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Urologic Oncology: Seminars and Original Investigations 37 (2019) 628–636

UROLOGIC ONCOLOGY

Seminars article

Proton therapy for prostate cancer: A review of the rationale, evidence, and current state

Trevor J. Royce, M.D., M.S., M.P.H.[a,*], Jason A. Efstathiou, M.D., D.Phil.[b]

[a] *Department of Radiation Oncology, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC*
[b] *Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA*

Received 18 September 2018; received in revised form 7 November 2018; accepted 12 November 2018

Abstract

Men diagnosed with localized prostate cancer have many curative treatment options including several different radiotherapeutic approaches. Proton radiation is one such radiation treatment modality and, due to its unique physical properties, offers the appealing potential of reduced side effects without sacrificing cancer control. In this review, we examine the intriguing dosimetric rationale and theoretical benefit of proton radiation for prostate cancer and highlight the results of preclinical modeling studies. We then discuss the current state of the clinical evidence for proton efficacy and toxicity, derived from both large claim-based datasets and prospective patient-reported data. The result is that the data are mixed, and clinical equipoise persists in this area. We place these studies into context by summarizing the economics of proton therapy and the changing practice patterns of prostate proton irradiation. Finally, we await the results of a large prospective randomized clinical trial currently accruing and also a large prospective pragmatic comparative study which will provide more rigorous evidence regarding the clinical and comparative effectiveness of proton therapy for prostate cancer.

Keywords: Prostate; Radiation; Protons

1. Introduction

Prostate cancer is the most common new cancer diagnosis among men in the United States [1] and the great majority are diagnosed with localized disease [2]. Localized prostate cancer patients have several curative guideline-recommended treatment options, including surgical removal (i.e., radical prostatectomy) and radiation therapy [3]. Radiation therapy can be delivered via brachytherapy (the physical placement of radioactive sources within the prostate), or more commonly with external beam radiation therapy (EBRT), or a combination thereof. EBRT can be delivered via photons or particle therapy (e.g., protons).

EBRT was traditionally delivered with three-dimensional conformal radiation therapy but has been replaced by intensity modulated radiation therapy (IMRT) as the standard of care [4]. IMRT achieves great conformality, optimizing radiation dose deposition within the target (i.e., the prostate) while sparing the adjacent normal tissues (e.g., the bladder and rectum) [5], thereby increasing the therapeutic ratio. Proton beam therapy (PBT), a radiotherapeutic technique with unique physical properties that has been used in prostate cancer since the 1970s [6], may increase the therapeutic ratio by further minimizing the normal tissue exposure to radiation—a feature that is particularly advantageous for pediatric cancers and tumors of the central nervous system [7]. However, for prostate cancer, PBT has remained one of the more controversial topics in radiation therapy for the last decade, largely due to the high cost associated with treatment for an unknown benefit [8,9]. Herein, we review the rationale, evidence, and current state of PBT for localized prostate cancer.

Funding/Support: JAE serves as the principal investigator of the PARTIQoL multi-center randomized phase III 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.

*Corresponding author. Tel.: 984-974-0400; fax: 984-974-8607.
E-mail address: trevor_royce@med.unc.edu (T.J. Royce).

https://doi.org/10.1016/j.urolonc.2018.11.012
1078-1439/

2. Theoretical benefit

Traditional EBRT, such as IMRT, is delivered via high-energy photons that deposit dose in a characteristic pattern involving an initial buildup of deposited energy after the beam enters the patient, followed by an exponential decrease as the beam travels through tissue. Conversely, protons, which are relatively large charged particles and therefore have different physical properties, deposit most of their energy at the end of their path through tissue, a phenomenon called the "Bragg Peak" (Fig. 1). The energy of the proton beam can be modulated so that the Bragg Peak exists at the target, and therefore results in an absence of dose deposition beyond the target. This may permit greater low-dose sparing of the normal tissue (Fig. 2) [10].

