Prostate Cancer and Prostatic Diseases (2019) 22:509–521
https://doi.org/10.1038/s41391-019-0140-7

REVIEW ARTICLE

Proton versus photon-based radiation therapy for prostate cancer: emerging evidence and considerations in the era of value-based cancer care

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Received: 24 October 2018 / Revised: 30 January 2019 / Accepted: 25 February 2019 / Published online: 9 April 2019

Abstract

Background Advances in radiation technology have transformed treatment options for patients with localized prostate cancer. The evolution of three-dimensional conformal radiation therapy and intensity-modulated radiation therapy (IMRT) have allowed physicians to spare surrounding normal organs and reduce adverse effects. The introduction of proton beam technology and its physical advantage of depositing its energy in tissue at the end-of-range maximum may potentially spare critical organs such as the bladder and rectum in prostate cancer patients. Data thus far are limited to large, observational studies that have not yet demonstrated a definite benefit of protons over conventional treatment with IMRT. The cost of proton beam treatment adds to the controversy within the field.

Methods We performed an extensive literature review for all proton treatment-related prostate cancer studies. We discuss the history of proton beam technology, as well as its role in the treatment of prostate cancer, associated controversies, novel technology trends, a discussion of cost-effectiveness, and an overview of the ongoing modern large prospective studies that aim to resolve the debate between protons and photons for prostate cancer.

Results Present data have demonstrated that proton beam therapy is safe and effective compared with the standard treatment options for prostate cancer. While dosimetric studies suggest lower whole-body radiation dose and a theoretically higher relative biological effectiveness in prostate cancer compared with photons, no studies have demonstrated a clear benefit with protons.

Conclusions Evolving trends in proton treatment delivery and proton center business models are helping to reduce costs. Introduction of existing technology into proton delivery allows further control of organ motion and addressing organs-at-risk. Finally, the much-awaited contemporary studies comparing photon with proton-based treatments, with primary end-points of patient-reported quality-of-life, will help us understand the differences between proton and photon-based treatments for prostate cancer in the modern era.

Localized prostate cancer can be treated with either surgical resection or radiation (the latter of which can include either brachytherapy, external beam radiation therapy (EBRT) ± androgen deprivation therapy, or a combination, depending on the clinical circumstances). EBRT for prostate cancer has achieved remarkable technological advances in the past few decades. Initially treated with large, open fields (also known as the "four-field box"), conventional two-dimensional (2D) radiotherapy for prostate cancer evolved to three-dimensional (3D) conformal radiation therapy in the 1990s [1]. In the early 2000s, intensity-modulated radiation therapy (IMRT) was introduced, which was shown to better "conform" the radiation beam to the target tumor. IMRT was rapidly adopted for multiple solid tumor treatments, including prostate cancer, despite lack of randomized controlled prospective trials to definitively demonstrate improvement in clinical outcomes over 3D conformal radiation therapy. This adoption was initially criticized due to its increased cost over 3D conformal radiation therapy, with many questioning the benefits of this highly complex technology [2]. Now there are a number of studies

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demonstrating superiority of IMRT over 3D conformal therapy, particularly for prostate cancer [3–6]. The advent and commercialization of proton beam treatment, a form of EBRT using protons, which have promising physical properties related to its stopping power and distribution within tissue, rings similar to the story about the introduction and adoption of IMRT. One important difference is that proton beam therapy comes with a higher price tag than any other form of radiation treatment, including IMRT, thus highlighting the need to justify the clinical and cost-effectiveness of such a technology in prostate cancer. Fortunately, we have ongoing studies that are going to inform the field regarding these critical questions. In this review, we discuss the physical properties of proton beam therapy, its history for cancer therapy, the experience of proton beam treatment for prostate cancer to date, as well as a critical overview of some of the controversies associated with treatment for prostate cancer. We then highlight some of the coming data that will shed light upon these various questions and help us to understand its role in the treatment of prostate cancer.

Physics of proton therapy

Proton therapy delivers high doses of radiation to a target tumor while sparing dose to adjacent organs near the target or the path of the beam due to the unique physical characteristics of the proton beam. Protons are positively charged subatomic particles, which interact differently in tissue compared with photons [7]. Most of their energy is deposited in tissue at their end-of-range maximum, which is also known as the Bragg peak (Fig. 1). Manipulation of this Bragg peak creates the "spread-out-Bragg-peak", which can be further manipulated so that it covers the entire length of a tumor target. This allows proton beam therapy to carefully target a tumor while delivering minimal dosage to any surrounding tissue or organs.

Photons, by comparison, deposit energy throughout the entirety of their beam path, which can result in an "exit dose" measured for any photon beam that is delivered to tissue behind the intended target tumor. The depth of maximal energy deposited depends on the initial energy of the photon beams used. Despite this, even high-energy megavoltage photon beams only deposit their maximal energy a few centimeters after initial tissue penetration, hence when treating the prostate, a deeply seated tumor, multiple beams are required to maximize conformality to the target, contributing a wider "bath" of dose to the body [8, 9] (Fig. 2). For certain malignancies, such as pediatric tumors and tumors of the brain and eye, which require very accurate targeting, proton beam therapy provides an

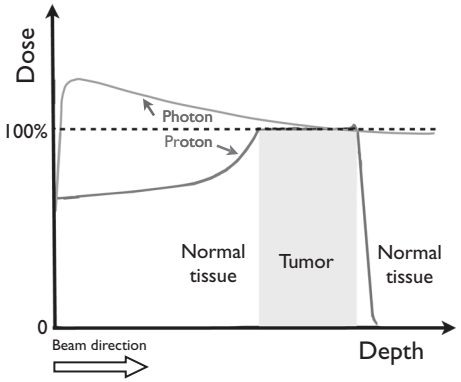

Fig. 1 Depth-dose distributions for proton and photon irradiation. An X-ray photon dose distribution curve (gray curve), which is comprised of multiple composite beam angles or arcs, has an initial build-up in tissue followed by an exponential decrease as the beam traverses further into the tissue. In contrast, the proton curve (red) is a result of a several individual "Bragg peak" curves, which, in sum, cover the target (light blue) (color figure online)

essential advantage [10–12]. Given that the prostate is in very close proximity to the bladder and rectum, and maximal sparing of these organs is key, proton beam therapy has an enticing theoretical advantage for treating prostate tumors. However, it is not clear just how well this theoretical advantage of proton treatment translates into demonstrably better clinical outcomes for prostate cancer patients.

Brief history of proton therapy

Proton treatment has been in use for cancer treatment since the time of Dr. Robert Wilson who postulated that high-energy protons could penetrate deeply into tissue so as to treat tumors that reside deep within the body cavity [13]. Shortly thereafter, a collaboration between the Harvard Cyclotron Laboratory and the Massachusetts General Hospital (MGH) resulted in the treatment of over 9,000 cancer patients with protons between 1961 and 2002 [7]. The first prostate cancer patient treated with proton therapy in the United States was in 1976 using the Harvard Cyclotron [14, 15]. Feasibility data of 17 prostate patients published out of MGH [15] and other experiences demonstrated tolerability and efficacy of such a treatment modality [16–18]. Today, there are now >28 operational proton centers in the United States, with that number expected to increase substantially with approximately 23 facilities in planning phases (Particle Therapy Co-Operative Group. Facilities in operation) (Fig. 3). Part of the justification for these new centers is the treatment of pediatric, brain, and eye tumors, where the benefit of proton beam treatment is essential. However, many proton centers opened with a business

