Proton therapy needs further technological development to fulfill the promise of becoming a superior treatment modality (compared to photon therapy)

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INTRODUCTION

There has been an ongoing debate over the superiority of proton beam therapy versus photon beam therapy for more than two decades.¹–³ Proton versus photon has been just like two ends of a seesaw, one gaining superiority over the other as technologies advances during these years. Even though we are all familiar with the distinct benefit of the proton “Bragg Peak” for reducing exit dose compared to photon beams, there has never been a definitive answer as to which modality is superior. Additionally, Level I evidence demonstrating measurable clinical advantage of proton therapy is lacking. Superiority can be defined in two different aspects, the technology aspect and the clinical aspect. Technological superiority may or may not lead to superior clinical outcomes. From a physicist’s point of view, it is safe to say that we would not see clinical outcome improvements if there is no clear advancement in the technology aspect. Yet in recent years, several major multicenter, prospective, randomized phase III trials comparing the two modalities have been initiated.⁴,⁵ One might wonder, with the recent technology development in intensity-modulated proton therapy based on pencil beam scanning, robustness optimization, etc., is proton therapy mature enough to enter such a level of clinical trials? In other words, do we have confidence that proton therapy is a superior treatment modality that should lead to positive improvement in clinical outcomes? Herein, Dr. Daniel Hyer argues for the proposition “Proton therapy needs further technological development to fulfill the promise of becoming a superior treatment modality (compared to photon therapy),” while Dr. Xuanfeng Ding arguing against it.

Dr. Daniel Hyer received his PhD in Medical Physics from the University of Florida in 2010 and was certified by the American Board of Radiology in 2013 after completing his residency at the University of Iowa. Dr. Hyer is currently an Associate Professor and the Director of Clinical Physics at the University of Iowa. His research interests include MRI-guided radiotherapy and proton beam therapy. On the latter topic, Dr. Hyer currently holds a National Cancer Institute grant as PI for the development of a proton collimator and has been actively engaged in proton therapy technological development for the past decade with two patents and over 30 peer-reviewed manuscripts. He has also served as President of the Missouri River Valley chapter of the AAPM.

Dr. Xuanfeng Ding received his PhD in Physics from Wake Forest University in 2012, and finished his residency training at the University of Pennsylvania in 2014. After commissioning the first pencil beam...
scanning (PBS) compact proton system in Willis-Knighton Cancer Center, Dr. Ding joined William Beaumont Hospital, Royal Oak, MI in 2015, as the lead proton physicist and Assistant Professor. Dr. Ding’s research interests include proton arc technique, adaptive therapy, and motion management. He has received several extramural research grants as the PI and was granted multiple patents. Dr. Ding published over 30 peer-reviewed papers and hundreds of conference abstracts. He is certified by the American Board of Radiology in Therapeutic Radiologic Physics. He also served as President of the Great Lakes Chapter AAPM and committee members of several AAPM Task Groups.

2 OPENING STATEMENT

2.1 Daniel E. Hyer, PhD

In its current form, proton therapy fulfills a niche role in radiation therapy. While it has been published that proton therapy could potentially provide benefits for approximately 15% of radiation therapy cases, a much smaller percentage of patients are actually treated with proton therapy each year. Despite decades of clinical and technical research, why has proton therapy not emerged as a clinically dominant modality for the cases that might benefit? To answer this question, it is critical to understand the clinical advantage that proton therapy provides over photon therapy. Fundamentally, the advantage of proton therapy rests in the fact that protons have a finite range, virtually eliminating exit dose and significantly reducing the “low-dose radiation bath” for a given treatment plan. This reduction in the low-dose radiation bath is associated with a potential reduction in secondary malignancy rates in young patients and was the initial driving force to migrate proton therapy from the laboratory and into the clinical environment over the last 20 years. During this same time, photon therapy has continued to evolve and has seen numerous technological developments (intensity-modulated radiotherapy [IMRT], volumetric modulated arc therapy [VMAT], image-guided radiotherapy [IGRT], adaptive radiotherapy [ART]) that have successfully improved the conformity of the high-dose radiation bath, and in some circumstances (ART and IGRT), allowed for the reduction in margins due to reduced setup uncertainties and the ability to account for daily anatomical variations. Entire treatment paradigms, such as stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT), are now reliant on high-dose conformity and small margins. While modern pencil beam scanning (PBS) proton therapy systems exhibit an improved conformity compared to initial double scattering systems, these systems still lag behind state of the art photon therapy systems in achievable conformity for SRS and in some SBRT cases when accounting for range uncertainties. These facts force clinicians using proton therapy to use larger margins and give up the ability to perform online adaptive therapy to capture the potential benefits of improved conformity of the low-dose radiation bath. In some cases, this tradeoff may be reasonable, especially in young patients with large clinical target volumes. However, I argue that if proton therapy is going to reach its full potential as a superior treatment modality, further technological developments are needed to eliminate such tradeoffs.