The potential dosimetric benefit of PBT for prostate cancer has been demonstrated in a number of modeling studies comparing PBT plans to photon IMRT plans [11–22]. While these studies have consistently demonstrated that the coverage of the prostate is essentially equivalent between IMRT and PBT, they also consistently show that PBT can reduce the integral nontarget dose, or the total dose to the normal, nontarget structures outside the prostate, as shown in Fig. 2b. These dosimetric modeling studies are summarized in Table 1 with mean doses acting as a rough surrogate for integral nontarget dose. However, when considering metrics of higher doses delivered to the adjacent normal structures, the superiority of PBT is less clear. For example, Table 1 also summaries the "rectal V70," or the volume of the rectum receiving 70 Gy or more, between photon vs. proton plans, and the metrics are more similar between the 2 modalities across studies, with some studies even showing a slight disadvantage with PBT [13,20]. Aside from the rectum and bladder dosimetry shown in Table 1, an avoidance structure metric, which is underreported in these studies, is the dose to the femoral heads. PBT delivered using 2 lateral beams can result in higher

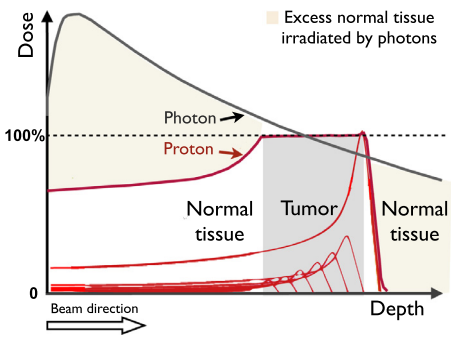

Fig. 1. Dose-depth curve for proton vs. photon irradiation. The photon curve (grey) shows dose deposition with an initial build-up region followed by an exponential decrease as the beam goes deeper in tissue. The proton curve (burgundy) is the summation of several "Bragg peaks" (red curves) permitting dose deposition over a specific depth in tissue (e.g., the target). The beige-shaded regions demonstrate areas of excessive normal tissue irradiation by photons that could otherwise be spared by protons. (Color version of figure is available online.)

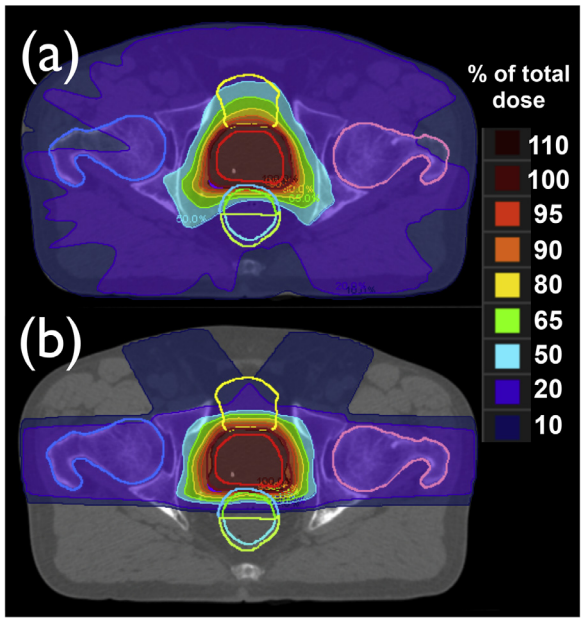

Fig. 2. Proton vs. intensity-modulated photon prostate radiation plans. Identical cross sectional computed tomography images of the pelvis showing the prostate (outlined in red), bladder (yellow), rectum (light blue/green), and bilateral femoral heads (dark blue and pink) outlined. The color wash shows the radiation dose (in %) being deposited to any given area. The prostate is receiving 100% of the dose. A) The intensity modulated radiation therapy plan shows much of the cross section receiving a "low-dose bath" of at least 20% of the dose (in purple) whereas B) shows the proton plan, which spares many of the normal tissues, such as large parts of the rectum, of this low-dose radiation. (Color version of figure is available online.)

femoral head doses which may increase fracture risk [18,23]; this dose can be mitigated with alternative field angles such as anterior oblique beams (Fig. 2b) [24].

Important limitations of these dosimetric studies are their heterogeneous designs and also that over time the sophistication of both photon and proton delivery techniques (e.g., for protons, passive scatting vs. pencil beam scanning [8,25], for photons, IMRT vs. volumetric arc therapy [14]) continue to improve, which may further tilt the dosimetric advantage of one modality over the other. Also worth noting is the increasing adoption of photon-based stereotactic body radiation therapy, which allows the precise delivery of high doses of radiation over a few treatments. Stereotactic body radiation therapy is a guideline-support radiotherapeutic technique, which has its own dosimetric and radiobiological advantages, a discussion of which is beyond the scope of this review [3]. Finally, novel techniques to minimize the risk to the normal nontarget structures, such as the placement of hydrogel between the rectum and prostate, have had promising results and may further improve the dosimetry of radiation plans [26].

