Technical Innovations & Patient Support in Radiation Oncology 11 (2019) 1–13

Contents lists available at ScienceDirect

Technical Innovations & Patient Support in Radiation Oncology

journal homepage: www.elsevier.com/locate/tipsro

Review article

Proton therapy- the modality of choice for future radiation therapy management of Prostate Cancer?

Sophie Mangan, Michelle Leech *

Applied Radiation Therapy Trinity, Discipline of Radiation Therapy, Trinity College Dublin, Dublin 2, Ireland

ARTICLE INFO

Article history:
Received 1 November 2018
Received in revised form 9 August 2019
Accepted 30 August 2019
Available online 11 October 2019

Keywords:
Prostate cancer
Proton therapy
Photon therapy

ABSTRACT

Background: Proton Therapy (PR) is an emerging treatment for prostate cancer (Pca) patients. However, limited and conflicting data exists regarding its ability to result in fewer bladder and rectal toxicities compared to Photon Therapy (PT), as well as its cost efficiency and plan robustness.
Materials and Methods: An electronic literature search was performed to acquire eligible studies published between 2007 and 2018. Studies comparing bladder and rectal dosimetry or Gastrointestinal (GI) and Genitourinary (GU) toxicities between PR and PT, the plan robustness of PR relative to motion and its cost efficiency for Pca patients were assessed.
Results: 28 studies were eligible for inclusion in this review. PR resulted in improved bladder and rectal dosimetry but did not manifest as improved GI/GU toxicities clinically compared to PT. PR plans were considered robust when specific corrections, techniques, positioning or immobilisation devices were applied. PR is not cost effective for intermediate risk Pca patients; however PR may be cost effective for younger or high risk Pca patients.
Conclusion: PR offers improved bladder and rectal dosimetry compared to PT but this does not specifically translate to improved GI/GU toxicities clinically. The robustness of PR plans is acceptable under specific conditions. PR is not cost effective for all Pca patients.

© 2019 The Authors. Published by Elsevier B.V. on behalf of European Society for Radiotherapy & Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Contents

Abbreviations: PR, Proton Therapy; PT, Photon Therapy; IMRT, Intensity Modulated Radiation Therapy; GI, Gastrointestinal; GU, Genitourinary; QALY, Quality-Adjusted Life Year; RTOG, Radiation Therapy Oncology Group; HT, Helical Tomography; SW, Sliding Window; RA, Rapid Arc; CTCAE, Common Terminology Criteria Adverse Effects; IPSS, International Prostate Symptom Scale; EPIC, Expanded Prostate Cancer Index Composite; VMAT, Volumetric Modulated Arc Therapy; USPT, Uniform Scanning Proton Therapy; LR, Low Risk; int/HR, intermediate/High risk; RBE, Radiobiological Effectiveness; MFO-IMPR, Multi Field Optimisation-Intensity Modulated Proton Therapy; PBS, Pencil Beam Scanning; US, Uniform Scanning; SFUD, Single Field Uniform-Dose; SBRT, Stereotactic Body Radiation; BT, Brachytherapy; 3DC-PR, 3D Conformal- Proton Therapy; IMPR, Intensity Modulated Proton Therapy; CT, Computed Tomography; ITV, Internal Target Volume; IGRT, Image Guidance Radiation Therapy.

* Corresponding author.
E-mail address: leechm@tcd.ie (M. Leech).

https://doi.org/10.1016/j.tipsro.2019.08.001
2405-6324/© 2019 The Authors. Published by Elsevier B.V. on behalf of European Society for Radiotherapy & Oncology.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Over the last decade, the clinical application of Proton Therapy (PR) for Prostate Cancer (Pca) patients has grown rapidly. However, much controversy still remains as to whether its improved dosimetry translates to clinically meaningful reductions in toxicities compared to Photon Therapy (PT). Similarly, controversy surrounds the robustness of PR plans as well as the cost-benefit of PR for Pca patients.

With the implementation of PSA screening, an increasing number of Pca cases are being diagnosed [1] with PT playing a major role in its management. PR is considered one of the more advanced radiotherapy options in the treatment of Pca patients in recent decades, of which treatment planning and delivery techniques continue to evolve and improve by reducing the dose delivered to healthy tissues [2]. With the proven benefit of protons in the management of sites such as medulloblastoma [3] and base of skull chordoma [4], owing to the unique dose distribution of protons [5], and their ability to reduce entrance/exit dose caused by the Bragg Peak [6–8], efforts have been made to translate this benefit to other sites, such as Pca.

It has been determined that the spread out Bragg peak (SOBP) results in a highly localised deposition of energy, which can be utilised for increasing dose to tumours while minimising irradiation to adjacent normal tissues [9]. Therefore, the expectation is that PR will provide improved dosimetry and hence fewer toxicities to organs at risk such as bladder and rectum. However, given the increased sensitivity of the Bragg Peak to motion caused by rectal and bladder filling, plan robustness remains a major concern alongside the cost efficiency of this treatment modality.

As of 2015, there were 43 PR centres in the world, and approximately 50% of them are located in the USA and Japan. There has been a substantial increase in the number of proton facilities built, and direct-to-consumer advertising is likely to lead to an increase in its use [10–13]. To date, more than 95,000 patients have been treated with PR worldwide [14].

The dosimetric benefits to bladder and rectal constraints of PR compared to PT are well established [15,16]. However, despite the planning gains, no randomised control trial (RCT) data exists as to whether bladder and rectal dosimetric improvements translate to clinically meaningful improved GU and GI toxicities compared to PT. An RCT comparing PT and Intensity Modulated Radiation Therapy (IMRT) has been opened, however the comparative impact on late effects will not be known for some years (NCT01617161) [17].

