



Protons, Photons, and the Prostate – Is There Emerging Evidence in the Ongoing Discussion on Particle Therapy for the Treatment of Prostate Cancer?

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Proton therapy is actively and repeatedly discussed within the framework of particle therapy for the treatment of prostate cancer (PC). The argument in favor of treating the prostate with protons is partly financial: given that small volumes are treated, treatment times are low, resulting in a hypothetical high patient throughput. However, such considerations should not form the basis of medical decision-making. There are also physical and biological arguments which further support the use of particle therapy for PC. The only relevant randomized data currently available is the study by Zietman and colleagues, comparing a high to a low proton boost, resulting in a significant increase in PSA-free survival in the experimental (high dose) arm (1). With modern photon treatments and image-guided radiotherapy (IGRT), equally high doses can be applied with photons and, thus, a randomized trial comparing high-end photons to protons is warranted. For high-linear energy transfer (LET) particles, such as carbon ions, the increase in relative biological effectiveness could potentially convert into an improvement in outcome. Additionally, through the physical differences of protons and carbon ions, the steeper dose gradient with carbon ions and the lack of beam broadening in the carbon beam lead to a superior dose distribution supporting the idea of hypofractionation. Biological and clinical data are emerging, however, has practice-changing evidence already arrived?

Keywords: protons, prostate cancer, carbon ions, clinical trials, IMRT

INTRODUCTION

Proton beam therapy (PBT) among particle therapy for prostate cancer (PC) remains a highly topical subject in the uro-oncological community. It is fueled by discussions concerning questionable superiority to photon treatment with regard to survival or local control, higher costs and cost-effectiveness, better tolerance for patients due to fewer side effects, and, last but not least, continuous patient inquiries regarding the therapy (2). This is represented by numerous ongoing trials and publications; the search for “proton therapy AND PC” on clinicaltrials.gov generates 36

hits alone (3). As biological and clinical data are emerging, the question remains: has practice-changing evidence already been uncovered?

PHOTONS

The goal in radiotherapy (RT) of localized PC is a lethal dose to tumor cells, while ensuring that the smallest possible dose is applied to surrounding tissues, such as rectum and bladder, and thereby avoiding side effects and toxicities for patients.

Nowadays photons are the most commonly used treatment in RT for PC. Photons have no mass and no charge and, therefore, travel easily through target materials. There is an initial increase of energy as they interact with the target material electrons (e.g., the body), which enhances the radiation effect. As a result of this, their peak dose is reached within a few centimeters from the entrance surface – the so-called “dose accumulation effect.” In the deeper trajectory through the body subsequently, the radiation dose decreases until it exits the body. 3D plans initially had a significant dose deposition in the entry and exit fields. With multiple field plans, rapid arc or helical techniques, these doses tend to be significantly smaller, but often a dose bath with low-to-moderate doses over surrounding organs cannot be avoided in order to deliver a deathly dose to cancer cells (4). The possible side effects include gastrointestinal (GI) and genitourinary (GU) problems and a potentially slightly higher risk for secondary malignancies (5). Therefore, photon radiation therapy does not seem appropriate in terms of its physical characteristics to treat those organs located at a great depth within the body. Despite modern improvements in technologies, such as multi-leaf collimators, intensity-modulated radiotherapy (IMRT), or image-guided radiotherapy (IGRT), photon-beam therapy will always include a certain level of entrance and exit doses, resulting in healthy tissue receiving low-to-moderate radiation doses. While these doses are most likely not associated with a prominent side effect risk, such issues necessitate a serious consideration of alternative treatment options, including particle therapy.