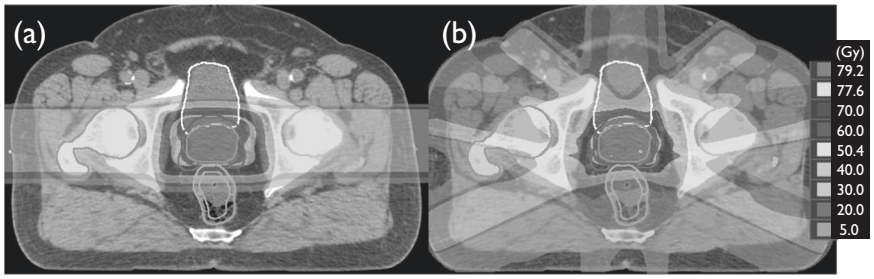

Fig. 2 Dose distribution radiation plans for **a** proton beam treatment and **b** intensity-modulated radiation treatment (photons) of the prostate. Cross-sectional image demonstrates the prostate (red), rectum (light blue/green), bladder (yellow), right femoral head (dark blue) and left femoral head (pink). The prostate was treated to 79.2 Gy (RBE) in both plans. The photon creates a "low-dose bath" affecting many tissues, whereas the proton plan effectively spares more of the normal tissues from receiving the lower-dose radiation (color figure online)

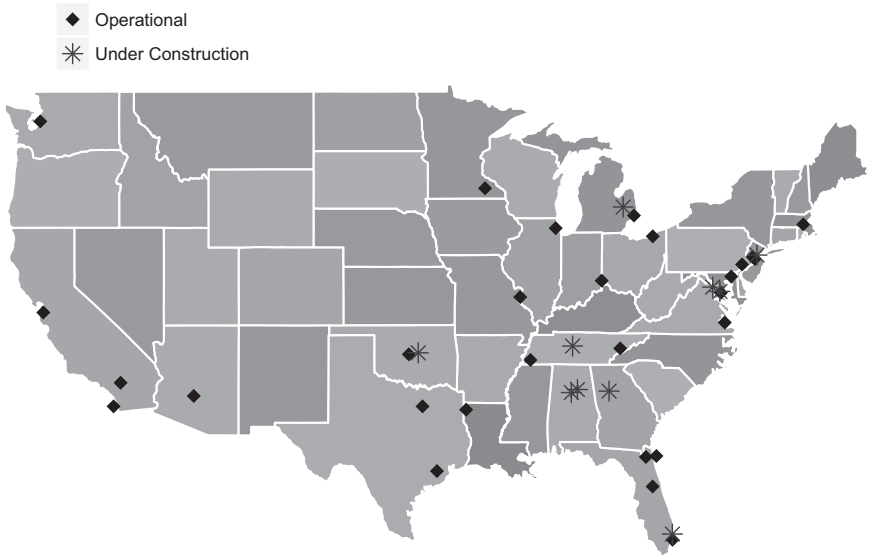

Fig. 3 Proton therapy centers in operation or in development in the United States. There are currently 28 centers in operation (black diamond) with approximately 23 centers under construction or in development (blue star; 10 shown on the map). Available from The National Association for Proton Therapy (http://www.proton-therapy.org/) (color figure online)

model that incorporated the treatment of prostate cancer patients [19]. Using this model, the opening of a proton center has served as a cautionary tale as the operating costs have sometimes outpaced the revenue generated [20]. Hence, it is imperative to clearly understand the role of proton therapy for prostate cancer, and its clinical and cost-effectiveness compared with more standard external beam treatments, such as IMRT. Over time, the reality of operating costs for a proton center has led to modified business models, with the opening of centers that are largely one-gantry facilities to account for this challenge.

Proton therapy for prostate cancer

Localized prostate cancer radiation treatment delivered in the United States today is largely via the use of IMRT or brachytherapy [21]. Novel advances in EBRT include image-guided radiotherapy and more sophisticated daily immobilization techniques, which have been adopted for prostate radiation treatment to further allow for accurate targeting of the external beam. In addition, the recent publications of the RTOG 0415, PROFIT, and CHHiP trials demonstrate the safety and feasibility for moderate hypofractionation in prostate cancer, thereby reducing the number of external beam fractions necessary to treat [22–24]. However, there has been a lack of completed phase 3 studies comparing protons with photons in this field, which has led some to criticize the adoption of proton therapy in common disease sites (e.g., lung, breast, and prostate) where there is not a definitive proven benefit over the standard of care technology [25–29].

Cancer control

Despite the scarcity of data upon which to base recommendations, in general, the body of evidence has demonstrated clinical outcomes, measured in terms of cancer control rates, to be equivalent between protons and photons for prostate cancer, but this has been largely limited to

retrospective comparisons or non-comparative single cohorts. A randomized clinical trial performed by Shipley and colleagues comparing protons with photons was initiated in the 1980s, when older techniques were used and before the era of prostate-specific antigen (PSA)-detected disease [18]. No difference in outcomes was seen, however, this finding is difficult to interpret in the context of its limitations and the changes in modern-day practice. Cancer control rates with proton therapy were shown to be equivalent to those obtained with photon radiation in separate studies [30, 31], and a case-matched comparative study demonstrated identical cancer control rates between proton beam treatment and brachytherapy [32]. Of note, protons uniquely have a different biological effect in tissues compared with photons, an effect that is corrected for using the relative biological effectiveness, or RBE. It has been suggested that tumors with a lower alpha/beta ratio, such as prostate cancer, will experience a higher RBE with protons, and therefore improved tumor control, although this is more difficult to model [33–35] and has not yet been demonstrated clinically.

Organs-at-risk: dosimetric models

Given the physics of protons, the theoretical advantage may be less related to cancer control outcomes but more so to their ability to reduce the radiation dose inadvertently delivered to nearby critical organs, which can result in considerable side effects. Several modeling studies were implemented comparing the dosimetry of IMRT with protons [36–38]. These ultimately did not result in a definitive conclusion of one modality over the other as both demonstrated superiority depending on planning system and choice of beam arrangement used, yet all three modeling studies did demonstrate a significant reduction in whole-body radiation exposure when using proton therapy. IMRT of the prostate results in the creation of a low-dose radiation "bath" in the pelvic field due to the need for utilization of five or more coplanar beams so that conformality is maximized. A potential side effect of IMRT due to radiation scatter is reduced serum testosterone, which can lead to symptoms of hypogonadism, although data on this are mixed [39–41]. Extra exposure to radiation may also increase the long-term risk of radiation-induced second malignancies, a rare, but potentially deadly, complication. This may be of great concern to younger men treated with prostate cancer as this toxicity does not typically arise until 10–20 years after completion of treatment [42, 43]. Computer models examining the lower whole-body radiation exposure between proton therapy compared with IMRT demonstrated a 40% reduction in the risk of developing a secondary malignant neoplasm [44–46]. A small dosimetric study of six patients sought to determine the impact of interfractional motion in hypofractionated radiotherapy between pencil beam scanning (PBS) proton therapy and volumetric modulated arc therapy (VMAT) for prostate cancer [47]. It was found that the delivered doses were comparable between the two treatment modalities. Prescription dose remained within clinical tolerance and deviations were minor. Organs-at-risk also were within compliance between the two modalities, hence suggesting that hypofractionation is robust to interfractional motion for both PBS and VMAT.