One major concern with PR for Pca is its increased sensitivity to target motion because of the steep dose depletion beyond the SOBP [18,19]. As the prostate is not in a fixed position and varies depending on bladder and rectal filling [20], concern exists in relation to the effect of inter and intrafraction motion on the dose distributions achieved with PR. Some studies have investigated the sensitivities of PR plans to motion and provide suggestions as to how to improve the robustness of plans caused by the relative motions.

Cost efficiency is an important consideration given that the estimated cost of a PR facility for Pca patients is $180 million [20]. Few studies have been conducted to evaluate the cost effectiveness of PR for Pca patients and of those available the cost per QALY data displays conflicting conclusions [21]. It has been suggested that the study of cost benefit in relation to the clinical significance of PR for these patients is lacking mainly due to the dearth of clinical and toxicity data available [22,23].

The primary aim of this paper is to ascertain whether PR results in improved bladder and rectum dosimetry and subsequently, fewer toxicities, the secondary aim is to review issues of plan robustness and cost efficiency of PR compared to PT in the management of Pca patients.

Methods and materials

Search strategy for identification of studies

An electronic search was carried out using the following databases: PubMed, Embase and ScienceDirect. The search terms used are outlined in Appendix 1. Search strategies commenced on 13th February 2016. References from the data collected were hand searched to ensure any additional relevant studies were considered. Predefined inclusion and exclusion criteria were used to select the appropriate interventions of interest for this study as outlined below the final electronic search took place on the 13th September 2018.

Prospective and retrospective cohort studies, observational studies, single/multi institutional studies, systematic reviews and meta-analyses were included. Non-systematic reviews and non-English studies were excluded. Where an article title or abstract were of interest, access to the full article was requested from the corresponding author via email. Abstracts where the full article could not be accessed were excluded.

Studies for inclusion required participants who had a histologically proven Pca, treated with a form of external beam radiation therapy; PR, IMRT, volumetric modulated arc therapy, stereotactic body radiation therapy (SBRT) or helical tomotherapy. Single cohort studies with patients treated with PT only were excluded. Any risk category or age range was included. No minimum or maximum population size was established.

Studies comparing bladder and/or rectal dose metrics or acute and/or late toxicities between PR and PT were included, while single arm studies evaluating these endpoints were excluded. However, single arm PR studies evaluating the acceptability of plan robustness were included. Studies comparing cost effectiveness between PR and PT cohorts were reported, as were single-arm studies evaluating the cost effectiveness of PR.

Outcome measures

A wide range of bladder and rectal dose values were reported. Clinical outcomes such as acute and late GI/GU toxicities were reported. Acute GI/GU toxicities were reported within <6 months. Late GI/GU toxicities were reported within a 2 to $\leq$65 month follow-up. The favourability of proton plan robustness was assessed by evaluating the effects of anatomical interfractional and intrafractional motion on plans. Cost efficiency between both treatment modalities was also compared.

Table 1
Bladder and rectum dosimetry and gastrointestinal and genitourinary toxicity results.

Author	Year	N	Treatment modality	Dosimetric endpoint	Dosimetric value	Toxicities reported	Toxicit grade/ endpoint	Toxicity scoring method	Time interval of toxicity	Outcome
Sheets et al. [24]	2012	1368	IMRT PR	–	–	Late GI morbidities Late GU morbidities	–	RTOG	12 m post treatment	PR vs. IMRT treated patients were associated with more GI morbidities No significant difference in PR vs. IMRT treated patients for GU morbidities
Yu et al. [25]	2012	2205	IMRT PR	–	–	Acute GU toxicities	GU toxicity (6 m); IMRT = 9.6% PR = 5.9% GU toxicity (12 m); IMRT = 17.5% PR = 18.8%		6m 12m	PR vs. IMRT reduces GU toxicitiy at 6m No statistically significant difference in GU toxicities between PR and IMRT at 12 m
						Acute GI toxicities	GI toxicity (6 m); IMRT = 3.6% PR = 2.9% GI toxicity at 12 m; IMRT = 10.2% PR = 9.9%			No statistically significant difference in GI toxicities at 6 m/12 m between PR and IMRT treated patients
*Sciobola et al. [26]	2016	20	HT VMAT PR SW	Bladder	**HT:** V10 (%) = 42.0 ± 23.8, V30 (%) = 26.2 ± 18.6, V50 (%) = 16.8 ± 12.5, V70 (%) = 6.0 ± 4.9 **SW:** V10 (%) = 39.3 ± 23.3 V30 (%) = 23.5 ± 16.4 V50 (%) = 15.6 ± 11.6 V70 (%) = 5.4 ± 4.8 **RA:** V10 (%) = 46.8 ± 23.2 V30 (%) = 27.0 ± 19.1 V50 (%) = 17.0 ± 13.3 V70 (%) = 6.4 ± 4.8	-	-	-	-	PR results in improved bladder dosimetic values than HT, SW and RA at all endpoints
				Rectum	**PR:** V10 (%) = 30.2 ± 18.5, V30 (%) = 21.2 ± 14.7 V50 (%) = 15.3 ± 11.5 V70 (%) = 5.3 ± 4.7 **HT:** V10 (%) = 59.1 ± 17.9, V30 (%) = 24.8 ± 7.6 V50 (%) = 12.8 ± 4.0, V70 (%) = 1.1 ± 0.7 **SW:** V10 (%) = 62.7 ± 16.6, V30 (%) = 32.8 ± 5.7, V50 (%) = 17.3 ± 2.5, V70 (%) = 1.5 ± 0.8, **RA:** V10 (%) = 69.0 ± 18.7, V30 (%) = 41.7 ± 11.3, V50 (%) = 23.5 ± 7.5, V70 (%) = 3.4 ± 1.8 **PR:** V10 (%) = 24.6 ± 9.2 V30 (%) = 15.7 ± 5.8 V50 (%) = 9.3 ± 3.8 V70 (%) = 1.0 ± 0.8					PR results in improved rectal dosimetric values than HT, SW and RA at all endpoints

