to reduce acute and late effect risks, thereby, allowing a better QOL for cancer survivors.

Though many dosimetric and modeling studies support the theoretical benefits of PT, actual clinical results are only now starting to emerge. Existing challenges include the small patient numbers, late-effect latency, inconsistent objective toxicity measures, low incidence of significant late effects, costs associated with long term follow-up studies or registries. Habrand et al. summarize the available literature and demonstrate the dearth of comparison studies that objectively evaluate the practical benefit of PT in comparison to alternative approaches Table 1 [2].

This paper summarizes the potential applications, research opportunities, challenges and benefits of PT in pediatric cancer management.

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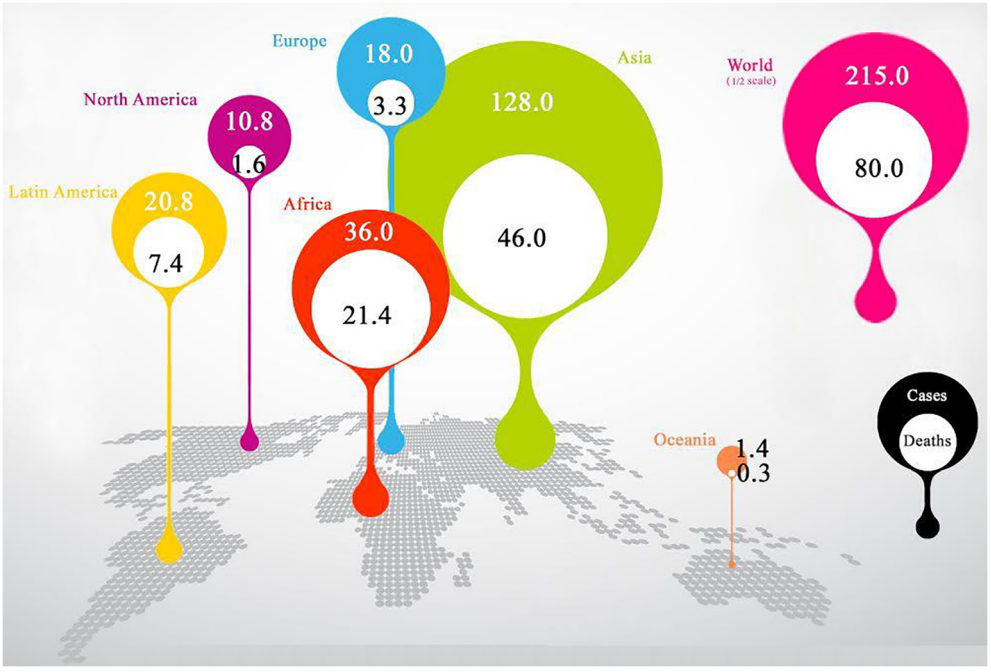

Fig. 1. Estimated numbers of cases and death in ages 0–14 years (2010s).

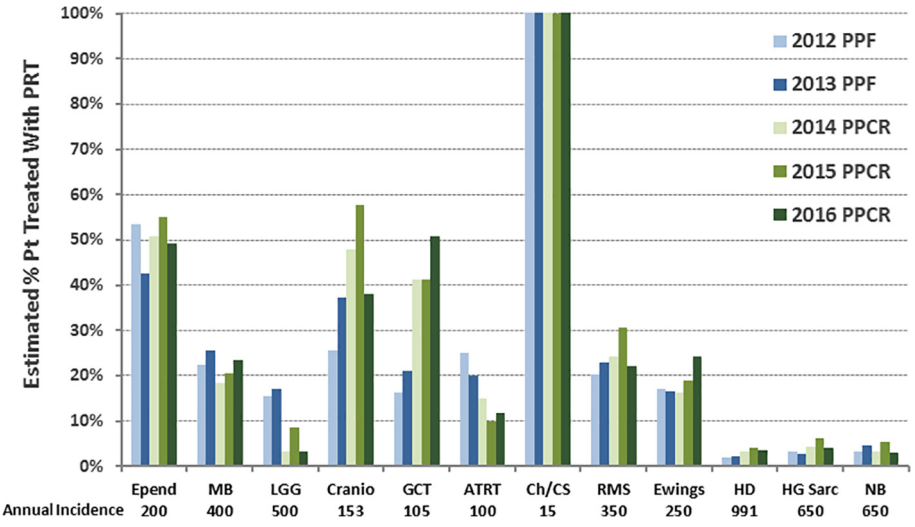

Fig. 2. Estimate of the proportion of total specific new pediatric cancer diagnosis treated at proton centers over five years in the US. 2012–2013 data from the Pediatric Proton Foundation (PPF) and 2014–2016 from the Pediatric Proton Consortium Registry (PPCR) assuming a 60% national participation.

Challenges in level I evidence generation

Despite many more publications examining outcomes and toxicities of PT in comparison to the number examining X-ray RT (XRT), the concern about efficacy and the extent clinical benefit by oncologists, bioethicists, and insurance companies are raised even for children since PT is usually associated with additional expense, treatment complexity and inconvenience. Phase III randomized trials comparing PT to XRT are on-going for adult lung, esophageal and prostate cancer, but the possibility of prospective trials for childhood malignancies remains challenging due to clinical equipoise and several other reasons listed below that cause challenges in clinical trial design and completion: First, which question should be addressed – disease related outcomes? Late effects from therapy? Dosimetrically, PT almost universally results in lower non-target tissue dose than XRT. The normal tissue dose difference may be enough to raise ethical concerns of patient randomization. Single and multi-institutional publications document the efficacy of PT, and though the majority of these do not provide level 1 evidence, none have raised concern that LC rates are lower with PT.

Second, is the long-term toxicity lowered by non-target tissue dose reduction? These question is premature because PT has been used consistently in children for the past decade – late effect risks may start manifesting now. It is likely that reports are forthcoming; however, the absence of robust XRT related late effects and QOL data limits historical comparisons. Third, perhaps the most important one, is that comparison of one radiation modality to another is meaningless without rigorous understanding of dosimetric parameters. The meaningful comparison is not XRT versus PT, but instead outcomes based on integral organ/patient doses with other dosimetric parameters. The future of research in pediatric radiation oncology will depend on this understanding, and on creative trial design that allows incorporation of various modalities with dose-related outcomes.

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