Organs-at-risk: database analyses

As the main theoretical advantage of proton beam technology over standard photon radiotherapy is that it reduces unintended dosage to nearby organs-at-risk, different studies have sought to prove or refute that claim. An additional important consideration with proton beam technology is its associated higher RBE, which may translate to a higher risk of toxicity to normal tissues in the radiation field, such as the prostatic urethra. Currently, the higher RBE is taken into account during treatment planning, but if the RBE is higher than what is currently accounted for, studies may demonstrate an increase in both tumor control and toxicity. A study by Yu and colleagues examined 27,647 Medicare recipients treated with IMRT ($n = 27{,}094$) or proton therapy ($n = 553$) and examined toxicity profiles between the two groups [48]. To account for the small numbers of proton patients, the authors employed a sophisticated statistical technique of Mahalanobis matching [49] to accurately assess for differences in toxicities between IMRT versus protons. The authors found a statistically significant lower 6-month rate of genitourinary (GU) toxicity for patients receiving proton treatment versus IMRT (5.9 versus 9.5%, $p = 0.03$). This did not persist at 12 months post treatment, and there were no differences in gastrointestinal (GI) toxicities between the two modalities. In contrast, however, two separate studies using the Surveillance, Epidemiology, and End Results (SEER) Medicare database did not support the findings from Yu et al. [50, 51], and in fact reported higher rates of GI toxicity in patients receiving proton treatment versus IMRT. Many limitations inherent to large Medicare data sources exist, hence it is common to have differing interpretations and discrepancies in findings in these types of studies.

A recent study utilizing the MarketScan Commerical Claims and Encounters database identified 693 men who received proton therapy and matched them to 3,465 IMRT patients [52]. In addition to reviewing toxicities, the authors also calculated cost from a payer's perspective from claims. It was found that men treated with proton therapy had a lower risk of composite urinary toxicity (33 versus 42%, $p < 0.001$) and erectile dysfunction (21 versus 28%, $p < 0.001$) at 2 years

but a higher risk of bowel toxicity (20 versus 15%, $p = 0.02$). Mean radiation cost also significantly differed between the two ($115,501 for protons versus $59,012 for IMRT, $p < 0.001$). Of course, this study is still subject to inherent limitations as the database does not have information on radiation field or dose, but the data can provide real-world insight into costs for differing technologies.

Organs-at-risk: non-randomized comparative and single-arm cohort series

Both non-randomized comparisons and single-arm cohort studies have been performed to evaluate the impact of proton beam technology on organs-at-risk. A large study reviewing patient-reported outcomes data collected prospectively using validated instruments assessing bowel and urinary quality-of-life (QoL) among patients with localized prostate cancer who received 3D conformal radiotherapy (3DCRT), IMRT, or proton beam therapy found a clinically meaningful decrement in bowel QoL at the first post-treatment follow-up in those who received 3DCRT or IMRT [53]. At 12 and 24 months, all three groups reported decrements in bowel QoL. At the first post-treatment follow-up, those who received IMRT reported clinically meaningful decrements in urinary irritation/obstruction. Interestingly, at 12 months, clinically meaningful decrements in urinary irritation/obstruction were reported among patients who received proton beam therapy (but not among patients who received IMRT or 3DCRT). These urinary QoL decrements all normalized by 24 months post-treatment in all three groups. A case-matched study out of the University of Pennsylvania assessing provider-reported acute and late GI/GU toxicities using the Common Terminology Criteria for Adverse Events (CTCAE) between men who received IMRT ($n = 213$) versus proton beam therapy ($n = 181$) found no statistically significant difference in acute or late grade ≥ 2 GI or GU toxicity [54]. The University of Florida Proton Therapy Institute has contributed much to the body of evidence regarding the use of proton therapy for prostate cancer. A prospective cohort of 211 men with localized prostate cancer treated with proton therapy demonstrated minimal toxicities, with 1.9% experiencing grade 3 GU toxicities and < 0.5% with grade 3 GI toxicities at 2 years [55]. A comparative effectiveness study between men who received proton-based treatment ($n = 1,243$) versus photon-based treatment ($n = 204$) using patient-reported QoL data found no statistically significant difference in GI, GU, or sexual summary scores in the first 2 years of early follow-up, but men who received IMRT were noted to report significantly more issues with rectal urgency and frequent bowel movements compared with men who received proton therapy [56]. In a separate study looking at men ≤ 60 years old who were treated with protons assessing patient-reported health-related QoL, it was found that, with 2 years of follow-up, men had good outcomes with respect to erectile dysfunction, urinary incontinence, and bowel function [57]. At 7 years of follow-up, potency (defined as erections firm enough for sexual intercourse) was 90% at baseline, declined to 72% at the first-year follow-up, and declined to 67% at 5 years [58]. In the cohort, 2% developed urinary incontinence requiring pads. Seven-year biochemical control was 98%. In contrast to photon-based studies that have demonstrated minor testosterone suppression after prostate radiotherapy [39–41], a study of 171 men treated with proton radiation did not demonstrate evidence of testosterone suppression within the first 2 years after treatment [59]. Results of two prospective trials using proton therapy for low- to intermediate-risk prostate cancer patients found that 5-year urologic toxicity outcomes were minimal, including among patients with significant pretreatment GU symptoms [60]. A large, multi-institutional retrospective study of long-term outcomes (median follow-up: 69 months) of low-, intermediate-, and high-risk prostate cancer patients treated with proton therapy in Japan was recently published [61] and demonstrated excellent biochemical control with incidence rates of grade 2 or higher late GI or GU toxicities of 4.1 and 4.0%, respectively.

In summary, the studies mentioned above demonstrate excellent tolerance of proton radiotherapy, with photon/proton comparative studies hinting potential early GI/GU benefit with proton over photon radiotherapy that is not sustained over the longer term, with possible increase in late GI toxicity, although the data are mixed (Table 1). Despite the promising results from these studies, these consist of non-randomized, mostly single-institution or multi-institutional pooling of parallel cohorts, further emphasizing the need for a randomized, prospective trial.

Uncertainties and controversies with proton beam technology

Despite the allure of proton dose distribution maps depicting highly conformal treatment plans, several uncertainties surrounding proton dose delivery do exist. For deep-seated tumors, such as the prostate, there is an "end-of-range uncertainty" due to a penumbra that develops laterally and around the distal end of the beam, blurring the beam's sharp edge. This commonly occurs at depths past 10 cm in tissue [8]. Due to this, most prostate proton treatments are planned such that the beams enter the body laterally through the femoral heads. At this time, patients with bilateral hip prostheses are generally not eligible for proton beam treatment [62]. Patients with a unilateral hip prosthetic may be

Table 1 Current proton versus photon therapy comparative evidence for localized prostate cancer

Study	Design	Source of data	Years	Toxicities: Protons compared to photons					
				Acute			Late[a]		
				GU	GI	Sexual	GU	GI	Sexual
Kim 2011[50]	Database	SEER	1992–2005	NA	↑	NA	NA	↑	NA
Sheets 2012[51b]	Database	SEER	2000–2009	NA	NA	NA	=	↑	=
Yu 2012[48c]	Database	Medicare	2008–2009	↓	=	NA	=	=	NA
Pan 2018[52d]	Database	MarketScan	2008–2015	↓	=	↓	↓	↑	↓
Gray 2013[53e]	Non-randomized comparative	MGH PROST-QA Harvard-affiliated[f]	2003–2008	↓/↑	↓/=	NA	=	=	NA
Hoppe 2014[56]	Non-randomized comparative	UF PROST-QA	2003–2010	=	=[g]	=	=	=[g]	=
Fang 2015[54]	Non-randomized comparative	University of Pennsylvania	2010–2012	=	=	NA	=	=	NA

SEER Surveillance, Epidemiology, and End Results, *MGH* Massachusetts General Hospital, *PROST-QA* Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment Consortium, *UF* University of Florida, *GI* Gastrointestinal, *GU* Genitourinary, *NA* not available

Symbols:

↑: Refers to increased toxicity with protons compared to photons

↓ : Refers to decreased toxicity with protons compared to photons

= : Refers to equivalent toxicity (no statistically significant difference observed between the two modalities

[a]Late toxicities are defined differently in different studies based on longest follow-up data available

[b]propensity-score matched comparison, rate per 100 person-years

[c]Acute toxicities defined as at 6 months, late toxicities defined at 12 months

[d]Acute toxicities defined as up to 12 months after start of radiation; late toxicities defined as after 12 months.