(*continued on next page*)

Table 1 (*continued*)

Author	Year	N	Treatment modality	Dosimetric endpoint	Dosimetric value	Toxicities reported	Toxicit grade/ endpoint	Toxicity scoring method	Time interval of toxicity	Outcome
Hoppe et al. [27]	2014	1447	IMRT PR	–	–	Bowel Function Toxicities; urgency, frequency, faecal incontinence, bloody stools, rectal pain Urinary Incontinence Urinary irritative/ Obsructive	**PR:** 25% at 6 months, 41% at 1 year, 37% at 2 years **IMRT:** 39% at 6 months, 37% at 1 year, 38% at 2 years **PR:** 22% at 6 months, 31% at 1 year, 32% at 2 years **IMRT:** 28% at 6 months, 29% at 1 year, 34% at 2 years **PR:** 18% at 6 months, 23% at 1 year, 17% at 2 years **IMRT:** 25% at 6 months, 20% at 1 year, 18% at 2 years	EPIC-26 questionnaire	6 m, 1 yr, 2 yrs	PR vs. IMRT offers a statistically significant improvement of bowel toxicities at 6 m. Toxicities at 1 year and 2 years were similar for both modalities. Urinary symptoms (incontinence, irritation/obstruction) were similar between cohorts
*Fang et al [28]	2015	394	IMRT PR	Bladder	**IMRT:** V5(%) = 75.4 ± 2.6 V20(%) = 58.7 ± 2.7 V40(%) = 35.6 ± 1.6 V65(%) = 15.0 ± 0.7 V70(%) = 12.4 ± 0.6 **PR:** V5(%) = 33.7 ± 1.6 V20(%) = 24.8 ± 1.3 V40(%) = 17.8 ± 0.9 V60(%) = 10.1 ± 0.6 V70(%) = 8.1 ± 0.5	Acute GI toxicity	IMRT (86.2%) and PBT (95.7%) reported maximum grade 1 13 IMRT patients (13.8%) and 4 PBT patients (4.3%) reported grade ≥ 2	CTCAE version 3.0, IPSS, EPIC	90 days, 1 yr and 2 yrs	Although PR dose distributions to the bladder and rectum were lower, these differences did not translate to a demonstrable clinical benefit in acute or late GI or GU toxicity
				Rectum	**IMRT:** V5(%) = 92.2 ± 1.0 V20(%) = 77.4 ± 1.6 V40(%) = 35.8 ± 0.9 V65(%) = 16.3 ± 0.3 V70(%) = 10.4 ± 0.3 **PR:** V5(%) = 47.6 ± 1.1 V20(%) = 34.0 ± 1.0 V40(%) = 23.4 ± 0.5 V60(%) = 12.1 ± 0.3 V70(%) = 9.5 ± 0.3	Acute GU toxicity Late GI toxicity Late GU toxicity	No patients (IMRT/PR) reported grade 3 toxicity IMRT (71.2%) and PBT (78.7%) groups reported maximum grade 1 toxicity Grade ≥ 2 acute GU toxicity was recorded in 27 IMRT patients (28.7%) and 20 PBT patients (21.3%) No patients (IMRT/PR) reported grade 3 toxicity Grade ≥ 2 late GI toxicity was recorded in 10 IMRT patients (10.8%) and 12 PBT (12.8%) patients Two IMRT patients experienced late grade 3 hematochezia 1-year and 2-year GI toxicity rates were 3.4% and 9.9%, respectively, in the IMRT group and 9.7% and 13.7%, respectively, in the PBT group Grade ≥ 2 late GU toxicity was recorded in 17 patients (18.3%) and 12 patients (12.8%) in the IMRT and PBT groups, respectively Two PBT patients experienced late grade 3 urinary retention The 1-year and 2-year GU toxicity rates were 11.1% and 12.4%, respectively, in the IMRT group and 11.8% and 13.1%, respectively, in the PBT group			