First and foremost, proton therapy needs better online imaging systems. This has been especially evident in recent years as photon therapy has blossomed with onboard fan-beam CT (FBCT) and MR imaging systems, while proton therapy has only recently been equipped with commercially available gantry mounted cone-beam CT (CBCT). The lack of integrated high-contrast and high-resolution imaging puts proton therapy at an inherent disadvantage with respect to planning target volume margins required to account for setup uncertainties. This is exacerbated by the fact that proton therapy is also more sensitive to patient misalignments and anatomical changes due to the finite particle range and associated steep distal dose fall-off. Investigators have proposed MR guidance for adaptive proton therapy to address this challenge, and it is reasonable to believe a technological development of this magnitude will be necessary to allow clinicians to minimize uncertainties associated with daily anatomical changes using a proton therapy approach.

As outlined in the introduction, improvements in the high-dose conformity are also necessary for some cases. Since protons are often used to treat sensitive areas in the brain or in pediatric patients, improving the high-dose conformity is critical to achieve favorable long-term outcomes. It has previously been shown that the lateral dose conformity in PBS proton therapy can be improved by reducing the beam size, but this is a difficult task to achieve, especially when treating superficial targets which requires the use of low-energy beams. One potential method to reduce the effective beam size is through the use of advanced collimation systems designed specifically for proton therapy. In preclinical studies, utilization of collimation systems have been shown to provide a substantial improvement in high-dose conformity when treating both brain and head and neck cancers. These dosimetric advantages are far superior to traditional aperture-based collimation approaches while still yielding robust treatment plans. Arc geometries have also recently been proposed as an alternative method to improve high-dose conformity of proton therapy. In addition to conformity improvements, by spreading out the treatment over an entire arc instead of just a few treatment angles, range uncertainty is distributed over a greater volume rather than just a few limited directions, thereby improving plan robustness.
The final development that warrants discussion is the accurate determination of relative biological effectiveness (RBE). Currently, the RBE for clinical proton therapy is assumed to be 1.1, regardless of beam energy or tissue type. However, based on the characteristics of the Bragg peak and the increased linear energy transfer at the end of the proton track, it is universally known that the true RBE is not a constant. In fact, protons have been shown to reach an RBE of up to 3 in the Bragg peak via in vitro studies. Unfortunately, RBE depends on complex physical and biological responses and is difficult to accurately calculate. Once these biological effects are better understood, treatment planning system developments that simultaneously optimize placement of particle linear energy transfer (LET) along with RBE dose hold the key to unlocking the full dosimetric advantages of proton therapy. In the meantime, our limited understanding of proton RBE limits our options from a proton treatment planning perspective. With current planning systems, it is difficult to ascertain where high-LET particles are expected in the patient, which in turn limits our ability to assess plan quality and response.

In summary, without technological advances in online imaging, collimation, arc delivery, and RBE-based treatment planning, proton therapy will fall short of achieving its full clinical potential.

2.2 Xuanfeng Ding, PhD

In this debate, I will explain why proton therapy has already fulfilled its promise as a superior treatment modality at its current technology level from a physicist’s point of view. First, proton therapy has demonstrated a substantial advantage over photon therapy by utilizing its unique characteristic, “Bragg Peak.” More specifically, the integral dose with proton is about 60% lower than the photon technique. While it appears most cost-effective for pediatric patients maximizing the clinical gain, it is also essential for adult patients for minimizing the dose to any healthy tissue. In fact, the motivation to further reduce dose to patient’s healthy organs has been a driving factor of technology innovations in the radiation oncology community including higher dose conformity, improved on-board volumetric imaging, motion management devices, etc. Thus, the capability of integral dose reduction itself is evidence of a superior treatment modality. Such advantage offers a safe and effective curative reirradiation strategy for varieties of disease sites including recurrence of head–neck cancer, chordoma, non-small cell lung cancer (NSCLC), and breast cancer.

Additionally, the IMPT, based on the PBS technique, has further improved the normal tissue dose sparing both in the distal end and the proximal end of the target volume. In the last decade, the vast majority of the new proton institutions worldwide have adopted IMPT in routine clinical practice. Numerous peer-reviewed publications have shown its significant dosimetric advantages over a wide range of clinical indications compared to photon therapy, not only in the integral dose reduction but also in the improvement of medium- and high-dose conformity. More interestingly, the results from ProKnow (Elekta, Stockholm, Sweden) planning competitions showed IMPT plans dominated the top plan quality scores in the recent challenging cases such as GYN (2018), Liver SBRT (2020), and advanced-stage lung cancer (2021). Though these planning exercises depend on the planners’ skills, availability, and experience, it provides strong support to the IMPT’s superiority over photon technique.