[e]Acute toxicities defined as at first post-treatment follow-up/12 month follow-up, late toxicities defined as at 24 months follow-up

[f] Harvard-affiliated hospitals

[g]Patients in photon-cohort more likely to report specific issues with bowel urgency ($p = 0.02$) and rectal frequency ($p = 0.05$)

evaluated on a case-by-case basis. To circumvent this problem, some groups have started to use anterior-oriented proton beams. Cuaron et al. treated 20 patients between 2010 and 2014 with organ-confined prostate cancer and a history of hip prosthesis using at least one anterior oblique beam [63]. With a median follow-up of 6.4 months, acute grade 2 urinary toxicity was 40%, grade 2 erectile dysfunction occurred in two patients, one patient developed late grade 2 rectal proctitis, and 25% of patients experienced hip pain. Further investigation of this technique is needed to characterize the role of anterior beams in proton therapy for prostate cancer.

Proton beams are also exquisitely sensitive to tissue density and heterogeneity, especially in the pelvis when passing through bone followed by muscle and fat. Variance of dose can be significant with organ motion, or inadequate immobilization. Of course, organ motion is a concern with photon-based therapy as well, however, accurate, reproducible immobilization may be even more critical with proton-based treatment, which predominantly uses lateral beams that pass through the femoral heads and can affect the dose to the target even with minor setup errors [64, 65]. There is also concern about generation of high-energy neutrons from the head of proton machines, which have high radiobiological effects and increased risk of causing secondary cancers compared with standard photon treatment [66, 67]. Data have also raised concern that the RBE of protons may increase beyond the Bragg peak [68], which may in fact increase normal tissue toxicity. On the other hand, if this RBE can be contained within the tumor itself (and not normal tissue), this may translate to improved cancer control [33–35]. These dosimetric concerns have contributed to debate within the radiation oncology community regarding the advantages/disadvantages of proton beam technology.

Technology trends in proton beam treatment

Motion matters

Proton beam technology for the prostate relies heavily on accurate positioning and most centers now employ implanted fiducial markers and 2D orthogonal X-ray imaging for accurate set-up and treatment delivery. Interestingly, despite the concern that interfractional set-up variations lead to more delivery uncertainties using proton beam therapy compared with IMRT, a study out of MGH demonstrated that there were no statistically significant differences between

target coverage and organs-at-risk dose deviations between the two modalities [69]. Nevertheless, it is still important to minimize uncertainty in set-up, no matter the treatment modality.

The next step in image guidance for protons is a move toward integrating cone-beam CT into daily treatment. Cone-beam 3D imaging has already been adopted on traditional EBRT systems, and already many centers have purchased or plan to purchase cone-beam technology for installation on their proton beam systems [62]. This will allow for improved localization, set-up, and evaluation of dose variation of the proton beam path. A study by Moteabbad et al. demonstrated a method for evaluation of delivered IMRT dose using the daily cone-beam CT and the deformable image registration for prostate cancer treatments [70]. This work brings treatment one step closer toward image-guided adaptive radiotherapy. If cone-beam technology can be integrated for proton beam treatments, image-guided adaptive radiotherapy may one day be translated to proton treatments as well.

Addressing organs-at-risk

Prostate radiation has always been challenging due to its location in the pelvis and its proximity to the rectum. However, the introduction and growing usage of injected hydrogel spacers between the prostate and rectum (SpaceOAR, Augmenix Inc.) has been proven to reduce incidence of rectal or GI side effects [71]. With respect to protons, this offers the option to use anterior-based beams [63], making proton end-of-range uncertainty posteriorly less of a concern (Fig. 4). A study by Underwood et al. [72] that modeled anterior oblique proton plans in a cohort of prostate patients with rectal spacers demonstrated feasibility and reproducibility of such a technique.

Proton therapy in post-prostatectomy setting or for pelvic lymph nodes

There is very little reported on the use of proton therapy in the post-prostatectomy setting, where the role of radiotherapy has been previously defined [73]. A prospective study of 10 patients who received post-prostatectomy IMRT examined interfraction motion and target volume variability throughout the treatment course using serial magnetic resonance imaging (MRI), the results of which suggested that proton therapy was feasible in this context [74]. A separate study reviewed GU and GI toxicity outcomes in 100 patients treated with post-prostatectomy proton therapy with a median follow-up of 25 months [75]. Toxicity-free survival at 24 months was GU grade 2 (83%) and GI grade 1 (74%), demonstrating feasibility with a favorable toxicity profile both acutely and in early follow-up.

In patients with high-risk prostate cancer, radiation therapy is often delivered to the prostate, seminal vesicles, and pelvic lymph nodes [76]. Dosimetric studies have demonstrated safety and feasibility of the use of proton therapy when treating pelvic lymph nodes. One study evaluating dosimetric differences between IMRT, VMAT, and intensity-modulated proton therapy (IMPT) found that IMPT succeeded in producing the best biological and physical treatment plans compared with both IMRT and VMAT plans [77]. Proton beam treatment plans were similarly demonstrated to be superior to photon treatment plans when treating the pelvic nodes in a separate study out of the University of Florida [78].

Stereotactic body radiation therapy (SBRT) and protons

As radiation technologies become more precise with continued improvements in imaging and planning, there has

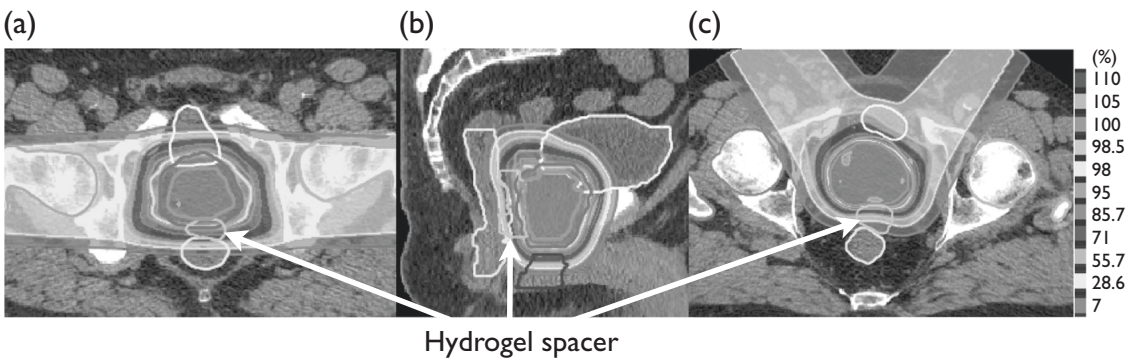

Fig. 4 Proton therapy dose distribution plans of the prostate with a hydrogel spacer. Cross-sectional images of an axial (**a**) and sagittal slice (**b**) in a plan with lateral beams demonstrate the prostate (red), rectum (light blue), hydrogel rectal spacer (brown), bladder (yellow), right femoral head (dark blue), and left femoral head (pink). The prostate was treated to 79.2 Gy (RBE). Cross-sectional axial image (**c**) of an anterior-oriented beam plan with a rectal spacer (brown). The use of a rectal spacer makes proton end-of-range uncertainty less of a concern when using anterior beams (color figure online)

been a move towards more moderate hypofractionated treatments (defined as less number of overall treatments compared with standard fractionation, with higher dose per delivery of treatment ranging between 240 and 340 cGy) for prostate cancer and some advocating for the use of more ultrahypofractionated therapy (defined as 5 or less treatments, with fraction sizes of ≥500 cGy) in prostate cancer. A recent evidence-based guideline that provides recommendations on the use of either moderate hypofractionation or ultrahypofractionation has been published [79]. There are obvious advantages to this type of treatment both for patient convenience and costs, however, the role of proton beam technology and hypofractionation has not been clearly defined, and more evidence is needed. One study by Goddard and colleagues [80] compared photon- versus proton-based SBRT treatment plans in 10 patients with prostate cancer. It was found that similar treatment plans could be generated between the two modalities, however, photon-based plans outperformed proton-based plans with regards to achievable target conformity and organ-at-risk sparing. However, a similar, separate study by Kole et al. demonstrated mixed results between the two modalities, with lower dose to the penile bulb with protons but higher mean dose to the femoral heads [81]. The same study by Pan and colleagues discussed earlier that compared men treated with protons versus IMRT also matched 310 men treated with SBRT to 3100 men treated with IMRT, demonstrating that SBRT had a similar toxicity profile to IMRT with decreased cost ($49,504 versus $57,244, $p < 0.001$) [52]. Proton radiation and SBRT were not directly compared in this analysis, and it is unknown what the cost of performing SBRT with proton radiation would be, and what, if any, benefit it may have over SBRT with photon radiation. This critical question requires more investigation, as the use of an ultrahypofractionated schedule with protons may help to bring down the cost of proton radiotherapy for prostate cancer.