*Rana et al. [29]	2014	4 cases	VMAT USPR	Bladder	**VMAT:** Mean dose = 28.4 Gy, V30 (%) = 45.5, V50 (%) = 22.7, V70 (%) = 8.6 **PR:** Mean dose = 23.0 Gy, V30 (%) = 38.5, V50 (%) = 20.0, V70 (%) = 9.4	–	–	–	–	USPR offers a bladder and rectal dosimetric advantage over VMAT for prostate cancer patients with metal hip prosthesis
				Rectum	**VMAT:** Mean dose = 32.9 Gy, V30 (%) = 53.1, V50 (%) = 30.3, V70 (%) = 9.8 **PR:** Mean dose = 18.1 Gy, V30 (%) = 20.4, V50 (%) = 12.5, V70 (%) = 6.0					
*Doyle et al. [30]	2010	20	IMRT VMAT PR	Bladder	**PR** versus **VMAT** and **IMRT**; V30Gy, V17.1 Gy (32.58% vs 57.27% & 62.76%)					PR offers significant bladder and rectal dosimetric values compared to VMAT and IMRT
				Rectum	**PR** versus **VMAT** and **IMRT** was significant when comparing V40Gy, V34.2 Gy (28%, vs 48.16% and 45.33%)					
*Zheng et al. [31]	2012	–	USPR IMRT	Bladder	**IMRT**: V30(%) = 31.8%±14.3% (LR), 27.5%±7.7% (int/HR) V50(%) = 13.6 ± 7.3% (LR), 16.2 ± 5.5% (int/HR), V70(%) = 5.9 ± 3.8% (LR), 8.9%±3.0% (int/HR) **PR: V30(%)** = 20.6%±14% (LR), 18.9 ± 6.4% (int/HR) V50(%) = 15.3 ± 11.6% (LR), 14.1 ± 4.9% (int/HR) V70 (%) = 9.2 ± 8.3% (LR), 8.6 ± 2.9% (int/HR)	–	–	–	–	UPST spares more low dose volume in rectum and bladder thus offering an improved dosimetric advantage over IMRT
				Rectum	**IMRT**: V30 = 43.2%±11.3% (LR), 42.9%±15.7% (int/HR) V50 = 13.2 ± 6.3% (LR), 17.1 ± 6.4% (int/HR), V70 = 3.7 ± 3.0% (LR), 5.8%±3.5% (int/HR) **PR:** V30 = 15.4%± 8.3% (LR), 21.8 ± 9.6% (int/HR) V50 = 10.1 ± 6.1% (LR), 14.4 ± 8.7% (int/HR) V70 = 4.7 ± 3.9% (LR), 6.9 ± 4.0% (int/HR)					
*Vargas et al. [32]	2008	10	IMRT PR	Bladder	**IMRT:** V10(%) = 60.0 ± 20.1 V20(%) = 50.8 ± 18.0 V30(%) = 42.8 ± 15.1 V35(%) = 38.2 ± 13.2	–	–	–	–	PR offers improved dose- sparing advantages to the bladder and rectum, in particular

(*continued on next page*)

Table 1 (*continued*)

Author	Year	N	Treatment modality	Dosimetric endpoint	Dosimetric value	Toxicities reported	Toxicit grade/ endpoint	Toxicity scoring method	Time interval of toxicity	Outcome
					PR: V10(%) = 36.4 ± 13.2 V20(%) = 31.4 ± 12.1 V30(%) = 27.7 ± 11.1 V35(%) = 26.0 ± 10.6					
				Rectum	**IMRT:** V10(%) = 72.1 ± 7.6 V30(%) = 55.4 ± 5.7 V50(%) = 31.3 ± 4.1 V70(%) = 14.0 ± 2.9 V78(%) = 5.0 ± 1.2 V80(%) = 1.8 ± 1.8 **PR:** V10(%) = 27.9 ± 3.8 V30(%) = 23.8 ± 3.2 V50(%) = 19.0 ± 2.8 V70(%) = 13.2 ± 2.7 V78(%) = 6.7 ± 2.5 V80(%) = 0.1 ± 0.3					
*Trofimov et al. [33]	2007	10	IMRT 3DCPR	Bladder	**IMRT:** V30 (%) = 44.5 V50 (%) = 23.7 V60 (%) = 16.9 V70 (%) = 11.4 **PR:** V30 (%) = 32.8 V50 (%) = 25.4 V60 (%) = 21.9 V70 (%) = 17.3	–	–	–	–	In the range > 60 Gy, IMRT achieved significantly better sparing of the bladder, whereas the rectal sparing was similar for both modalities
				Rectum	**IMRT:** V30 (%) = 65.3 V50 (%) = 34.4 V60 (%) = 23.6 V70 (%) = 14.5 V75 (%) = 9.7 **PR:** V30 (%) = 43.8 V50 (%) = 28.2 V60 (%) = 20.4 V70 (%) = 14.0 V75 (%) = 10.3					
*Mendenhall et al. [34]	2017	301	IMRT PT			GU > 3	IMRT: 4.3% PR: 0.1%	CTCAE version 3.0, IPSS, EPIC	Toxicities at 5 years	In the range of GU and GI toxicities > grade 3, PR achieved significantly better clinical outcomes compared to IMRT.
						GI > 3	IMRT: 1.3% PR: 0.1%			
*Pan et al. [35]	2018	10	PR IMRT	4158		GI	IMRT: 15% PR: 20%	CTCAE version 3.0, IPSS, EPIC	Toxicities at 2 years	Among younger men with prostate cancer, proton radiation was associated with significant reductions in urinary toxicity but increased bowel toxicity compared to IMRT
						GU	IMRT: 42% PR: 33%			

Abbreviations:

IMRT = Intensity Modulated Radiation Therapy, PR = Proton Therapy, GI = Gastrointestinal, GU = Genitourinary, m = months, RTOG = Radiation Therapy Oncology Group, HT = Helical Tomography, SW = Sliding Window, RA = Rapid Arc, CTCAE = Common Terminology Criteria Adverse Effects, IPSS = International Prostate Symptom Scale, EPIC = Expanded Prostate Cancer Index Composite, VMAT = Volumetric Modulated Arc Therapy, USPR = Uniform Scanning Proton Therapy, LR = low risk, int/HR = intermediate/high risk.

* =Treatment Planning Studies.

Statistical analysis

Studies included used two-tailed paired t-tests to compare dosimetric values between PR and PT. Wilcoxon matched pair rank sum tests and Kaplan-Meier methods were used to compare toxicities between both modalities.

Studies analysed plan robustness by calculating the differences between the measured values of errors between control and test. Wilcoxon signed-ranked tests were used to compare the differences caused by motion between both plans. Studies that considered cost effectiveness used a Markov Model calculating the cost per QALY.