PARTICLE THERAPY

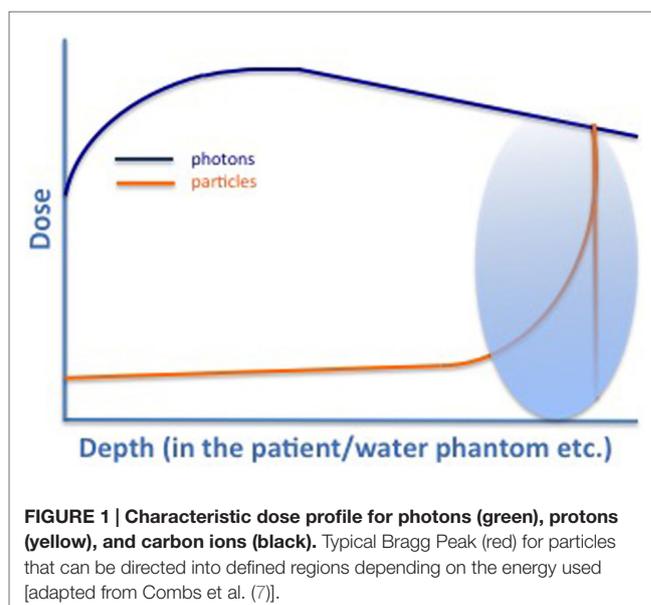
As of 2013, more than 123,000 patients had received therapy with heavy particles worldwide, PBT accounting for the majority of this, with over 106,000 patients treated (6). While protons can be termed particles, they are not considered “heavy,” and from their effect they can be categorized as low-linear energy transfer (LET) radiation, comparable to photons. Heavy particles include carbon ions, oxygen as well as neutrons, and others. Particles may be charged (protons, carbon ions) or neutral (neutrons). The term “heavy particle therapy” is generally used to distinguish it from conventional X-Ray RT, which uses massless photons. As most research undertaken so far has investigated protons, we shall mainly focus on them in the following article. Experience with other heavy particles is limited to a mere seven operating carbon ion facilities worldwide, treatment with carbon ions can be considered experimental and, therefore, reliable evidence is only just emerging and no conclusions can yet be drawn with regard to their effectiveness or toxicity.

PROTONS

Due to their physical characteristics, protons potentially offer a treatment method in which smaller areas receive radiation doses and, thus, bring about fewer side effects. Proton beams are created by a cyclotron or synchrotron, whereby the proton is separated from hydrogen molecules. Protons travel fast through tissue, with minimal room for interaction; in depth the velocity is reduced, interactions occur, and the energy is deposited: they, therefore, stop very abruptly in tissues reaching a very specific depth: the so-called “Bragg peak” (7), see **Figure 1**. Here, the majority of energy is being deposited. Heavy particles, compared to photons, have a greater radiobiological effect (1.1 times for protons and 2–3 for carbon ions) and, therefore, greater potential to damage cancer cells by interacting more densely with tissue, causing higher levels of ionization per unit length (8, 9). The dose then rapidly decreases to 0 as heavy particles (opposed to photons) stop within the body. Thus, the integral dose with protons is approximately 60% lower than that of any external beam photon technique (10, 11).

In theory, this is ideal for treating tumors near to sensitive structures, such as the brain and spinal cord, as well as for childhood cancers in order to reduce the dose to healthy surrounding organs. PBT can potentially show a clinical superiority compared to photons and is, to a certain extent, established in some populations such as pediatric indications or uveal melanoma, at least in some regions worldwide (12–14).

It is important in all populations to note that RT comes with the risk of developing secondary malignancies years to decades later. Although this risk is low with modern techniques, it is in focus for radiation oncologists, and patients alike. With the sharp dose deposition of particles, there are presumably a smaller number of secondary malignancies due to the lower dose to surrounding healthy structures. Nevertheless PBT, as opposed to photon therapy, generates neutrons as a by-product, which can



be scattered into adjacent normal tissues, especially with passive beam techniques. These neutrons have a strong biological effect and, thus, could theoretically increase the risk of secondary malignancies (15). Despite such theoretical concerns, a large retrospective study did not find statistically significant differences in secondary malignancies between patients treated with protons and those treated with photons – 5.2% of all PBT-treated patients had secondary malignancies versus 7.5% in the photon treatment group (16).