Resolving the debate between photons versus protons for prostate cancer

There is an urgent need for randomized data comparing photon- versus proton-based external beam radiation head-to-head for localized prostate cancer using modern techniques to rigorously inform the debate surrounding proton therapy for prostate cancer.

To that end, there is an ongoing, large randomized phase III trial of proton therapy versus IMRT for low- to intermediate-risk localized prostate cancer called Prostate Advanced Radiation Technologies Investigating Quality of Life, or PARTIQoL (ClinicalTrials.gov identifier: NCT01617161). It is a multi-center study, with 12 proton institutions among a total of 27 participating centers. As of January 2019, over 325 patients have been accrued with a total enrollment goal of 400 patients expected to be met by late 2019/early 2020. The primary endpoint of the trial is 24-month EPIC bowel scores, though other domain scores are also being collected as part of secondary endpoints (e.g., GU scores, erectile dysfunction, etc). Physician-graded toxicity and disease-specific outcomes are being collected as well. The use of androgen deprivation therapy is not allowed as it can complicate the interpretation of the QoL endpoints. In addition, patient tissue and blood samples are being collected for translational discovery. These biological samples will be used to evaluate biomarkers for prostate cancer behavior and treatment response. Economic data are being collected for future cost–benefit analyses. The trial allows and stratifies by fractionation (moderate hypofractionation versus standard fractionation), use of rectal spacer, and it has evolved to incorporate the best treatment delivery systems as they have been introduced into the clinic (e.g., PBS, etc.).

The recently opened study, a Prospective Comparative Study of Outcomes with Proton and Photon Radiation in Prostate Cancer, COMPPARE (ClinicalTrials.gov identifier: NCT03561220), will evaluate QoL, toxicity, and disease control outcomes in a prospective registry of 1,500 proton beam therapy and 1,500 IMRT patients treated at 42 centers, along with a randomized component of fractionation.

Based on results from the trial published by Iwata et al. [61], the Japanese recently opened a multi-institutional prospective registry (UMIN000025453) for prostate cancer patients treated with proton therapy. The primary outcome is 5-year biochemical relapse-free survival rate.

The results of these studies are expected to shed light on the debate between protons versus photons for localized prostate cancer. Patients, providers, and policy makers are eagerly awaiting the results to guide decisions regarding the use and justification for proton technology in the treatment of prostate cancer.

The relative costs dimension of the cost-effectiveness comparison

In order to judge the relative cost-effectiveness of proton versus photon beam radiation, some fairly accurate estimates of relative cost for the two modalities are needed. That requires careful analysis, particularly because each of the two treatment modalities have been evolving rather rapidly in recent decades. We do know that the capital cost of a proton beam facility is very large, substantially exceeding the capital cost of various photon-based equipment [82]. A proton facility is based upon a powerful but expensive proton accelerator, which can either be a cyclotron or synchrotron, and also must include the building in

which these rather large machines have to be safely housed. Historically, these capital costs have often exceeded $150 million dollars for a multiple (e.g., three to four) gantry site. Such a facility can treat numerous cancer patients in a day, assuming the demand is there, and can be used over a fairly long, though uncertain, effective lifetime. Therefore, the allocated capital costs per patient can be more reasonable, though still substantially larger than the equivalent capital costs for photon-based treatment, or, for that matter, other treatments for prostate cancer. We also know that there are substantial operating costs for these facilities, including the costs of staffing radiation oncologists, technicians, physicists, dosimetrists, and others. Simplified models of the relative costs of proton beam and IMRT treatment processes suggest that, taking into account both the capital and operating costs, the relative cost of proton-based treatment today may be approximately 1.5-2X greater than that of IMRT [52, 83–85]. But a static view of this relative cost differential may be too simplistic.

As described above, photon-based treatment has been evolving in recent decades as more accurate targeting of the tumor and protection of nearby organs-at-risk has continually improved. This has led to more complex, and hence more expensive, treatment modalities. A similar evolution of treatment processes has been occurring for proton-based treatment. Thus, the costs of both modalities must be considered as dynamic cost estimates that are changing through time, as are the relative costs.

In addition, the operating costs of these treatments are decreasing down learning curves as medical centers and their staff become more experienced in using them. The capital costs are similarly coming down a learning curve as the designers and manufacturers of the machines and buildings improve. As just one example, the capital costs of a small one-gentry proton facility may now be down to around $30 million dollars [8]. With the growing use of decreased fractionation for prostate cancer and ongoing studies exploring fewer treatments, proton beam delivery costs will decrease [22–24]. It is safe to assume that both proton- and photon-based therapies will continue to improve, become more complex, and all of these factors will produce changing costs and particularly relative costs.

There have been earlier historical studies which have included various estimates of relative costs for proton and photon treatments in the case of prostate cancer. For example, Yu et al. [48] used estimates of Medicare reimbursement rates as a proxy for cost. Unfortunately, we know very little about how these reimbursement rates from payers are determined and what their relationship is to the real capital and operating costs of these treatment modalities. And, of course, these costs have been changing rapidly such that older estimates of cost have fairly limited relevance for today's methods of treatment. Fortunately, as an adjunct to the above-cited PARTIQoL randomized trial, cost models will be developed to more accurately estimate the relative costs of proton beam therapy and IMRT-photon therapy under current and future treatment procedures for each.

The business behind the proton beam

While patients and providers alike await randomized trial data to fully understand the potential benefits of proton beam therapy for prostate cancer, the higher cost of proton beam technology relative to other available treatments has many policy makers paying close attention. Due to the lack of strong clinical evidence supporting the role of proton radiation therapy in the treatment of prostate cancer, some private insurers have decided to not cover proton therapy for prostate cancer [86–88]. This decision is at odds with the American Society for Radiation Oncology (ASTRO) model policy for proton beam therapy, which recommends coverage for patients with nonmetastatic prostate cancer enrolled in either an Institutional Research Board-approved study or a multi-institutional registry [89]. Despite this recommendation, there remains a discrepancy among private payers and how they address their minimum standards for insurance coverage of patients in clinical trials. This can lead to a barrier for patients to access clinical trials, as well as stall clinical trial accrual and affect timely completion of studies. Some states have implemented policy to prevent health benefit plans from holding proton beam therapy to a higher standard of clinical evidence than IMRT [90]. Policy initiatives, such as a move towards reference pricing, a model whereby proton therapy costs are set to be equivalent to competing treatment modalities with similar outcomes, are attractive as this could reduce barriers to build the clinical evidence needed to understand the benefits (if any) of proton therapy [91, 92]. All of this only underlines the need for clinical trials to better improve the cost-effectiveness judgements being made by insurers, providers, and patients in the search for better and more efficient prostate cancer care.