Results

The literature search yielded 56 publications. Of these, 50 were selected for review. 26 studies were eligible for inclusion; with 6286 participants overall and published between 2007 and 2018. No RCTs met the inclusion criteria. Retrospective, prospective, observational multi or single institutional studies were included.

Bladder and rectal dosimetry and toxicities in proton therapy versus photon therapy

11 studies demonstrated an improvement in dose metrics [26,28–33] or toxicities [25,27,34,35] related to the bladder and rectum for PR versus PT, as summarised in Table 1. Trofimov et al. demonstrated that bladder and rectal dosimetry were improved with 3D Conformal Proton Therapy(3DCPR) in the range >30 Gy compared with IMRT [33]. Similar improvements in GU toxicities at 6 months with PR relative to PT were reported [25,34]. Hoppe et al. demonstrated that PR decreased GI toxicities at 6 months [27].

However, 5 conflicting studies reported that PR does not offer an improvement in dosimetric results [33] or toxicities [24,25,27,29] to the rectum and bladder relative to PT, as summarised in Table1. Trofimov demonstrated that bladder dose >60 Gy was improved with IMRT compared to 3DCPR, whereas rectal sparing at this range was similar between both modalities [33].

Sheets et al. found that patients receiving PR were more likely to experience late GI morbidities compared to patients treated with IMRT while also highlighting no difference in GU morbidities between both cohorts [24]. Others also reported no statistically significant difference in GU toxicities at 12 months and GI toxicities at 6 and 12 months between modalities [25]. Hoppe et al. noted that bowel toxicities at 1/2 years were similar whereas urinary symptoms were similar at 6 months, 1 year and 2 years [27]. Interestingly, it was reported that improved bladder and rectal dosimetry of PR did not translate to improved toxicities [28].

Plan robustness for prostate proton plans

11 studies demonstrate plan robustness is acceptable for prostate proton plans [35,36,39,41–48], as summarised in Table 2. Soukup et al. reported that the sensitivities of Intensity Modulated-PR (IMPR) and IMRT plans to organ motion are similar if a rectal gas water-equivalent density overwrite on the original planning CT is applied [36]. Rectal balloons reduced motion, as also suggested by Thornqvist et al. [44].

Changes in dose distribution caused by interfraction variations were similar between PR and IMRT when due consideration was given to physical and biological parameters [37]. Seipal et al. reported that minor (<5°) patient and horizontal couch rotations did not confer clinically significant changes to the dose distribution of proton plans [39].

Plan robustness with respect to inter and intrafraction motion was discussed in 7 studies. Wang et al. and Moteabbed et al. stated that PR plans were generally robust to interfractional variations, but rectal gas was the leading cause of target coverage reduction [41,48], while Thornqvist et al. [42] found the prostate robust to interfraction motion with fiducial-based positioning. Seminal vesicle variation was a concern, and also reported elsewhere [37]. Others revealed that Multi Field Optimisation-IMPR offers robust CTV coverage without dose perturbations to normal tissues despite rotational or translational alignment errors of 5° and 5 mm, respectively [43]. CTV coverage was degraded by 2% for the worst case scenario of a 10 mm intrafraction prostate drift using Pencil Beam Scanning (PBS) [44]. Others reported similar target coverage between IMPR plans and Single Field Uniform Dose (SFUD). PBS and Uniform Scanning (US) were equally robust to anatomic interfraction variations as a single- field-per-day technique [45]. Similarly, Tang et al. demonstrated that although intrafraction and residual interfraction prostate motion degrade CTV coverage, it is within an acceptable level [44]. Others reported that dosimetric uncertainties due to interfraction motion were minimal for ITV coverage [45].However, 3 studies highlight that proton plans are robust [38,40,45], as summarised in Table 3.

Yoon et al [38] reported that small target movements in the longitudinal direction reduce target dose while others found that femur rotation and soft tissue deformation causes perturbation to the dose distribution across the target volume [40]. Both studies reported that the target margin and compensators should be expanded in the longitudinal direction to prevent target dose loss [38,40]. Others stated that SFUD/IMPR may be less robust to interfraction anatomic variations compared to PBS [45].

Proton therapy for prostate cancer may be as cost effective as photon therapy

Only 3 studies analysed cost effectiveness of PR for prostate radiotherapy [49–51]. Of these, 1 study evaluated the cost efficiency of PR only [50]. Konski et al. concluded that over a 15-year period, PR could be cost effective for younger-presenting patients and reported a cost-per-QALY of $63,578 for a 70 year old and $55,726 for a 60 year old; with both over the accepted standard of $50,000 [49]. Lundkvist et al. demonstrated that PR is cost effective having a cost-per-QALY of €26,776 [50]. However, Parthan et al. reported that SBRT is more cost effective than PR from both payer and societal perspectives with SBRT and PR having a cost-per-QALY of $24,873 and $69,412 from a payer perspective and $25,097 and $71,657 from a societal perspective, respectively [49]. Konski et al. concluded that PR was not cost effective for most Pca patients [49].

Bladder and rectal dosimetry and toxicities in proton therapy versus photon therapy

Several treatment planning studies highlighted that bladder and rectal dosimetry was significantly improved for PR compared to PT [26,28–33]. PR offered a range of 1.85–57.01% and 3.44–64.35% bladder and rectal sparing benefit respectively, compared to modulated photon techniques. Superior sparing of these structures is evident owing to the intrinsic dose distribution of the SOBP of the proton beam [52] which provides a steep dose gradient reducing entry and exit doses, thereby reducing the dose to surrounding healthy tissues [53].