Furthermore, such dosimetric advantage increases the tolerance of chemotherapeutic agents by reducing toxicity and permitting higher drug doses than photon therapy. A phase II study of concurrent chemotherapy for unresectable stage III NSCLC showed promising clinical outcomes and rate of toxic effect compared with historical photon therapy data. When studying the structural and hemodynamic changes of contralateral healthy brain tissue following proton and photon radiochemotherapy, Petr et al. reported a reduced brain-volume loss in the proton therapy group. A more recent analysis of 1483 adult patients with nonmetastatic, locally advanced cancer treated with concurrent chemoradiotherapy showed that proton chemoradiotherapy was associated with significantly less acute adverse events, for example, 90-day unplanned hospitalizations. These emerging clinical evidence filled the immediate needs of toxicity and side-effect mitigation utilizing concurrent chemo-RT that photon therapy cannot offer.

Dose-escalation strategies are generally considered to offer better local tumor control. However, it was sometimes associated with more side-effects in some challenging disease sites due to the dosimetric limitation of photon therapy in which more radiation dose spills into the healthy tissue. For example, a phase III study in prostate cancer treatment showed increased acute bowel and bladder reaction as well as late rectal side-effects. RTOG 0126, a randomized clinical trial for intermediate-risk prostate cancer (1532 patients), concluded that photon therapy dose escalation did not improve overall survival, and high dose resulted in more late toxic effects. The result from a randomized clinical trial for inoperable stage III NSCLC, RTOG 0617, concluded that the photon dose escalation provides no benefit in overall survival, and it might be potentially harmful. Therefore, more effective and safe treatment techniques are urgently needed for these cancer patients. In contrast to the photon randomized clinical trial results, Gomez et al. summarized the proton clinical experience from multiple institutions. They found that hypofractionated dose-escalated proton therapy for NSCLC is feasible, and the evidence is more
3 | REBUTTAL

3.1 | Daniel E. Hyer, PhD

I will start my rebuttal by stating that I agree with Dr. Ding—the future of proton therapy is exceptionally bright and there are many promising avenues of research that could substantially increase the relevance of this modality. However, in its current state, it is hard to argue against the need for further technological development of proton therapy. The main evidence that Dr. Ding uses to demonstrate the current superiority of proton therapy includes integral dose reduction, treatment planning studies/competitions, and a variety of dose-escalation clinical trials, none of which represent a high level of evidence.

The issue with treatment planning studies is that they assume a single anatomical image and reference anatomy, usually concluding that a specific dosimetric criterion is superior in one case over another. Such theoretical studies may be reasonable when comparing intramodality (i.e., photons versus protons), but are largely inadequate to provide direct intermodality comparisons in practice. For example, we know that proton therapy is much more sensitive than photon therapy to pathlength differences and range uncertainties. A fair comparison between photons and protons must consider the robustness of the plans to daily anatomical variations and intrafraction motion, an area where photon-based modalities hold a key advantage due to the lack of a finite range. Ultimately, adaptive proton therapy is an example of a technological advancement required to overcome this challenge. Such a development would ensure that the radiation dose is placed appropriately with respect to daily anatomy.

With regards to dose escalation, the comparisons given by Dr. Ding reach across multiple disease sites, stages, and modalities. It is difficult to conclude a direct correlation between protons and photons from these studies. However, if these studies are indeed applicable in this type of comparison, they demonstrate that at a minimum we need more knowledge regarding the biological effects of proton therapy. Without such knowledge, we may see unintended consequences, such as brainstem toxicities, that have been observed in pediatric patients receiving PBS proton therapy. Further development surrounding the biological effects of proton therapy would not only help us avoid such negative side-effects, but also begin to reveal why proton therapy may be beneficial in some cases and the scenarios where its application pays the greatest dividends. Currently, our best guess is that a reduction in integral dose is responsible for the improvements in outcomes for some cases, but I believe integral dose only tells part of the story.