Future directions

Proton therapy likely has a place in modern radiotherapy for prostate cancer. Based on the evidence that is available, there are potentially tangible benefits to treating the prostate with protons, with lower integral body dose, which may in turn lead to decreased incidence of secondary malignancies (though given their rarity this will be difficult to prove), and possible decreased impact on long-term erectile function. Some studies hint at potential early benefits for GI/GU toxicity outcomes that may not be sustained in the long

term, and possible increase in late GI toxicity. Ultimately, the results of the randomized comparisons are necessary to robustly and fully inform the toxicity/QoL outcomes—these data are coming in the not too distant future.

In the meantime, optimization of proton therapy is ongoing to make it as efficient as possible, with decreased operational costs [91], introduction of different payment models, and further understanding of which patients to treat. These strategies combined are all in an effort to make proton beam technology a more cost-effective therapy in the time of value-based cancer care.

Looking to the future, as the field moves further into the era of precision oncology, it will be important to explore whether there are subgroups of prostate patients who particularly benefit from proton beam treatment, based on genomic and/or molecular profiles, in terms of either cancer control or reduction in toxicities. The translational applications from the randomized comparisons provide stimulating opportunities for discovery of prostate patient populations that are better treated with protons.

In summary, the role for proton beam therapy for prostate cancer patients will be realized as the ongoing trials report their findings. In the interim, we must continue efforts to make proton beam therapy more accessible, cost-effective, and efficient along with advances in cancer biology and radiation techniques to ultimately translate to improved treatment decisions and outcomes for prostate cancer patients.

Acknowledgements We thank Maryam Moteabbed, PhD, for her assistance with the Figures. JAE serves as the principal investigator of the PARTIQoL multi-center randomized phase 3 clinical trial of proton therapy versus intensity-modulated radiotherapy for localized prostate cancer and acknowledges funding support from the Federal Share of program income earned by Massachusetts General Hospital (grant C06 CA059267) and the Prostate Cancer Foundation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Dearnaley DP, Khoo VS, Norman AR, Meyer L, Nahum A, Tait D, et al. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. Lancet (Lond, Engl). 1999;353:267–72.
2. Gray PJ, Efstathiou JA. Prostate cancer: proton therapy–revolutionary advance or diminishing returns? Nat Rev Urol. 2013;10:128–9.
3. Alicikus ZA, Yamada Y, Zhang Z, Pei X, Hunt M, Kollmeier M, et al. Ten-year outcomes of high-dose, intensity-modulated radiotherapy for localized prostate cancer. Cancer. 2011;117:1429–37.
4. Alongi F, Fiorino C, Cozzarini C, Broggi S, Perna L, Cattaneo GM, et al. IMRT significantly reduces acute toxicity of whole-pelvis irradiation in patients treated with post-operative adjuvant or salvage radiotherapy after radical prostatectomy. Radiother Oncol. 2009;93:207–12.
5. Kuban DA, Tucker SL, Dong L, Starkschall G, Huang EH, Cheung MR, et al. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys. 2008;70:67–74.
6. Latorzeff I, Mazurier J, Boutry C, Dudouet P, Richaud P, de Crevoisier R. [Benefit of intensity modulated and image-guided radiotherapy in prostate cancer]. Cancer Radiother: J De la Soc Fr De Radiother Oncol. 2010;14:479–87.
7. Gray PJ, Efstathiou JA, Bekelman JE, Lee WR. Proton therapy for prostate cancer: history, uncertainties, and opportunities. In: DeVita VT, Lawrence TS, Rosenberg SA, editors. DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology, 9th edn, vol. 27. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2013.
8. Efstathiou JA, Gray PJ, Zietman AL. Proton beam therapy and localised prostate cancer: current status and controversies. Br J Cancer. 2013;108:1225–30.
9. Royce TJ, Efstathiou JA. Proton therapy for prostate cancer: A review of the rationale, evidence, and current state. Urol Oncol. 2018. https://doi.org/10.1016/j.urolonc.2018.11.012 [Epub ahead of print].
10. Munzenrider JE, Liebsch NJ. Proton therapy for tumors of the skull base. Strahlentherapie und Onkologie 1999;175:57–63.
11. Gragoudas ES, Lane AM, Munzenrider JE, Egan KM, Li W. Long-term risk of local failure after proton therapy for choroidal/ciliary body melanoma. Trans Am Ophthalmol Soc. 2002;100:43–48.
12. MacDonald SM, Safai S, Trofimov A, Wolfgang J, Fullerton B, Yeap BY, et al. Proton radiotherapy for childhood ependymoma: initial clinical outcomes and dose comparisons. Int J Radiat Oncol Biol Phys. 2008;71:979–86.
13. Wilson RR. Radiological use of fast protons. Radiology. 1946;47:487–91.
14. Efstathiou JA, Trofimov AV, Zietman ALLife. liberty, and the pursuit of protons: an evidence-based review of the role of particle therapy in the treatment of prostate cancer. Cancer J (Sudbury, Mass). 2009;15:312–8.
15. Shipley WU, Tepper JE, Prout GR Jr., Verhey LJ, Mendiondo OA, Goitein M, et al. Proton radiation as boost therapy for localized prostatic carcinoma. JAMA. 1979;241:1912–5.
16. Benk VA, Adams JA, Shipley WU, Urie MM, McManus PL, Efird JT, et al. Late rectal bleeding following combined X-ray and proton high dose irradiation for patients with stages T3-T4 prostate carcinoma. Int J Radiat Oncol Biol Phys. 1993;26:551–7.
17. Duttenhaver JR, Shipley WU, Perrone T, Verhey LJ, Goitein M, Munzenrider JE, et al. Protons or megavoltage X-rays as boost therapy for patients irradiated for localized prostatic carcinoma. An early phase I/II comparison. Cancer. 1983;51:1599–604.
18. Shipley WU, Verhey LJ, Munzenrider JE, Suit HD, Urie MM, McManus PL, et al. Advanced prostate cancer: the results of a randomized comparative trial of high dose irradiation boosting with conformal protons compared with conventional dose irradiation using photons alone. Int J Radiat Oncol Biol Phys. 1995;32:3–12.
19. Corkum MT, Liu W, Palma DA, Bauman GS, Dinniwell RE, Warner A, et al. Online advertising and marketing claims by providers of proton beam therapy: are they guideline-based? Radiat Oncol. 2018;13:43.