The width of the Bragg peak is within the millimeter range and usually not wide enough to cover a whole treatment volume. Several of those peaks must be superimposed to treat effectively a tumor of a certain length and volume – the so-called “spread-out Bragg peak” (SOBP). There can be some uncertainty about the exact location of the Bragg peak due to tissue inhomogeneities. Here, PBT skeptics argue that there is no widely used method for confirming the proton range, or that the SOBP encompasses the prostate *in vivo*, making sufficient margins essential for a successful therapy and thereby diminishing the possible advantage of smaller radiation volumes.

Another technical challenge is that, because of the steep dose gradient (Bragg peak), the plan parameters and patient positioning must be highly precise in order to obtain a high dose within the tumor region while maximizing the protection of organs at risk (OAR). This makes the uncertainty regarding the range of motion in human tissue one of the major hurdles of RT with protons, meaning that particle therapy is more vulnerable to target motion than photon irradiation (17).

Yoon et al. also describe an increased sensitivity to target motion of PBT because of deep dose depletion beyond the SOBP (18).

In RT of PC, the range of motion can be divided into inter- and intrafractional movements. Interfractional movements occur between two radiation appointments, e.g., due to filling of the bladder and rectum. Intrafractional movements happen within one radiation session, e.g., due to breathing, bowel gas, or small patient movements. Because of this, measurements in PBT should be made even during dose delivery and can be accomplished via positron emitters (PET camera) or induced gamma radiation (Compton camera) (19, 20). Motion mitigation strategies are essentially important to exploit the full potential of particle therapy; this includes scanning approaches, such as rescanning, gating, or implementation of motion-surrogates, such as markers (21–23).

CARBON IONS

As opposed to protons, which can be considered to have radiobiological features similar to photons [relative biological effectiveness (RBE) = 1.1 for protons], other heavy particles have higher LET characteristics, leading to substantial differences in radiobiological interactions. Due to their mass, carbon ions have a higher biological effectiveness compared to protons with a comparable depth-dose profile. The RBE of the carbon ion beams has been estimated as 2.0–3.0 (9). This means that they are twice to three times more effective in killing cancer cells than proton or photon beams as they are more likely to cause deathly DNA

double-strand breaks. Thus, carbon ions have radiobiological advantages, including more effective killing of intrinsic radio-resistant tumors, hypoxic tumor cells, and tumor cells in the G0 or S phase (24).

Furthermore, they possess an even sharper dose distribution than protons, but the dose in the region beyond the distal end of the peak is higher in carbon ion beams than proton beams, because carbon ions undergo nuclear interactions producing a fragmentation tail beyond the dose peak (25, 26).

In terms of its medical application, carbon ion therapy has been described as being advantageous *inter alia* for PC. Regarding the anti-tumor effect of carbon ion RT for PC, Ishikawa et al. reported survival data and biochemical relapse-free rates for almost 1000 patients with 20 or 16 fractions at the ion beam center in Chiba, Japan. The 5-year overall survival and cause-specific survival rates for all patients were 95.3 and 98.8%, respectively; the 5-year relapse-free and local control rates were 90.6 and 98.3%, respectively. Especially noteworthy is that the outcomes for biochemical relapse-free survival also included the high-risk group and that hypo-fractionated carbon ion RT seems to have had radiobiological benefit for PC (24, 27). In a more recent Phase I/II study from 2014, Nomiya et al. described a shortened course with only 12 fractions as another feasible option, however, the long-term outcome of such an approach is still pending (28).

Certainly, there are advantages of carbon ion RT, as an option with high biological effectiveness over low-LET radiations, such as photon therapy or PBT, and carbon ion therapy may prove to make a substantial difference in certain patient populations. However, precise definition of clinical study protocols and critical evaluation of patient data together with intake of molecular characteristics of tumors and normal tissue can help to optimally stratify patients for different radiation modalities leading to individualized radiotherapy (iRT). (Figure 2).