Lastly, Dr. Ding states that integral dose with proton therapy is less than that of contemporary photon techniques. I agree with this statement, but at the same time must conclude that a reduction in integral dose alone is not enough to unequivocally demonstrate proton therapy as a superior modality for most cases. There are certainly promising studies that make a compelling case that the reduction in the low-dose radiation bath could meaningfully improve secondary malignancy rates in very young patients, xerostomia in head and neck cancer patients, and cardiac injury from lung cancer treatment. I argue that these investigations demonstrate the importance and ongoing need to technically develop and clinically study the promising field of proton therapy as a community. They exemplify the potential of proton therapy, but more work is needed for proton therapy to fulfill its promise of becoming a superior treatment modality.

3.2 | Xuanfeng Ding, PhD

Dr. Hyer has raised an excellent question: “Why has proton therapy not emerged as a clinically dominant modality for the cases that might benefit?” In my opinion, it is not because of the limitations in the dosimetric plan quality or technology. Instead, the investment cost and accessibility to our communities are the two major factors limiting our patients’ chance to choose such a superior treatment modality. The initial investment of a proton therapy center could cost from $20 million to $200 million on top of the high operation and...
maintenance cost. As a result, there are only about 90 particle therapy centers worldwide, where 40 of them are located in the US compared to approximately 1500 cancer centers nationally. Every patient deserves a better treatment option. Unfortunately, even with 24-h shifts in all these PTCs, there is no way to meet such clinical demands. Sometimes it requires a justification of cost-effectiveness utilizing such a precious medical resource. Though the scale of financial benefit to the patient population, the healthcare system, and society may vary among different countries and policies, one thing was found in common that there are potential benefits in terms of cost and quality-adjusted life-years for many disease sites. Excluding the economic factors, the normal tissue complication probability model-based patient selection system for head and neck cancer was implemented in the Netherlands as a National Indication Protocol. Such a protocol served as an excellent starting point and an example of serving more cancer patients in need of advanced treatment modalities worldwide. We will see more countries and investigations to join such direction for varieties of clinical indications.

This debate is not on "clinically dominant modality" but on the technological superiority comparison. The imaging system has been a critical part of radiation therapy. I agree with Dr. Hyer that integrating new imaging techniques in a proton system is relatively slower than photon radiotherapy due to the cost and engineering challenges. FBCT is always nice to have. Today, CT on-rail has been clinically implemented in some proton institutions, which provides valuable information for adaptive therapy. The current CBCT on proton gantry is also sufficient for adaptive planning decisions utilizing the artificial intelligence-based synthetic CBCT approach. Such a platform allows a direct proton dose calculation on the daily CBCT which has been clinically implemented in some institutions to assist the adaptive planning decision including Beaumont proton therapy center. MR-guided proton system is an exciting topic that is now under active research and development and is expected to be clinically available in 5–10 years. This technique will provide additional benefits to proton therapy.

RBE uncertainty is indeed one of the major challenges. However, the emerging evidence showed that LET is correlated to the clinical endpoint, for example, rectal bleeding and MRI changes in the normal brain tissue. With the current IMPT technique, we could optimize such a physical parameter accurately and directly during the planning without worrying too much about the RBE uncertainties.

In summary, current technologies and tools in proton therapy have sufficiently addressed the outstanding issues such as adaptive proton therapy based on CBCT and CT on-rail, robust optimization/evaluation, and LET optimization/evaluation. The clinical evidence is growing in favor of proton beam therapy translated from its dosimetric advantage and less integral dose. Admittedly, there are still opportunities to further develop the proton therapy technique by sharpening the dose fall-off and integrating MR-guided system, but these incremental improvements will not affect the overall picture of its superiority in the dosimetric advantage and clinical benefits as of today.

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AUTHOR CONTRIBUTION
DH and XD contributed in drafting the manuscript, YR contributed in moderating and modifying the paper.

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REFERENCES
1. Chuong MD, Mehta MP, Langen K, Regine WF. Is proton beam therapy better than standard radiation therapy? The available evidence points to benefits of proton beam therapy. Clin Adv Hemato Oncol. 2014;12(12):861-864.
2. Allen AM, Pawlicki T, Dong L, et al. An evidence based review of proton beam therapy: the report of ASTRO's emerging technology committee. Radiother Oncol. 2012;103(1):8-11.
3. Koto M. Is charged particle therapy superior to photon therapy? Lancet Oncol. 2014;15(9):918-919.
4. NCI N.C.I., Image-Guided, Intensity-Modulated Photon or Proton Beam Radiation Therapy in Treating Patients With Stage II-IIIB Non-small Cell Lung Cancer. https://clinicaltrials.gov/ct2/show/NCT01629498; Accessed on 10/01/2021.
5. Oncology, N.C.I.N.N Comparing Photon Therapy To Proton Therapy To Treat Patients With Lung Cancer. https://clinicaltrials.gov/ct2/show/NCT01993810; Accessed on 10/01/2021.
6. Baron MH, Pommier P, Favrel V, Truc G, Balosso J, Rochat J. A "One-day survey": as a reliable estimation of the potential recruitment for proton- and carbon-ion therapy in France. Radiother Oncol. 2004;73:215-S17.
7. Glimelius B, Ask A, Bjelkengren G, et al. Number of patients potentially eligible for proton therapy. Acta Oncol (Madr). 2005;44(8):836-849.
8. Mayer R, Mock U, Jäger R, et al. Epidemiological aspects of hadron therapy: a prospective nationwide study of the Austrian project MedAustron and the Austrian Society of Radiooncology (OEGRO). Radiother Oncol. 2004;73:S24-S28.
9. Orecchia R, Krengli M. Number of potential patients to be treated with proton therapy in Italy. *Tumori*. 1998;84(2):205-208.