20. Hancock J. For cancer centers, proton therapy's promise is undercut by lagging demand. New York, NY: New York Times; 2018. Available at: https://www.nytimes.com/2018/04/27/business/proton-therapy-finances.html. Accessed Nov 2018.
21. Bekelman JE, Mitra N, Efstathiou J, Liao K, Sunderland R, Yeboa DN, et al. Outcomes after intensity-modulated versus conformal radiotherapy in older men with nonmetastatic prostate cancer. Int J Radiat Oncol Biol Phys. 2011;81:e325–34.
22. Dearnaley D, Syndikus I, Sumo G, Bidmead M, Bloomfield D, Clark C, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial. Lancet Oncol. 2012;13:43–54.
23. Catton CN, Lukka H, Gu CS, Martin JM, Supiot S, Chung PWM, et al. Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. J Clin Oncol. 2017;35:1884–90.
24. Lee WR, Dignam JJ, Amin MB, Bruner DW, Low D, Swanson GP, et al. Randomized phase III noninferiority study comparing two radiotherapy fractionation schedules in patients with low-risk prostate cancer. J Clin Oncol. 2016;34:2325–32.
25. Elnahal SM, Kerstiens J, Helsper RS, Zietman AL, Johnstone PA. Proton beam therapy and accountable care: the challenges ahead. Int J Radiat Oncol Biol Phys. 2013;85:e165–72.
26. Lievens Y, Pijls-Johannesma M. Health economic controversy and cost-effectiveness of proton therapy. Semin Radiat Oncol. 2013;23:134–41.
27. Ojerholm E, Bekelman JE. Finding value for protons: the case of prostate cancer? Semin Radiat Oncol. 2018;28:131–7.
28. Pollack A. Cancer fight goes nuclear, with heavy price tag. New York, NY: New York Times; 2007. Available at: https://www.nytimes.com/2007/12/26/health/25cnd-proton.html. Accessed Oct 2018.
29. Wallner PE, Steinberg ML, Konski AA. Controversies in the adoption of new healthcare technologies. Front Radiat Ther Oncol. 2011;43:60–78.
30. Zietman AL, Bae K, Slater JD, Shipley WU, Efstathiou JA, Coen JJ, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. J Clin Oncol. 2010;28:1106–11.
31. Slater JD, Rossi CJ Jr., Yonemoto LT, Bush DA, Jabola BR, Levy RP, et al. Proton therapy for prostate cancer: the initial Loma Linda University experience. Int J Radiat Oncol Biol Phys. 2004;59:348–52.
32. Coen JJ, Zietman AL, Rossi CJ, Grocela JA, Efstathiou JA, Yan Y, et al. Comparison of high-dose proton radiotherapy and brachytherapy in localized prostate cancer: a case-matched analysis. Int J Radiat Oncol Biol Phys. 2012;82:e25–31.
33. Paganetti H, Giantsoudi D. Relative biological effectiveness uncertainties and implications for beam arrangements and dose constraints in proton therapy. Semin Radiat Oncol. 2018;28:256–63.
34. Girdhani S, Sachs R, Hlatky L. Biological effects of proton radiation: what we know and don't know. Radiat Res. 2013;179:257–72.
35. Paganetti H. Advancing (proton) radiation therapy. Int J Radiat Oncol Biol Phys. 2013;87:871–3.
36. Trofimov A, Nguyen PL, Coen JJ, Doppke KP, Schneider RJ, Adams JA, et al. Radiotherapy treatment of early-stage prostate cancer with IMRT and protons: a treatment planning comparison. Int J Radiat Oncol Biol Phys. 2007;69:444–53.
37. Vargas C, Fryer A, Mahajan C, Indelicato D, Horne D, Chellini A, et al. Dose-volume comparison of proton therapy and intensity-modulated radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys. 2008;70:744–51.
38. Zhang X, Dong L, Lee AK, Cox JD, Kuban DA, Zhu RX, et al. Effect of anatomic motion on proton therapy dose distributions in prostate cancer treatment. Int J Radiat Oncol Biol Phys. 2007;67:620–9.
39. Pickles T, Graham P. What happens to testosterone after prostate radiation monotherapy and does it matter? J Urol. 2002;167:2448–52.
40. Segal RJ, Reid RD, Courneya KS, Sigal RJ, Kenny GP, Prud'-Homme DG, et al. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. J Clin Oncol. 2009;27:344–51.
41. Zagars GK, Pollack A. Serum testosterone levels after external beam radiation for clinically localized prostate cancer. Int J Radiat Oncol Biol Phys. 1997;39:85–89.
42. Davis EJ, Beebe-Dimmer JL, Yee CL, Cooney KA. Risk of second primary tumors in men diagnosed with prostate cancer: a population-based cohort study. Cancer. 2014;120:2735–41.
43. Murray L, Henry A, Hoskin P, Siebert FA, Venselaar J. ESTRO PgoG. Second primary cancers after radiation for prostate cancer: a systematic review of the clinical data and impact of treatment technique. Radiother Oncol. 2014;110:213–28.
44. Fontenot JD, Lee AK, Newhauser WD. Risk of secondary malignant neoplasms from proton therapy and intensity-modulated x-ray therapy for early-stage prostate cancer. Int J Radiat Oncol Biol Phys. 2009;74:616–22.
45. Rechner LA, Howell RM, Zhang R, Etzel C, Lee AK, Newhauser WD. Risk of radiogenic second cancers following volumetric modulated arc therapy and proton arc therapy for prostate cancer. Phys Med Biol. 2012;57:7117–32.
46. Yoon M, Ahn SH, Kim J, Shin DH, Park SY, Lee SB, et al. Radiation-induced cancers from modern radiotherapy techniques: intensity-modulated radiotherapy versus proton therapy. Int J Radiat Oncol Biol Phys. 2010;77:1477–85.
47. Moteabbed M, Trofimov A, Khan FH, Wang Y, Sharp GC, Zietman AL, et al. Impact of interfractional motion on hypofractionated pencil beam scanning proton therapy and VMAT delivery for prostate cancer. Med Phys. 2018; https://doi.org/10.1002/mp.13091. [Epub ahead of print].
48. Yu JB, Soulos PR, Herrin J, Cramer LD, Potosky AL, Roberts KB, et al. Proton versus intensity-modulated radiotherapy for prostate cancer: patterns of care and early toxicity. J Natl Cancer Inst. 2013;105:25–32.
49. Rubin DB. Bias reduction using Mahalanobis-metric matching. Biometrics. 1980;36:293–8.
50. Kim S, Shen S, Moore DF, Shih W, Lin Y, Li H, et al. Late gastrointestinal toxicities following radiation therapy for prostate cancer. Eur Urol. 2011;60:908–16.
51. Sheets NC, Goldin GH, Meyer AM, Wu Y, Chang Y, Sturmer T, et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. JAMA. 2012;307:1611–20.
52. Pan HY, Jiang J, Hoffman KE, Tang C, Choi SL, Nguyen QN, et al. Comparative toxicities and cost of intensity-modulated radiotherapy, proton radiation, and stereotactic body radiotherapy among younger men with prostate cancer. J Clin Oncol. 2018;36:1823–30.
53. Gray PJ, Paly JJ, Yeap BY, Sanda MG, Sandler HM, Michalski JM, et al. Patient-reported outcomes after 3-dimensional conformal, intensity-modulated, or proton beam radiotherapy for localized prostate cancer. Cancer. 2013;119:1729–35.
54. Fang P, Mick R, Deville C, Both S, Bekelman JE, Christodouleas JP, et al. A case-matched study of toxicity outcomes after proton therapy and intensity-modulated radiation therapy for prostate cancer. Cancer. 2015;121:1118–27.
55. Mendenhall NP, Li Z, Hoppe BS, Marcus RB Jr., Mendenhall WM, Nichols RC, et al. Early outcomes from three prospective