The sparing of normal tissues from radiation exposure is a high priority for the radiation oncologist, perhaps second only to cancer cure. The "ALARA" approach, or "as low as

Table 1
Summary of dosimetric modeling studies comparing photon vs. proton-based prostate radiation plans regarding select normal tissue dose metrics. Studies used heterogeneous treatment techniques, target volumes, patient populations and prescriptions, so data are provided for comparison only within studies, not across studies. Proton doses are reported in gray-equivalents or relative biological effectiveness.

Metric	Study	Photon	Proton
Mean, nontarget tissues (% Rx)[a]	Cella et al., 2001 [11]	12.4%	9.5%
Mean, nontarget tissues[a]	Mock et al., 2005 [12]	11.9 Gy	6.3 Gy
Mean, rectum	Trofimov et al., 2007 [15]	39.4 Gy	29.2 Gy
	Vargas et al., 2008 [16]	34.8 Gy	14.2 Gy
	Dowdell et al., 2008 [17]	NR	31.7 Gy
	Chera et al., 2009 [18]	40.9 Gy	16.6 Gy
	Schwarz et al., 2011 [19]	36.5 Gy	25.0 Gy
	Georg et al., 2014 [20]	28.2 Gy	19.5 Gy
	Vees et al., 2015 [21]	46.2 Gy	22.4 Gy
	Scobioala et al., 2016 [22]	17.3 Gy	9.00 Gy
	Tran et al., 2017 [13],[b]	24.0 Gy	25.0 Gy
	Rana et al., 2017 [14]	41.9 Gy	16.9 Gy
Mean, Bladder	Trofimov et al., 2007 [15]	29.9 Gy	24.1 Gy
	Vargas et al., 2008 [16]	28.9 Gy	18.4 Gy
	Dowdell et al., 2008	22.8 Gy	9.40 Gy
	Chera et al., 2009 [18]	42.1 Gy	21.2 Gy
	Schwarz et al., 2011 [19]	40.4 Gy	22.2 Gy
	Georg et al., 2014 [20]	16.0 Gy	12.4 Gy
	Vees et al., 2015 [21]	50.4 Gy	22.3 Gy
	Scobioala et al., 2016 [22]	17.4 Gy	13.3 Gy
	Tran et al., 2017 [13],[b]	22.0 Gy	18.0 Gy
	Rana et al., 2017 [14]	32.5 Gy	17.5 Gy
Rectum V70[c]	Cella et al., 2001 [11][b]	8%	18%
	Mock et al., 2005 [12],[b,c]	37%	23%
	Trofimov et al., 2007 [15]	15%	14%
	Vargas 2008[b]	14%	8%
	Dowdell et al., 2008 [17],[b]	19%	24%
	Chera et al., 2009 [18][b]	15%	12%
	Schwarz et al., 2011 [19],[b]	1%	1%
	Georg et al., 2014 [20]	4.1 ml	4.5 ml
	Vees et al., 2015 [21],[b]	15%	3%
	Scobioala et al., 2016 [22]	1.1%	1.0%
	Tran et al., 2017 [13],[b]	10 ml	15 ml
	Rana et al., 2017 [14]	12.8%	6.9%
BladderV70[c]	Cella et al., 2001 [11],[b]	0%	0%
	Mock et al., 2005 [12],[b,c]	12%	10%
	Trofimov 2007	11%	17%
	Vargas et al., 2008 [16],[b]	15%	13%
	Dowdell 2008[b]	7%	8%
	Chera et al., 2009 [18],[b]	14%	14%
	Schwarz et al., 2011 [19],[b]	17%	15%
	Georg et al., 2014 [20]	3.2 ml	3.4 ml
	Vees et al., 2015 [21],[b]	25%	5%
	Scobioala et al., 2016 [22]	6.0%	5.3%
	Tran et al., 2017 [13],[b]	17 ml	19 ml
	Rana et al., 2017 [14]	10.5%	9.7%

[a] Reported the mean dose to all normal tissues (rectum, bladder, and femoral heads).
[b] Estimated from manuscript figures.
[c] Volume (%) getting 70 Gy, unless otherwise specified.
Abbreviation: NR, not reported.

reasonably achievable," is a fundamental principle of radiation oncology dictating that the lower dose exposure one can achieve to normal structures, the better [27]. This principle is driven in part by the rare but feared long-term risk of second malignancies caused by radiation [28,29]. One systematic review found the risk of radiation-induced second malignancy after prostate cancer to be from 1 in 220 to 290 men (<0.5%) and dependent, in part, on length of follow-up. How much the use of PBT with its lower total body dose of radiation could decrease the risk of second cancer in prostate cancer patients is unclear, but remains a theoretical benefit [30,31]. Dosimetric modeling studies have consistently shown secondary malignancy risk reduction with proton techniques, with some studies showing the risk reduced by more than 50% [31,32].