10. Zhang R, Howell RM, Giebeler A, et al. Comparison of risk of radiogenic second cancer following photon and proton craniospinal irradiation for a pediatric medulloblastoma patient. *Phys Med Biol*. 2013;58(4):807-823.

11. Goddard LC, Brodin NP, Bodner WR, Garg MK, Tomé WA. Comparing photon and proton-based hyperfractionated SBRT for prostate cancer accounting for robustness and realistic treatment deliverability. *Br J Radiol*. 2018;91(1085):20180010.

12. Wang D, Dirksen B, Hyer DE, et al. Impact of spot size on plan quality of spot scanning proton radiosurgery for peripheral brain lesions. *Med Phys*. 2014;41(12):121705.

13. Hoffmann A, Oborn B, Moteabbed M, et al. MR-guided proton therapy: a review and a preview. *Radiat Oncol*. 2020;15(1):129.

14. Oborn BM, Dowell S, Metcalfe PE, Crozier S, Mohan R, Keall PJ. Future of medical physics: real-time MRI-guided proton therapy. *Med Phys*. 2017;44(8):e77-e890.

15. Nenoff L, Matter M, Hedlund Lindmar J, Weber DC, Lomax AJ. Chemotherapy during spot scanning proton therapy in Italy. *Tu m o r i* *Med Phys*. 2018;84(2):205-208.

16. van de Water TA, Lomax AJ, Bijl HP, Schilstra C, Hug EB, Lagendijk JJ. Using a reduced spot size for intensity-modulated proton therapy potentially improves salivary gland-sparing in oropharyngeal cancer. *Int J Radiat Oncol Biol Phys*. 2012;82(2):e313-e319.

17. Bues M, Newhauser WD, Titt U, Smith AR. Therapeutic step and shoot proton beam spot-scanning with a multi-leaf collimator: a Monte Carlo study. *Radiat Prot Dosimetry*. 2005;115(1-4):164-169.

18. Daart J, Bangert M, Bussière MR, Engelsman M, Kooy HM. Characterization of a mini-multileaf collimator in a proton beamline. *Med Phys*. 2009;36(5):1866-1894.

19. Winterhalter C, Lomax A, Oxley D, Weber DC, Safai S. A study of lateral fall-off (penumbra) optimisation for pencil beam scanning (PBS) proton therapy. *Phys Med Biol*. 2018;63(2):025022.

20. Geoghegan TJ, Nelson NP, Flynn RT, Hill PM, Rana S, Hyer DE. Design of a focused collimator for proton therapy spot scanning using Monte Carlo methods. *Med Phys*. 2020;47(7):2725-2734.

21. Hyer DE, Hill PM, Wang D, Smith BR, Flynn RT. A dynamic collimation system for penumbra reduction in spot-scanning proton therapy: proof of concept. *Med Phys*. 2014;41(9):091701.

22. Moignier A, Gelover E, Smith BR, et al. Toward improved target conformity for two spot scanning proton therapy delivery systems using dynamic collimation. *Med Phys*. 2016;43(3):1421-1427.

23. Moignier A, Gelover E, Wang D, et al. Theoretical benefits of dynamic collimation in pencil beam scanning proton therapy for brain tumors: dosimetric and radiobiological metrics. *Int J Radiat Oncol Biol Phys*. 2016;95(1):171-180.

24. Moignier A, Gelover E, Wang D, et al. Improving head and neck cancer treatments using dynamic collimation in spot scanning proton therapy. *Int J Part Ther*. 2016;4(2):544-554.

25. Smith B, Gelover E, Moignier A, et al. Technical note: a treatment plan comparison between dynamic collimation and a fixed aperture during spot scanning proton therapy for brain treatment. *Med Phys*. 2016;43(8):4693-4699.