Yu et al stated that GU toxicities at 6 months were improved with PR compared to IMRT. Despite this, it was reported that patients receiving PR were younger and healthier; that is being in better general condition with fewer co-morbidities, with fewer patients receiving ADT and requiring physician visits in the

Table 2
Plan Robustness Results.

Author	Year	No. of participants	Treatment modalities compared	Type of motion evaluated	Conclusion
Soukup et al. [36]	2009	4 with 16 CT datasets	IMPR IMRT	Interfractional organ motion	Sensitivities of IMPR and IMRT to organ movement are of the same order if rectal gas water equivalent density overwrite on original planning CT and preoptimisation of beam weights of each field separately is applied. Study suggests the use of rectal balloons to reduce motion i.e. increase the plans robustness
Zhang et al. [37]	2007	10	IMRT PR	Interfractional anatomical motion	Changes in the dose distribution due to interfractional anatomical changes were no worse than those for IMRT plans when consideration to the range uncertainties and RBE approximations was given to the PR beams
Yoon et al. [38]	2008	12	PR	Inter and intra- fractional movement	Small target movements can significantly reduce target PRV dose. Attention should be given to interfractional target movement along the longtitudinal direction. IGRT may not be sufficient if margins are not sufficient
Sejpal et al. [39]	2009	7	PR	Rotational setup errors	Patient rotational movements of 3° and 5° and horizontal couch shifts of 3° did not confer clinically significant dose changes to the prostate target volumes/critical structures
Trofimov et al. [40]	2011	10	IMPR	Interfractional setup changes of pelvic bone anatomy and soft tissue	Femur rotation and soft tissue deformation may cause perturbation in the shape of prescription isodose volume. Application of target margin expansion in the longitudinal direction and compensator expansion technique prevents loss of target dose
Wang et al. [41]	2011	5	PR	Interfractional anatomic variations	PR plans are generally robust to interfractional anatomical variations
Thörnqvist et al. [42]	2013	4	IMPR	Interfraction motion	Prostate target was found robust to such changes when fiducial-based positioning was used
Pugh et al. [43]	2013	10	MFO-IMPR	Rotational and transitional errors in 3 axes	MFO-IMPR results in robust CTV coverage without clinically meaningful perturbations to normal tissue despite extreme rotational and transitional alignment errors
Tang et al. [44]	2013	10	PBS	Intrafraction prostate motion	CTV D99% coverage degraded only approximately 2% even with extreme rotational or translational errors such as 5° and 5%, respectively
Kirk et al. [45]	2015	10	US SFUD PBS	Interfractional anatomic variations	PBS equally as robust to anatomic variations with single field per day technique. SFUD and IMPR may be less robust to interfractional anatomic variations
Tang et al. [46]	2014	10	PBS-PR	Intrafraction and residual interfraction prostate motion	Both motions degrade CTV coverage within an acceptable level
Wang et al. [47]	2013	3	Hypofractionated PR	Interfraction motion	Dosimetric uncertainties due to interfraction motion were minimal for the the ITV2 coverage at 95% isodose level and dose received by 95% isodose of the ITV2
Moteabbed et al. [48]	2016	20	PR IMRT	Interfractional variation and anatomic motion	The differences in target coverage and organs at risk were not statistically significant under the guidelines of this protocol

Abbreviations:
RBE = Radiobiological effectiveness, MFO-IMPR = Multi field optimisation-Intensity Modulated Proton Therapy, CTV = Clinical Target Volume, PBS-PR = Pencil Beam Scanning-Proton Therapy, US = Uniform Scanning, SFUD = Single field uniform-dose.

previous 9 months than patients receiving IMRT [25]. This leaves one to question the influence of the difference in patient related factors between the two cohorts on the validity of the GU results in favour of PR. Previous studies reported patient related factors such as increasing age [54] and comorbidities or pre-treatment urinary symptoms [53–55] as determining factors in increasing the risk of urinary toxicities post radiotherapy. However, such toxicity improvements may also be due to the physical properties of protons [6–8,56] resulting in improved dosimetric bladder and rectal sparing [25,28–33] and being exposed to low to intermediate levels of radiation [33,57]. This, or other confounding factors such as the differing use of image-guided therapy, aspirin or other anticoagulants, target margins, interobserver variability, or larger prostate volumes in the IMRT group relative to PR may also be factors [58].

However, Trofimov et al. demonstrated that in the range >60 Gy, IMRT achieved significantly better bladder sparing. Additionally, no differences in rectal dosimetry existed between PR and PT [35]. This may be due to the use of anterior oblique (AO) beams in experimental 3DCPT plans which reduced the rectal dose, but at the cost of increasing bladder dose. A potential issue of AO beams is an increased proton penetration depth uncertainty from the intrafractional variation of bladder filling [35].The 3DCPT technique may result in a higher bladder dose delivered due to broader penumbra and the smearing effect of the compensator [35]. Additionally, Sheets et al [26] and Cella et al [59] concluded that late GI toxicities were worse, with no significant difference in GU toxicities, with PR compared to IMRT, despite improved dosimetry. A possible explanation for this is the higher vulnerability of PR to organ movement leading to an unintentional delivery of high dose to the rectum [6,36,60]. An implication for improved bladder dosimetry and GI toxicities mentioned in both studies [24,35] may be the use of modulated techniques. Studies reported that IMRT/IMPT decrease the volume of normal tissues receiving low to moderate radiation dose compared to a lateral field configuration [61–63]. Further investigation is merited into the use of IMPT compared to 3DCPT to reduce bladder dose [33]. The use of prostate and rectal immobilisation devices have been shown to improve GU/GI toxicities [64].