An additional open question in proton therapy is whether protons themselves demonstrate different mechanistic effects of radiation action on cells, and whether these effects have implications in regards to prostate cancer control [33]. How relatively effective protons are biologically compared to photons is an area of uncertainty and in need of further investigation. An improved understanding of the unique radiobiological characteristics of proton therapy could optimize their effectiveness [34,35].

Collectively, the aforementioned suggest that the known benefit of PBT lies largely in the potential sparing of normal tissues from lower dose exposure. This is a particularly appealing feature in the treatment of prostate cancer, where the majority of patients with their low-risk disease will have excellent disease outcomes among several competing treatment choices [36]. Many men, particularly those with minimal comorbidity, will live years after treatment and thus deal with the post-treatment morbidity. Consequently, the impact on quality of life (QoL) in the treatment of prostate cancer is paramount [37,38]. If the normal tissues can be better spared with PBT, and thus minimize treatment-related toxicity, perhaps there is a therapeutic advantage in regards to QoL. However, it remains unclear whether the primary toxicities from prostate cancer radiation, namely gastrointestinal (GI; i.e., rectal) and genitourinary (GU; i.e., bladder and erectile dysfunction) toxicities, are driven by the higher point doses to the organs at risk or the lower integral doses; if they are driven by the latter, then PBT becomes increasingly appealing. To help answer this type of question, radiation oncologists formed a working group called QUANTEC, or the Quantitative Analysis of Normal Tissue Effects in the Clinic, who modeled the risk of normal tissue toxicity across radiation doses. Their results suggest that higher rectal (e.g., ≥60 Gy) and bladder (e.g., ≥65 Gy) doses may be the primary drivers of increased toxicity risk [39,40].

In summary, PBT has the exciting potential to lessen treatment-related morbidity, compared to the standard radiation treatment of photon-based IMRT, by reducing the volume of normal tissue exposed to radiation [41,42].

Table 2
Available clinical evidence comparing the toxicity of proton beam therapy to intensity modulated radiation therapy for localized prostate cancer

	Study type	Years	Database	Sample size		Toxicity with protons relative to IMRT				Reference
				Photons	Protons	GI	GU	Sexual	ACT	
1.	Claim-based	1992–2005	SEER-Medicare	4445	337	Incr[a]	-	-	-	Kim et al., 2011 [55]
2.	Claim-based	2000–2009	SEER-Medicare	684	684	Incr[b]	No diff[b]	No diff[b]	No diff[c]	Sheets et al., 2012 [4]
3.	Claim-based	2008–2009	Medicare	628	314	No diff[d]	No diff[d]	-	-	Yu et al., 2012 [56]
4.	Claim-based	2008–2015	MarketScan	3,465	693	Incr[h]	Decr[h]	Decr[h]	-	Pan et al., 2018 [57]
5.	Prospective, patient-reported	2003–2008	MGH, PROST-QA	153	95	No diff[e]	No diff[e]	-	-	Gray et al., 2013 [58]
6.	Prospective, patient-reported	2003–2010	UF, PROST-QA	204	1243	No diff[f]	No diff[f]	No diff[f]	-	Hoppe et al., 2014 [59]
7.	Prospective, provider-reported	2010–2012	UPENN	94	94	No diff[g]	No diff[g]	No diff[g]	-	Fang et al., 2015 [60]

Abbreviations: ACT = additional cancer therapy; Decr = decreased; IMRT = intensity-modulated radiation therapy; GI, gastrointestinal; GU, genitourinary; Incr = increased; MGH = Massachusetts General Hospital; No diff = no difference; PROST-QA = Prostate Cancer Outcome and Satisfaction with Treatment Quality Assessment Consortium; SEER, Surveillance, Epidemiology, and End Results Program; UF, University of Florida; UPENN, University of Pennsylvania.

[a] Any toxicity ≥6 months after diagnosis.