26. Smith BR, Hyer DE, Flynn RT, Culberson WS. Technical note: optimization of spot and trimmer position during dynamically collimated proton therapy. *Med Phys*. 2019;46(4):1922-1930.

27. Wang D, Smith BR, Gelover E, Flynn RT, Hyer DE. A method to select aperture margin in collimated spot scanning proton therapy. *Phys Med Biol*. 2015;60(7):N109-N119.

28. Smith BR, Hyer DE, Culberson WS. An investigation into the robustness of dynamically collimated proton therapy treatments. *Med Phys*. 2020;47(8):3545-3553.

29. Ding X, Li X, Zhang JM, Kabilozadeh P, Stevens C, Yan D. Spot-scanning proton arc (SPArc) therapy: the first robust and delivery-efficient spot-scanning proton arc therapy. *Int J Radiat Oncol Biol Phys*. 2016;96(5):1107-1116.

30. Toussaint L, Indelicato DJ, Holgersen KS, et al. Towards proton arc therapy: physical and biologically equivalent doses with increasing number of beams in pediatric brain irradiation. *Acta Oncol (Madr)*. 2019;58(10):1451-1456.

31. Seco J, Gu G, Marcelos T, Kooy H, Willers H. Proton arc reduces range uncertainty effects and improves conformity compared with proton volumetric modulated arc therapy in stereotactic body radiation therapy for non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2013;87(1):188-194.

32. Chaudhary P, Marshall TI, Perrozziello FM, et al. Relative biological effectiveness variation along monoenergetic and modulated bragg peaks of a 62-MeV therapeutic proton beam: a preclinical assessment. *Int J Radiat Oncol Biol Phys*. 2014;90(1):27-35.

33. Sorensen BS, Overgaard J, Bassler N. In vitro RBE-LET dependence for multiple particle types. *Acta Oncol (Madr)*. 2011;50(6):757-U268.

34. Lühr A, von Neubeck C, Krause M, Troost EGC. Relative biological effectiveness in proton beam therapy—current knowledge and future challenges. *Clin Transl Radiat Oncol*. 2019;35:41.

35. DeLaney TF. Proton therapy in the clinic. *Front Radiat Ther Oncol*. 2011:43:465-485.

36. Suit H, Kooy H, Trofimov A, et al. Should positive phase III clinical trial data be required before proton beam therapy is more widely adopted? No. *Radiother Oncol*. 2008;86(2):148-153.

37. Jaffray DA, Siewerdsen JH, Wong JW, Martinez AF. Flat-panel cone-beam computed tomography for image-guided radiation therapy. *Int J Radiat Oncol Biol Phys*. 2002;53(5):1337-1349.

38. Raaymakers BW, Raaijmakers AJ, Kotte AN, Jette D, Lagendijk JJ. Integrating a MRI scanner with a 6 MV radiotherapy accelerator: dose deposition in a transverse magnetic field. *Phys Med Biol*. 2004;49(17):4109-4118.

39. Stein J, Bortfeld T, Dörschel B, Schlegel W. Dynamic X-ray compensation for conformal radiotherapy by means of multi-leaf collimation. *Radiother Oncol*. 1994;32(2):163-173.

40. Wong JW, Sharpe MB, Jaffray DA, et al. The use of active breathing control (ABC) to reduce margin for breathing motion. *Int J Radiat Oncol Biol Phys*. 1999;44(4):911-919.

41. Chao HH, Berman AT. Multi-institutional prospective study of reirradiation with proton beam radiotherapy for locoregionally recurrent non-small cell lung cancer. *J Thorac Oncol*. 2017;12(2):281-292.

42. Gabani P, Patel H, Thomas MA, et al. Clinical outcomes and toxicity of proton beam radiation therapy for re-irradiation of locally recurrent breast cancer. *Clin Transl Radiat Oncol*. 2019;19:116-122.

43. McDonald MV, Linton OR, Shah MV. Proton therapy for reirradiation of progressive or recurrent chordoma. *Int J Radiat Oncol Biol Phys*. 2013;87(5):1107-1114.

44. Phan J, Sot TP, Nguyen TP, et al. Reirradiation of head and neck cancers with proton therapy: outcomes and analyses. *Int J Radiat Oncol Biol Phys*. 2016;96(1):30-41.

45. Lomax A. Intensity modulation methods for proton radiotherapy. *Phys Med Biol*. 1999;44(1):185-205.

46. Paganelli H, Beltran CJ, Both S, et al. Roadmap: proton therapy physics and biology. *Phys Med Biol*. 2021;66(5).

47. In ‘t Ven L, Roelofs E, Cabillos Mesías M, et al. The ROOCOCO performance scoring system translates dosimetric differences into clinically relevant endpoints: comparing IMPT to VMAT in an example pitoclyn Astrocytoma dataset. *Clin Transl Radiat Oncol*. 2021;28:32-38.