Hoppe et al. noted that bowel toxicities at 1 and 2 years were similar for both PR and PT, and urinary symptoms were similar at 6 months, 1 year and 2 years [27]. Patients were treated using

Table 3
Proton Therapy Cost effective analysis results.

Author	Year	Treatment modalities	Time analysis of cost effectiveness	Cost	QALY	Cost per QALY	Conclusion
Konski et al. [49]	2007	PR IMRT	15 years	PR: $63511 (70 y/o) IMRT: $36808 (70 y/o) PR: $64989 (60 y/o) IMRT: $39355 (60 y/o)	PR: 8.54 (70 y/o) IMRT: 8.12 (70 y/o) PR: 9.91 (60 y/o) IMRT: 9.45 (60 y/o)	$63578 (70 y/o) $55726 (60 y/o)	PR is not cost effective for most prostate cancer patients using the commonly accepted $50,000/QALY standard, however it could be cost effective for younger patients
Lundkvist et al. [50]	2009	PR		€7952.6 (standard case results)	0.297 (standard case results)	€26776 (standard case results)	PR is cost effective
Parthan et al. [51]	2012	SBRT PR IMRT		**Payer perspective:** SBRT: $24,873 IMRT: $33,068 PR: $69,412 **Societal perspective:** SBRT: $25,097 IMRT: $35,088 PR: $71,657	 8.11 8.05 8.06 8.11 8.05 8.06	-	SBRT is more cost effective than IMRT/PBT from a payer and societal perspective

Abbreviations:
SBRT = Stereotactic Body Radiation, BT = Brachytherapy, y/o = years old.

a passively scattered technique rather than PBS, which is currently more commonly used [65]. Passive scattering proton beams are associated with higher neutron scatter as a result of collisions with inelastic collision of particles [66], which could ultimately become damaging to normal tissue, with their high RBE [67]. This could account for the lack of benefit of PR over PT reported. Had PBS been used for PR delivery instead, the results may have been different, given that PBS can reduce bladder and rectal dose [32,33].

Fang et al. demonstrated that despite markedly lower bladder and rectal doses with PR compare to PT, these differences did not translate into a demonstrable clinical benefit in acute or late GI or GU toxicities [28], correlating with previous studies [24,25,70–78]. However, an internal validity limitation in these studies exists because of the influence of confounding variables on GI and GU toxicities in the results. Interestingly, Fang et al.'s study exploits controlled case matching, thus eliminating bias caused by previously discussed confounding factors. Given that the results concluded there was no difference between acute and late GI/GU toxicities [28], further investigation may be required to validate the use of PR in toxicity reduction as the translation of dosimetric advantages into clinical outcomes remains debatable.

Plan robustness

Proton beams are very sensitive to the densities of material that they traverse due to the uncertainties of the SOBP shifting in the presence of lateral heterogeneities [18,19]. Gaseous cavities have also been shown as problematic for PR due to their ability to distort and potentially shift dose distributions into healthy tissues [76]. Soukup et al. discuss a method to overwrite rectal gas with water equivalence with the intention of improving the dose distribution of the IMPT plan [36]. However, it is important to note that rectal gas can vary on a day to day basis [41] and gas in the rectum tends to decrease towards the end of treatment [77]. Therefore it is arguable that the use of the overwrite of rectal gas on the original treatment plan may be an 'overestimation' of rectal gas for subsequent fractions. Soukup et al. recommend the use of a rectal balloon to increase the volume of the rectum to render the robustness of proton plans acceptable [36]. Previous studies have diminished the influence of heterogeneities caused by rectal gas filling by using such devices to increase the volume of the rectum [78]. Other studies have validated that the daily use of an endorectal balloon can reduce intrafraction prostate motion for 90% of all fractions [79], thereby influencing the robustness of PR plans for Pca, When using the IMPT technique, dose distributions are expected to be more sensitive to organ motion, therefore care regarding the robustness of the treatment plans must be considered [80].

Interfraction and intrafraction prostate motion are inevitable, with Schiffner et al. reporting an interfractional standard deviation of 1–2 mm, 2–4 mm and 4–5 mm in the left-right, anterior-posterior and superior-inferior axes, respectively [81]. In extreme circumstances, prostate motion has been recorded up to 7.2 mm posteriorly, 9.2 mm anteriorly, 6.8 mm inferiorly and 12.9 mm superiorly [82]. It has been reported that prostate PR plans are robust to intrafraction motion when fiducial-based positioning is used [83,84] and that degradation in target dose is not significant even for the tightest margin of 4 mm compared to bony anatomy positioning [42]. Given that PR is very sensitive to motion, daily imaging with fiducials appears essential, which Pugh et al. also recommend [43].

Others [37,39,44] have reported that changes in dose distribution caused by interfraction anatomical variations were not deemed worse for PR compared to IMRT when specific parameter uncertainties related to CT numbers, stopping powers, motion and positioning and range uncertainties; the latter caused by inhomogeneities and compensators; as well as RBE approximations are given to proton beams [85]. Inter and intra fractional variations in the path of the beam and the presence of compensators must also be compensated for with the use of smearing [37] Studies have shown that with the use of this smearing margin based on Moyer et al.'s formula [84], target coverage is guaranteed [86].