TECHNOLOGICAL ASPECTS

Common passive scattering systems will be replaced by spot scanning systems in charged particle beam therapy in medium

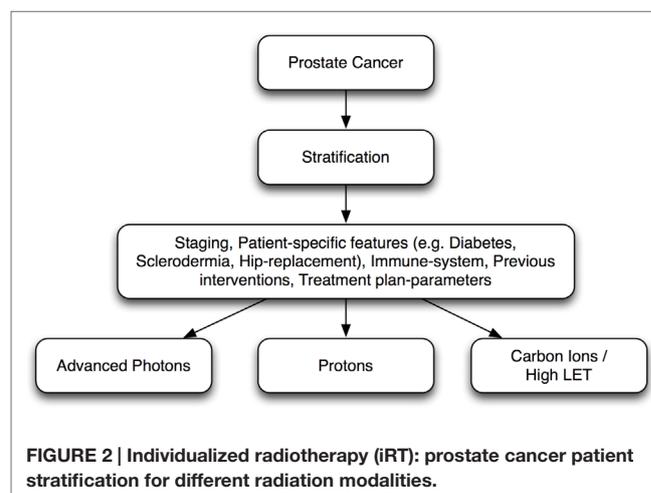


FIGURE 2 | Individualized radiotherapy (iRT): prostate cancer patient stratification for different radiation modalities.

term. It is in routine clinical use at the Paul Scherrer Institute (PSI) in Darmstadt. Advantages are the precise dose distribution and planning options for using intensity-modulated proton beam therapy (IMPT). The application is safe but several aspects for uncertainties, such as the robustness to movements of the target and to IMPT plans, must be taken into account when working with spot scanning techniques. Zhu et al. reported on the single-field integrated boost (SFIB) technique for spot scanning proton therapy based on single-field optimization (SFO) treatment planning techniques (29).

Regarding beam delivery, most experience has mainly been acquired with horizontal beam lines. The success of radiotherapy treatment is strongly increased through the possibility of applying the beam to the target using different angles, such as in IMRT. Hence, the worldwide first gantry for charged particle was brought online in October 2012 at the Heidelberg Ion Therapy Center (HIT), Heidelberg.

DISCUSSION

The success of irradiation in patients with localized PC correlates with the administered dose, meaning that a higher dose to the prostatic gland leads to better cancer control (1).

Several randomized trials have shown a benefit of dose escalation to 78–79 Gy for men treated with external radiation for localized PC. Previous data suggested a benefit with even higher doses. In a trial by Coen et al., the safety and efficacy of 82 Gy (a 2 Gy equivalent) delivered with conformal PBT was tested. The estimated rate of \geq Grade 3 late toxicity at 18 months was 6%, indicating that this may be the maximal dose that can be delivered safely with this technique and fractionation (30).

On the other hand, with new techniques such as IMRT (\pm rapid arc) or IGRT, photon radiation encumbers OAR with low-to-moderate doses. Such doses normally do not cause noticeable side effects for patients, and photon therapy has reached a high level of patient comfort and acceptance. In a similar way, IMRT is described to have excellent efficacy and low toxicity in the treatment of PC, even with elevated final doses (31, 32).

It has, thus, become the standard procedure for RT of PC in many institutes due to the significantly reduced toxicities compared with what has been observed with conventional 3D-approaches.

The feasibility of high-dose IMRT (up to 81 Gy) has been demonstrated in studies with large numbers of patients and has been proven to have comparably low side effects (33–35).

This was stated earlier by Mock et al.: they described IMRT as more effectively enabling dose reductions to OAR in the medium dosage range compared to 3D conformal radiotherapy. Furthermore, they indicated possible benefits of the two-field PBT technique, which reduces doses to surrounding tissues compared to photon-beam RT (36). The physical properties of protons may, thus, decrease common GI and GU side effects even further.