[b] Gastrointestinal, urinary, or erectile dysfunction events >1 year after treatment.

[c] Defined as additional cancer therapy, used as an indicator of disease recurrence.

[d] Proton therapy did have a significant reduction in genitourinary toxicity at 6 months but not at 1 year (1-year toxicity odds ratio).

[e] Proton beam therapy had improved bowel quality of life at 2 to 3 months post-treatment but no difference in bowel/rectal quality of life 1-year post-treatment. Urinary irritation/obstruction quality of life at 1-year post-treatment was worse with PBT, but no difference at 2 years follow-up.

[f] Difference at 1 year in summary scores. Proton beam therapy did have better in the specific domains of rectal urgency and bowel frequency.

[g] Acute (<90 days after treatment) and late toxicities (>90 days).

[h] At 2 years.

3. Clinical evidence

3.1. Efficacy

There is limited randomized data directly comparing the efficacy of protons vs. photons in prostate cancer. Massachusetts General Hospital, pioneers in PBT, conducted a randomized trial comparing 50.4 Gy of conventional photon radiation for T3 to T4 tumors followed by a photon boost of 16.8 Gy vs. a proton boost of 25.2 Gy(RBE). They found that the dose escalation with PBT did not improve disease control or survival and resulted in worse toxicity—but they used now-outdated radiation techniques (e.g., no IMRT), making this study mainly of historical interest [43].

Higher doses of radiation (at least 75.6 Gy of conventional fractionation [44]) are considered the standard in modern radiation therapy for prostate cancer. This is based on multiple randomized trials that have shown superiority in disease control with higher doses [45–49]—1 of these trials [49] used a 28.8 Gy(RBE) proton boost following 50.4 Gy of photons to achieve dose escalation. At 10 years, they found biochemical disease progression in 32.4% of the low-dose photon-only arm compared to 16.7% in the high-dose proton/photon arm ($P < 0.0001$), which is in line with the results of the other photon-only dose-escalation trials. Single institutional PBT experiences have also shown comparable efficacy to photon-based cohorts from similar eras [50,51], such as the Loma Linda experience of over 1,200 patients treated from 1991 to 1997 with a median follow-up of 62 months, which found an 8-year biochemical disease-free survival rate of 73% in men treated with PBT to 75 Gy(RBE) [52]. Another example is a case-matched analysis of nearly 400 patients which compared dose-escalated PBT to brachytherapy and found no difference in rates of disease control [53].

In summary, there is no high-level evidence to suggest that PBT is superior to photon-based therapies in regards to prostate cancer control [51,54]. As above, the theoretical benefit lies largely in the reduction of treatment-related morbidity, although the nuanced radiobiologic consequences of proton therapy need further investigation.

3.2. Toxicity: large retrospective database studies

While not prospective randomized trials, there are several clinical studies have examined the side effect profiles of these competing radiation techniques (Table 2). There are 4 primary large database studies that use billing code-derived data. The first was a 2011 study using the Surveillance Epidemiology and End Results (SEER)-Medicare data to evaluate GI toxicity in men with T1 to T2 prostate cancer treated with three-dimensional conformal radiation therapy, IMRT, brachytherapy, PBT, or conservative management treated from 1992 to 2005 [55]. On pairwise comparison, they found any GI toxicity ≥6 months after treatment to be over 3 times more likely with PBT than IMRT (hazard ratio [HR] 3.32, 95% confidence interval [CI]: 2.12–5.20). The incidence of GI toxicity in those treated with PBT decreased substantially for those treated in later years suggesting an improvement in PBT delivery technology. A second SEER study compared the late morbidity (>1 year from treatment) of IMRT and PBT for nonmetastatic prostate cancer patients treated from 2000 to 2009. In a propensity score analysis of 1,368 patients, they