trials of image-guided proton therapy for prostate cancer. Int J Radiat Oncol Biol Phys. 2012;82:213–21.
56. Hoppe BS, Michalski JM, Mendenhall NP, Morris CG, Henderson RH, Nichols RC, et al. Comparative effectiveness study of patient-reported outcomes after proton therapy or intensity-modulated radiotherapy for prostate cancer. Cancer. 2014;120:1076–82.
57. Hoppe BS, Nichols RC, Henderson RH, Morris CG, Williams CR, Costa J, et al. Erectile function, incontinence, and other quality of life outcomes following proton therapy for prostate cancer in men 60 years old and younger. Cancer. 2012;118:4619–26.
58. Ho CK, Bryant CM, Mendenhall NP, Henderson RH, Mendenhall WM, Nichols RC, et al. Long-term outcomes following proton therapy for prostate cancer in young men with a focus on sexual health. Acta Oncol. 2018;57:582–8.
59. Nichols RC Jr., Morris CG, Hoppe BS, Henderson RH, Marcus RB Jr., Mendenhall WM, et al. Proton radiotherapy for prostate cancer is not associated with post-treatment testosterone suppression. Int J Radiat Oncol Biol Phys. 2012;82:1222–6.
60. Henderson RH, Hoppe BS, Marcus RB Jr., Mendenhall WM, Nichols RC, Li Z, et al. Urinary functional outcomes and toxicity five years after proton therapy for low- and intermediate-risk prostate cancer: results of two prospective trials. Acta Oncol. 2013;52:463–9.
61. Iwata H, Ishikawa H, Takagi M, et al. Long-term outcomes of proton therapy for prostate cancer in Japan: a multi-institutional survey of the Japanese Radiation Oncology Study Group. Cancer Med. 2018;7:677–89.
62. Massett M. Protons for prostate cancer: Bragging points, trials, and treatment optimization. Appl Rad. Oncol. 2017;6:24–7.
63. Cuaron JJ, Harris AA, Chon B, Tsai H, Larson G, Hartsell WF, et al. Anterior-oriented proton beams for prostate cancer: a multi-institutional experience. Acta Oncol. 2015;54:868–74.
64. Trofimov A, Nguyen PL, Efstathiou JA, Wang Y, Lu HM, Engelsman M, et al. Interfractional variations in the setup of pelvic bony anatomy and soft tissue, and their implications on the delivery of proton therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. 2011;80:928–37.
65. Yoon M, Shin D, Kwak J, Park S, Lim YK, Kim D, et al. Characteristics of movement-induced dose reduction in target volume: a comparison between photon and proton beam treatment. Med Dosim. 2009;34:191–201.
66. Athar BS, Bednarz B, Seco J, Hancox C, Paganetti H. Comparison of out-of-field photon doses in 6 MV IMRT and neutron doses in proton therapy for adult and pediatric patients. Phys Med Biol. 2010;55:2879–91.
67. Brenner DJ, Elliston CD, Hall EJ, Paganetti H. Reduction of the secondary neutron dose in passively scattered proton radiotherapy, using an optimized pre-collimator/collimator. Phys Med Biol. 2009;54:6065–78.
68. Robertson JB, Williams JR, Schmidt RA, Little JB, Flynn DF, Suit HD. Radiobiological studies of a high-energy modulated proton beam utilizing cultured mammalian cells. Cancer. 1975; 35:1664–77.
69. Moteabbed M, Trofimov A, Sharp GC, Wang Y, Zietman AL, Efstathiou JA, et al. A prospective comparison of the effects of interfractional variations on proton therapy and intensity modulated radiation therapy for prostate cancer. Int J Radiat Oncol Biol Phys. 2016;95:444–53.
70. Moteabbed M, Sharp GC, Wang Y, Trofimov A, Efstathiou JA, Lu HM. Validation of a deformable image registration technique for cone beam CT-based dose verification. Med Phys. 2015;42: 196–205.
71. Hamstra DA, Mariados N, Sylvester J, Shah D, Karsh L, Hudes R, et al. Continued benefit to rectal separation for prostate radiation therapy: final results of a phase III trial. Int J Radiat Oncol Biol Phys. 2017;97:976–85.
72. Underwood TS, Voog JC, Moteabbed M, Tang S, Soffen E, Cahlon O, et al. Hydrogel rectum-prostate spacers mitigate the uncertainties in proton relative biological effectiveness associated with anterior-oblique beams. Acta Oncol. 2017;56: 575–81.
73. Thompson IM, Valicenti RK, Albertsen P, Davis BJ, Goldenberg SL, Hahn C, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. J Urol. 2013;190:441–9.
74. Swisher-McClure S, Yin L, Rosen M, Batra S, Berman AT, Both S, et al. Prospective MRI-based imaging study to assess feasibility of proton therapy for post-prostatectomy radiation. Acta Oncol. 2016;55:828–33.
75. Deville C, Jr., Jain A, Hwang WT, Woodhouse KD, Both S, Wang S, et al. Initial report of the genitourinary and gastrointestinal toxicity of post-prostatectomy proton therapy for prostate cancer patients undergoing adjuvant or salvage radiotherapy. Acta Oncol. 2018;57:1–9.
76. Aizer AA, Yu JB, McKeon AM, Decker RH, Colberg JW, Peschel RE. Whole pelvic radiotherapy versus prostate only radiotherapy in the management of locally advanced or aggressive prostate adenocarcinoma. Int J Radiat Oncol Biol Phys. 2009;75:1344–9.
77. Vees H, Dipasquale G, Nouet P, Zilli T, Cozzi L, Miralbell R. Pelvic lymph node irradiation including pararectal sentinel nodes for prostate cancer patients: treatment optimization comparing intensity modulated X-rays, volumetric modulated arc therapy, and intensity modulated proton therapy. Technol Cancer Res Treat. 2015;14:181–9.
78. Chera BS, Vargas C, Morris CG, Louis D, Flampouri S, Yeung D, et al. Dosimetric study of pelvic proton radiotherapy for high-risk prostate cancer. Int J Radiat Oncol Biol Phys. 2009;75:994–1002.
79. Morgan SC, Hoffman K, Loblaw D, Buyyounouski MK, Patton C, Barocas D, et al. Hypofractionated radiation therapy for localized prostate cancer: An ASTRO, ASCO, and AUA evidence-based guideline. J Clin Oncol. 2018; JCO1801097, https://doi.org/10.1200/JCO.18.01097. [Epub ahead of print].
80. Goddard LC, Brodin NP, Bodner WR, Garg MK, Tome WA. Comparing photon and proton-based hypofractionated SBRT for prostate cancer accounting for robustness and realistic treatment deliverability. Br J Radiol. 2018;91:20180010.
81. Kole TP, Nichols RC, Lei S, Wu B, Huh SN, Morris CG, et al. A dosimetric comparison of ultra-hypofractionated passively scattered proton radiotherapy and stereotactic body radiotherapy (SBRT) in the definitive treatment of localized prostate cancer. Acta Oncol. 2015;54:825–31.
82. Stapinski, H. The high-tech, big-footprint Cancer center. New York, NY: New York Times; 2017. Available at: https://www.nytimes.com/2017/12/26/nyregion/the-high-tech-big-footprint-cancer-center.html. Accessed Oct. 2018.
83. Konski A. Cost effectiveness of prostate cancer radiotherapy. Transl Androl Urol. 2018;7:371–7.
84. 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;25:3603–8.
85. Thaker NG, Ali TN, Porter ME, Feeley TW, Kaplan RS, Frank SJ. Communicating value in health care using radar charts: a case study of prostate cancer. J Oncol Pract. 2016;12:813–20.
86. Yu JB, Efstathiou JA, Bekelman JE. Proton radiotherapy for prostate cancer: how did we get here, and where do we go from here? Oncology 2013;27:1293–4.
87. Shah A, Ricci KI, Efstathiou JA. Beyond a moonshot: insurance coverage for proton therapy. Lancet Oncol. 2016;17:559–61.
88. Bekelman JE, Denicoff A, Buchsbaum J. Randomized trials of proton therapy: why they are at risk, proposed solutions, and implications for evaluating advanced technologies to diagnose and treat cancer. J Clin Oncol. 2018;36:2461–4.

89. ASTRO model policies: Proton beam therapy, 2017. Available at: https://www.astro.org/uploadedFiles/_MAIN_SITE/Daily_Practice/Reimbursement/Model_Policies/Content_Pieces/ASTROPBTModelPolicy.pdf. Accessed Nov 2018.
90. Oklahoma Insurance Department - Legislative Changes, 2015. Available at: https://www.ok.gov/oid/documents/100215_2015%20OID%20Legislative%20Update-reducedsize.pdf. Accessed Oct 2018.
91. Bortfeld TR, Loeffler JS. Three ways to make proton therapy affordable. Nature. 2017;549:451–3.
92. Bekelman JE, Hahn SM. Reference pricing with evidence development: a way forward for proton therapy. J Clin Oncol. 2014;32:1540–2.