As early as 1983, Duttenhaver et al. discussed proton versus a conventional megavoltage X-Ray (photon) boost, finding no

difference in local tumor control (LC), disease-free survival (DFS), or overall survival (OS), yet fewer side effects with an elevated proton boost. Photon RT has evolved since then, as described above, with numerous technical advances, while PBT has yet to prove itself through better LC, OS, or significantly fewer side effects (37).

In dosimetric studies of a small patient group Vargas et al. were able to show a reduced mean rectal (59%) and bladder (35%) dose for PBT compared to IMRT (38). Early outcomes from single arm, prospective trials confirmed these assumptions. Nihei et al. described the incidence of late \geq grade 2 rectal and bladder toxicity at 2 years to be 2.0 and 4.1%, respectively (39).

Similarly, Mendenhall et al. found good early outcomes with image-guided proton therapy, suggesting high efficacy and minimal toxicity with 1.9% grade 3 GU symptoms and $<0.5\%$ grade 3 GI toxicities (39, 40). Generally, the dose to healthy tissues in the range $<50\%$ of the target prescription was substantially lower with proton therapy (41).

A retrospective analysis of the Medicare database compared early toxicity in 421 men using PBT with 842 matched controls treated with IMRT. A statistically significant decrease in GU toxicity at 6 months for PBT was seen, but this difference had disappeared at one year. There were no other significant differences in toxicity between the two techniques at either 6 or 12 months post-treatment. Yu et al. concluded that although PBT is substantially more cost-intensive than IMRT, no difference in toxicity in a comprehensive cohort of Medicare beneficiaries with PC at 12 months post-treatment was found (42).

Keeping in mind that the amount of bladder exposed to low doses of radiation predicts early toxicity the difference in toxicity seen by Yu et al. is plausible, since in previous studies it has been shown that one improvement in radiation dose distribution for PBT compared to IMRT led to a reduction in the amount of bladder exposed to low and intermediate levels of radiation (36, 41, 43). This dose reduction was most likely responsible for the transient improvement in the Yu study.

However, other studies have found IMRT to be favorable over PBT with regard to toxicity. An analysis from the Medicare Surveillance, Epidemiology, and End Results (SEER) database in the USA identified 684 men treated with PBT between 2002 and 2007 and compared these with a cohort treated with IMRT.

Intensity-modulated radiotherapy was associated with significantly less GI morbidity. However, there were no statistically significant differences in other toxicities, nor a significant difference in the frequency with which patients required additional cancer therapy (44).

There are still no completed randomized trials comparing PBT with photon-beam therapy in men with clinically localized PC (45).

With regard to the OS data, a few major studies have been conducted. One of the major dose-escalation studies was carried out at The Proton Center in Boston. Zietman et al. randomized 393 patients with a PSA <5 ng/ml to a low-dose arm (50.4 Gy photon therapy + 19.8 GyE proton boost) and a high-dose arm (50.4 Gy photon + 28.8 GyE proton boost). The analysis revealed a significant difference in biochemical recurrence-free survival

in favor of the high-dose arm. Subgroup analysis of low and high-risk patients (depending on the Gleason score) showed a significant advantage for the high-dose group in both cases. An impact on the OS rate was not observed. Both acute and late toxicities were not increased in either arm compared to the incidence of comparable photon studies (1, 46). However, modern photon treatments allow comparable high-dose application with utmost precision and safety; thus, the latter trial might be termed mainly not as a trial comparing photons and protons, but high-dose to low-dose treatments.

Finally, the American Society for Radiation Oncology (ASTRO) released a list recommending the use of PBT after an evidence-based review for certain tumors, including central nervous system and pediatric malignancies. For others, among them PC, it recommends treatment only within the setting of clinical trials, as there was evidence for the efficacy of PBT but no suggestion that it is superior to photon-based approaches (47, 48).