found significantly fewer adverse GI events with IMRT compared to PBT (HR 0.66, 95% CI: 0.55–0.79), and no significant difference for GU events, or receipt of additional cancer therapy [4]. A third large database study-matched Medicare beneficiaries who received IMRT (n = 628) to those who received PBT (n = 314) from 2008 to 2009 [56]. They found PBT was associated with significantly lower risk of GU toxicity at 6 months compared to IMRT (HR 0.6, 95% CI 0.38–0.96) but found no difference in GU or GI toxicity at 12 months post-treatment. Finally, a fourth study used the MarketScan Commercial Claims and Encounter database, a nationwide, employment-based medical claims database of employees and dependents younger than 65 years of age from over 100 payers. With 693 proton patients and 3,465 IMRT patients from 2008–2015 they found PBT resulted in a lower risk of urinary and sexual toxicity at 2 years compared to IMRT (33% vs 42%, $p < 0.001$, and 21% vs 28%, $p < 0.001$, respectively) but greater bowel toxicity (20% vs 15%, $p = 0.02$) [57]. Limitations of these studies are the assumption that certain billing codes suggest toxicity (e.g., a screening colonoscopy procedure could be taken to indicate a GI toxicity event). Also, these studies generally have a relatively small number of proton patients compared to IMRT presenting opportunity for selection bias. Additionally, in the SEER studies, the proton patients were treated with earlier technology and likely came mostly from a single institution, due to the SEER geographic distribution and the few number of PBT centers at the time. For example, in Sheets et al., 80% of the PBT patients were from California, suggesting a single institution was overrepresented compared to the more diverse IMRT cohort [4]. The radiation details can also be difficult to accurately describe—the Kim et al. study, for example, could not adequately distinguish between proton-only vs. mixed proton/photon courses of radiation [55].

In summary, these retrospective claim-based studies rely on the validity of billing codes and lack important data on the specifics of treatment (e.g., radiation dose) and are not level I evidence. The data are mixed, but 3 of 4 suggest that GI toxicity may actually be worse with PBT.

3.3. Toxicity: prospective patient or provider-reported studies

Several studies have collected PBT and IMRT QoL data prospectively (Table 2). The first is from Massachusetts General Hospital, which looked at 95 men treated with PBT for localized prostate cancer from 2004 to 2008 and compared them to 153 men from 9 participating institutions who received IMRT from 2003 to 2006 [58]. Using validated instruments, patient-reported QoL scores were obtained at baseline, 3, 12, and 24 months from treatment. They found distinct patterns of toxicity between the modalities: patients who received IMRT reported significantly worse GI QoL compared to baseline at the first post-treatment follow-up, while PBT patients did not. At 12 and 24 months post-treatment, both groups reported decrements in GI QoL. At 24 months, neither group reported clinically meaningful changes in GU QoL. "Clinically meaningful" was defined as a decline exceeding half the standard deviation of the baseline mean value. A second study compared patient-reported QoL data at 2 years after treatment, collected prospectively using validated instruments in men treated with IMRT (n = 204, treated at 9 academic medical centers from 2003 to 2006) and PBT (n = 1,243, treated at the University of Florida from 2006 to 2010) [59]. They found no statistically significant difference in QoL scores in GU or GI domain summary scores. However, in the domains of rectal urgency and bowel frequency, they found men who received PBT did significantly better. Finally, a third study, this one from the University of Pennsylvania, conducted a matched comparison of prospectively collected provider-reported toxicity data on patients with localized prostate cancer treated with PBT (n = 191, median follow-up of 29 months) and IMRT (n = 213, median follow-up of 47 months) treated from 2010 to 2012 [60]. In the matched analysis, they found no statistically significant difference between IMRT and PBT in the risk of Common Terminology Criteria for Averse Events' acute or late GI or GU grade ≥2 toxicity.

Of note, there also exist some intriguing preliminary data suggesting that PBT may have QoL implications beyond what has been investigated. One example is the idea that PBT better preserves testosterone levels after treatment compared to EBRT, thought to be due partly to PBT's lower integral dose and testicular exposure [61]. This has not yet been well studied.

In summary, the data are mixed, with neither large database analyses nor prospectively collected toxicity data consistently demonstrating QoL superiority with protons or photons. Clinical equipoise persists in this area.

4. Practice patterns and economics

To this point, we have summarized the theoretical and clinical evidence regarding the superiority, if any, of proton therapy over standard IMRT. Essential to understanding the controversy of PBT for prostate cancer, one must also appreciate the economics and practice patterns of these competing modalities.