48. Baues C, Marnitz S, Engert A, et al. Proton versus photon deep inspiration breath hold technique in patients with Hodgkin lymphoma and mediastinal radiation: a planning comparison of deep...
inspiration breath hold intensity modulation radiotherapy and intensity modulated proton therapy. Radiat Oncol. 2018;13:122.

49. Cao H, Xiao Z, Zhang Y, et al. Dosimetric comparisons of different hypofractionated stereotactic radiotherapy techniques in treating intracranial tumors >3 cm in longest diameter. J Neurosurg. 2020;132(4):1024-1032.

50. Cozzi L, Comito T, Fogliata A, Franzese C, Tomatis S, Scorsetti M. Critical appraisal of the potential role of intensity modulated proton therapy in the hypofractionated treatment of advanced hepatocellular carcinoma. PLoS One. 2018;13(8):e0201992.

51. Lewis GD, Holliday EB, Kocak-Uzel E, et al. Intensity-modulated proton therapy for nasopharyngeal carcinoma: decreased radiation dose to normal structures and encouraging clinical outcomes. Head Neck-J Sci Specialist Head Neck. 2016;38(1886):E1895.

52. Loap P, Mirandola A, De Marzi L, et al. Cardiac substructure exposure in breast radiotherapy: a comparison between intensity modulated proton therapy and volumetric modulated arc therapy. Acta Oncol (Madr). 2021;60(8):1038-1044.

53. Manritz S, et al. Which technique for radiation is most beneficial for patients with locally advanced cervical cancer? Intensity modulated proton therapy versus intensity modulated photon treatment, helical tomotherapy and volumetric arc therapy for primary radiation - an intrapatient comparison. Radiat Oncol. 2015;1091.

54. Meijer TWH, Scandurra D, Langendijk JA. Reduced radiation-induced toxicity by using proton therapy for the treatment of oropharyngeal cancer. Br J Radiol. 2020;93(i1107).

55. Mondlane G, Gubanski M, Lind PA, Ureba A, Siegbahn A. Comparative study of the calculated risk of radiation-induced cancer after photon- and proton-beam based radiosurgery of liver metastases. Physica Med-Eur J Med Phys. 2017;42:263-270.

56. Elekta ProKnow ProKnow: Radiation Oncology Plan Studies, Contouring and Analytics. https://proknowsystems.com; Accessed on 10/01/2021.

57. Chang JY, Verma V, Li M. Proton Beam radiotherapy and concurrent chemotherapy for unresectable stage III non-small cell lung cancer: final results of a phase 2 study (vol 3, e172032, 2017). JAMA Oncol. 2017;3(12):1742-1742.

58. Petr J, Platel I, Hofheinz F, et al. Photon vs. proton radiochemotherapy: effects on brain tissue volume and perfusion. Radiother Oncol. 2018;128(1):121-127.

59. Baumann BC, Mitra N, Harton JG, et al. Comparative effectiveness of proton vs photon therapy as part of concurrent chemoradiotherapy for locally advanced cancer. JAMA Oncol. 2020;6(2):237-246.

60. Dearnaley DP, Hall E, Lawrence D, et al. Phase III pilot study of dose escalation using conformal radiotherapy in prostate cancer: pSA control and side effects. Br J Cancer. 2005;92(3):488-498.

61. Michalski JM, Moughan J, Purdy J, et al. Effect of standard vs dose-escalated radiation therapy for patients with intermediate-risk prostate cancer: The NRG Oncology RTOG 0126 Randomized Clinical Trial. JAMA Oncol. 2018;4(6):e180039.

62. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol. 2015;16(2):187-199.

63. Gomez DR, Chang JY. Accelerated dose escalation with proton beam therapy for non-small cell lung cancer. J Thorac Dis. 2014;6(4):348-355.

64. Chan AW, Bernstein KD, Adams JA, Parambi RJ, Loeffler JS. Dose escalation with proton radiation therapy for high-grade meningiomas. Technol Cancer Res Treat. 2012;11(6):607-614.

65. Paganetti H, Yu CX, Orton CG. Photon radiotherapy has reached its limit in terms of catching up dosimetrically with proton therapy. Med Phys. 2016;43(8):4470-4472.

66. Vogel J, Grewal A, O’Reilly S, et al. Risk of brainstem necrosis in pediatric patients with central nervous system malignancies after pencil beam scanning proton therapy. Acta Oncol (Madr). 2019;58(12):1752-1756.