COST ASPECT

Concerning costs, several aspects must be highlighted: the construction costs of proton facilities, maintenance costs and outcome, also concerning throughput compared to photon radiation.

First, Keener et al. estimated the building cost for a new PBT center to be between 100 and 250 million US-Dollars. This is the equivalent of about 40 times the price of setting up a state-of-the-art photon radiation center (49).

As for maintenance and cost-effectiveness, Johnstone et al. calculated that a high number (single gantry 85%) of “simple” cases with a faster throughput are necessary for proton facilities to work cost effectively (50).

Proton beam therapy for PC is often described as simple, compared to pediatric or central nervous system indications, where longer setup and/or treatment times are required. A modern proton center requires treating a caseload and emphasizing simple patients with high throughput even before operating costs or any profit are achieved (50). In theory, this means that a PBT facility treating only patients with PC would run cost effectively and profitably.

With regard to compensation, Yu et al. found median Medicare reimbursement in the USA to be over 32,000 US-Dollars for proton RT and over 18,000 for IMRT. In a retrospective study of over 27,000 patients, they found no toxicity difference at 12 months post-treatment, despite the cost being almost double (42).

Furthermore, in a cost utility analysis per quality-adjusted life year (QALY) from a literature search between 2003 and 2013, PBT was not found to be cost-effective in any of the analysis (51).

A very interesting open phase 3 study (NCT01230866) is underway and could make a significant difference to PBT cost-effectiveness, as well as to the life quality of patients. The study compares standard dose of RT (44 treatments) with a hypofractionation concept (five treatments) (52).

This study could dramatically decrease the treatment costs of PBT if the hypofraction arm performs similar or better than

normofractionated treatment. It could also improve the life quality of patients as a result of the decreased number of treatment appointments. However, only recently the biological rationale of hypofractionation was revisited questioning the current α/β concepts – newer data assume that prostate α/β are, after all, more closely comparable to those of rectal or other normal tissue than initially believed, thus, questioning the real rationale of hypofractionation (53).

In summary, technology for PC RT has made important advances. However, its associated costs have escalated, thus, making cost-effectiveness analysis critical to assess. So far, all aspects of PBT remain far more expensive than photon radiation therapy, meaning that cost consciousness should outweigh standard PBT for PC as long as there is no clear evidence from controlled randomized trials supporting the superiority of PBT, so that the surplus of money spent can be well-invested. However, data are available that proton therapy can be applied, and especially in the pediatric population referral to a high-end particle therapy center should be evaluated. For carbon ions, patients should be treated within clinical trials until the full potential and the biological rationale can be shown in patient treatments.

In conclusion, proton therapy is worth being discussed in modern oncology with assets leading to potentially advantageous treatments; however, this should not lead to unreflected discussions and recommendations that proton therapy is the necessary independently of indication patient age, comorbidities, and other factors. For PC, it will be interesting to follow the ongoing research to see which technique “will be the road less traveled.”

CONCLUSION

A high publication rate confirms continued high interest in PBT and its characteristics. Reading through such publications, one gets the impression that the authors often take a similar stance to ASTRO, who finished the abstract of their evidence-based review with the words: “More robust prospective clinical trials are needed to determine the appropriate clinical setting for PBT” (47).

There is much discussion and disagreement concerning toxicities, cost-effectiveness, and the potential for better outcomes (2). However, PBT is certainly cost-intensive and yet has great potential with regard to basic physics and biological principles. Nevertheless, the advantages so far seem to remain theoretical and are brought about by a better dose distribution.

Several trials are underway, among them a multi-institutional randomized phase III National Cancer Institute study (A Phase III Randomized Clinical Trial of Proton Therapy Versus IMRT for low or intermediate risk PC; clinicaltrials.gov ID NCT01617161) comparing PBT to IMRT (54). It is now in its third year and, together with others, will hopefully shed some more light onto the discussion of PC and RT with photons and particles, which in the end will lead to individualized radiotherapy (*iRT*) concepts.

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