The value (healthcare outcomes divided by cost [62]) of PBT for prostate cancer has been questioned [63–67]. The adoption of expensive technologies with unproven benefit in radiation oncology has invited scrutiny to the specialty, and prostate cancer epitomizes this [68,69]. Traditional PBT facilities require large infrastructure support for their complex operation and have high upfront capital costs [70,71]. Reports have 28 PBT centers operating in the United States and, when including those under construction or planned, the numbers double [72]. Roughly, half of the currently operating centers treated their first patient only within the last 5 years [73]. Some of these centers may have initially been planned on the assumed economic viability of treating prostate cancer patients, a common diagnosis requiring many weeks of daily EBRT, with the

technology marketed directly to consumers [74–76]. However, the financial models and patient mix of proton centers are likely continuously adapting with the changing insurance coverage landscape and evolving clinical data. While PBT remains a small fraction of all EBRT for prostate cancer in the United States, its use more than doubled from 2004 to 2012, with the PBT rate going from 2.3% to 4.8% [74,77]. Available estimates show PBT to be about 1.5–2× as expensive as IMRT [57]. Using 2008 to 2009 data, the median Medicare reimbursement for protons was $32,428 compared to $18,575 for IMRT. A 2007 modeling study found the cost of PBT at 15 years to be $63,511 vs. $36,808 for IMRT. The authors concluded that PBT was not a cost-effective option, even when modeled under a favorable assumptions [78]. Others have reached similar conclusions [79,80] and a recent review of the cost-effectiveness of IMRT and proton therapy for prostate cancer found that the quality of available evidence to be "very low" [81].

The proton "bubble" may have popped to some degree, as some centers have closed or struggled due to tenuous finances with lagging demand and insurance coverage difficulties [73,75,82]. The New York Times recently reported that "nearly a third of existing proton centers lose money, have defaulted on debt, or have had to overhaul their finances" [75]. This has led to a re-evaluation of proton centers' priorities. There is a trend toward smaller centers as PBT in the modern era becomes cheaper and less cumbersome. While they remain expensive, centers are now being developed with a single treatment room costing $15 to 25 million, compared to the traditional facilities with multiple treatment rooms costing over $100 million to build [9]. For prostate cancer, the durations of treatment are shortening in length, which would further decrease the price discrepancy between PBT and IMRT [44,83,84]. There are also progressive healthcare policy initiatives, such as reference pricing motivating evidence development, whereby competing treatment modalities would have a common level of payment therefore reducing the financial barriers to evidence development [73,85]. Finally, as technological advances continue to increase the applicability (i.e., clinical utility) and optimization of PBT dose delivery [24,86–89], it may become more affordable and efficacious [73,90].

5. Future studies

The need for randomized trials evaluating PBT has been argued for over a decade [41,69,91]. In 2015, the Department of Veterans Affairs issued a report on the comparative effectiveness of PBT and specifically highlighted the lack of reliable data from long-term randomized trials [92]. Challenges exist, including multiple treatment options, patient preference, and insurance coverage difficulties for PBT patients on trial despite clinical equipoise [93]. Insurance barriers have resulted in some states passing legislation prohibiting health benefit plans from holding PBT to a higher standard of clinical evidence than IMRT [94]. Fortunately, a multicenter randomized trial comparing PBT to IMRT is underway (Prostate Advanced Radiation Technologies Investigating Quality of Life, PARTIQoL; NCT01617161) which is accruing well despite these challenges with 12 proton centers and 27 facilities participating—completed accrual of 400 patients is expected by late 2019. This study is randomizing men to receive dose-escalated prostate irradiation delivered with either PBT or IMRT. The primary endpoint will focus on QoL and will compare the reduction in mean GI QoL scores at 24 months after radiation between the 2 arms. Secondary outcomes include disease-specific QoL, cost effectiveness, and dosimetry analyses including the radiation dose to the bowel. Preliminary dosimetric studies have demonstrated the robustness of treatment delivery techniques in both trial arms, reinforcing investigator confidence in a fair comparison [95]. There is also a recently opened large, prospective, pragmatic, controlled comparison study (A Prospective Comparative Study of Outcomes with Proton and Photon Radiation in Prostate Cancer, COMPPARE; NCT03561220) which will evaluate the QoL and cancer outcomes for 1,500 PBT patients and 1,500 IMRT patients treated in 42 US centers. The hope is that these trials will finally clarify whether the promising dosimetry of protons, driven by their unique physical properties, is manifested in improved clinical outcomes (e.g., improved QoL or reduced treatment-related toxicity), for patients with localized prostate cancer.

Financial disclosures and conflicts of interest

JAE serves as the principal investigator of the PARTI-QoL multi-center randomized phase III 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.

Acknowledgments

Special thanks to Maryam Moteabbed, PhD, from the Massachusetts General Hospital Department of Radiation Oncology, Boston, Massachusetts, for help with the Figures.

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