67. Banfill K, Giuliani M, Azzani G, et al. Cardiac toxicity of thoracic radiotherapy: existing evidence and future directions. J Thorac Oncol. 2021;16(2):216-227.

68. HemOnc Today Proton beam therapy holds ‘great promise’ at a steep cost. https://www.healio.com/news/hematology-oncology/20120827/proton-beam-therapy-holds-great-promise-at-a-steep-cost; Accessed on 10/01/2021.

69. Wikipedia NCI-designated Cancer Center, 2021. https://en.wikipedia.org/wiki/NCI-designated_Cancer_Center; Accessed on 10/01/2021.

70. PTOOG Particle Therapy Co-operative Group. www.ptcog.ch; Accessed on 10/01/2021.

71. Smith WL, Smith CD, Patel S, et al. What conditions make proton beam therapy financially viable in western Canada? Cureus. 2018;11(11):e3644.

72. Verma V, Shah C, Rwigema JC, Solberg T, Zhu X. Cost-comparativeness of proton versus photon therapy. Chin Clin Oncol. 2016;5(4):56.

73. Brodin NP, Kabarriti R, Schechter CB, et al. Individualized quality of life benefit and cost-effectiveness estimates of proton therapy for patients with oropharyngeal cancer. Radiat Oncol. 2021;16(1):19.

74. Konski A, Speier W, Hanlon A, Beck JR, Pollack A. Is proton beam therapy cost effective in the treatment of adenocarcinoma of the prostate? J Clin Oncol. 2007;25(24):3603-3608.

75. Lundkvist J, Ekman M, Ericsson SR, Isacsson U, Jönsson B, Glimelius B. Economic evaluation of proton radiation therapy in the treatment of breast cancer. Radiother Oncol. 2005;75(2):179-185.

76. Lundkvist J, Ekman M, Ericsson SR, Jönsson B, Glimelius B. Proton therapy of cancer: potential clinical advantages and cost-effectiveness. Acta Oncol (Madr). 2005;44(8):850-861.

77. Lundkvist J, Ekman M, Ericsson SR, Jönsson B, Glimelius B. Cost-effectiveness of proton radiation in the treatment of childhood medulloblastoma. Cancer. 2005;103(4):793-801.

78. Langendijk JA, Hoebers FJP, de Jong MA, et al. National protocol for model-based selection for proton therapy in head and neck cancer. Int J Particle Therap. 2021;8(1):354-365.

79. Teoh S, Fiorini F, George B, Vallis KA, Van den Heuvel F. Proton vs photon: a model-based approach to patient selection for reduction of cardiac toxicity in locally advanced lung cancer. Radiat Oncol. 2020;152:151-162.

80. Tommasino F, Durante M, D’Avino V, et al. Model-based approach for quantitative estimates of skin, heart, and lung toxicity risk for left-side photon and proton irradiation after breast-conserving surgery. Acta Oncol (Madr). 2017;56(8):730-736.

81. Freeman T. Mobile CT scanner lines up for adaptive proton therapy. Physics World, 2018.

82. Thummerer A, Zaffino P, Meijers A, et al. Comparison of CBCT based synthetic CT methods suitable for proton dose calculations in adaptive proton therapy. Phys Med Biol. 2020;65(9):095002.

83. Qin A, Chen S, Liu G, et al. The feasibility and accuracy of utilizing CBCT and generative-adversarial-network (GAN) to perform proton treatment dose evaluation for lung and head and neck patients. Int J Radiat Oncol Biol Phys. 2020;108(3):S41-S42.

84. Yang Y, Vargas CE, Bhangoo RS, et al. Exploratory investigation of dose-linear energy transfer (LET) volume histogram (DLVH) for adverse events study in intensity modulated proton therapy (IMPT). Int J Radiat Oncol Biol Phys. 2021;110(4):1189-1199.
85. Bertolet A, Abolfath R, Carlson DJ, et al. Correlation of LET with MRI changes in brain and potential implications for normal tissue complication probability for meningioma patients treated with pencil beam scanning proton therapy. *Int J Radiat Oncol Biol Phys*. 2021.

86. Fager M, Toma-Dasu I, Kirk M, et al. Linear energy transfer painting with proton therapy: a means of reducing radiation doses with equivalent clinical effectiveness. *Int J Radiat Oncol Biol Phys*. 2015;91(5):1057-1064.

87. Liu W, Zhang X, Li Y, Mohan R. Robust optimization of intensity modulated proton therapy. *Med Phys*. 2012;39(2):1079-1091.

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