However, Trofimov et al. found that femur rotation and soft tissue deformation potentially caused dose distribution perturbation and that standard target margin expansion in the longitudinal direction and compensator margin expansion should be applied to ensure adequate target dose [40]. However, this comes at the cost of increasing dose to healthy tissues. Additionally, it was reported that their standard institutional 5 mm PTV margin may not be sufficient for PR treatment of obese prostate patients due to the increased difficulty of target localisation, alignment and

Table 4
Proton Therapy Cost effectiveness analysis results.

Author	Year	Treatment modalities	Time analysis of cost effectiveness	Cost	QALY	Cost per QALY	Conclusion
Konski et al. [47]	2007	PR IMRT	15 years	PR: $63511 (70 y/o) IMRT: $36808 (70 y/o) PR: $64989 (60 y/o) IMRT: $39355 (60 y/o)	PR: 8.54 (70 y/o) IMRT: 8.12 (70 y/o) PR: 9.91 (60 y/o) IMRT: 9.45 (60 y/o)	$63578 (70 y/o) $55726 (60 y/o)	PR is not cost effective for most prostate cancer patients using the commonly accepted $50,000/QALY standard, however it could be cost effective for younger patients
Lundkvist et al. [48]	2009	PR		€7952.6 (standard case results)	0.297 (standard case results)	€26776 (standard case results)	PR is cost effective
Parthan et al. [49]	2012	SBRT PR IMRT		**Payer perspective:** SBRT: $24,873 IMRT: $33,068 PR: $69,412 **Societal perspective:** SBRT: $25,097 IMRT: $35,088 PR: $71,657	 8.11 8.05 8.06 8.11 8.05 8.06	-	SBRT is more cost effective than IMRT/PBT from a payer and societal perspective

Abbreviations:
SBRT = Stereotactic Body Radiation, BT = Brachytherapy, y/o = years old.

immobilisation of internal bony anatomy [40,87]. Further investigation into the appropriate application of margins for obese patients using PR is warranted as studies have shown that patients with a BMI > 30 are more susceptible to interfraction variations [88]. One study has suggested that using pod immobilisation to reproduce the posterior contour for obese patients allows a repeatable water equivalent target [87]. This will in turn minimise range uncertainty, also highlighted as a concern by Zhang et al. [37].

Kirk et al. stated that SFUD and IMPT may be less robust to interfraction anatomic variations compared to PBS because of the likely higher degree of spot weight modulation [45]. In a study testing the robustness of IMPT against anatomic changes for lung cancer, the use of repeated imaging and adaptive planning was recommended to reduce setup uncertainties and the implication of anatomic changes [89]. Adaptive planning for prostate cases may also be warranted as here, IMPT has also been shown as very sensitive to setup errors and range uncertainties [90].

Cost effectiveness of proton therapy for prostate cancer

The cost per QALY data for both a 60 and 70 year old man are outlined in Table 4. From this, PR may be cost effective for younger patients, due to their longer life expectancy [49] as studies have shown that such patients are more likely to experience recurrence [91,92]. In addition, recent evidence has shown that PR can significantly decrease the risk of long term secondary malignancies [93] compared to that of IMRT; however this still remains controversial [94]. As the presentation of younger patients <50 years old has increased 6-fold in the last 20 years [95], PR may be cost effective for these patients given their longer survival time. Konski et al. [49] stated that a significant portion of intermediate risk Pca patients may not benefit from PR as the freedom from biochemical failure (FFBF) rates were similar for both PT and PR [96,97]. However, this leaves one to speculate as to the use of PR for high risk prostate cancer patients (HRPca) given that they are more likely to recur long term [98]. As PT has the ability to facilitate dose escalation [97], further investigation is merited into its ability to improve FFBF rates for HRPca. The results of a current clinical trial of PR for HRPca may influence the cost efficiency of PR for this cohort in the future [99].

Lundkvist et al. [50] demonstrated that PR was cost effective for Pca patients with a QALY of €26,776, which is below the considered standard QALY of $50,000 [100]. For the calculation of cost efficiency in this study, it was assumed that PR would be delivered with a higher target dose prescription and that PR would provide a lower risk of adverse effects, both short and long term [61]. Further investigation is merited into cost efficiency evaluation given that data are increasing in relation to toxicities [25,27].

Peeters et al. stated that PR was cost effective for patients given the reduction of adverse effects, both short and long term [101]. A phase 3 study comparing standard PR to hypofractionated PR is also underway [102]. If the concluding results are in favour of hypofractionated PR, treatment costs would be decreased given the significantly reduced fractionation. This is also reinforced by Muralidhar et al., who stated that PR may be cost effective for favourable-risk prostate cancer if shorter, simpler PR treatments, similar to SBRT or BT are proposed [103].

Opposingly, Parthan et al [51] stated that SBRT was more cost effective than PR based on the cost per QALY data from a payer and societal perspective outlined in Table 4. One reason for this is likely due to the current reduced fractionation with SBRT, relative to PR, as well as the use of traditional linear accelerators for SBRT. Another reason for this may be that patients treated using SBRT were expected to have a more favourable short and long term toxicity profile compared to those treated using PR [51]. While no evidence comparing short and long term toxicities between SBRT and PR currently exists, a dosimetric study found that SBRT can reduce bladder and femoral head dose compared to PR [104]. Further investigation into short and long term toxicity comparison between both modalities is required. Some studies have also shown that PR- treated patients may not necessarily experience fewer short and long term GU/GI toxicities [24,25,27,28,105], implying that PR may not be cost effective if resultant toxicities are comparable to those using IMRT/SBRT [1] but may be less expensive in terms of lifetime costs [106–108].

Konski et al. [49] found that PR was not cost effective for the majority of Pca patients and showed increased costs at all levels compared to IMRT. They concluded that men with a low risk of recurrence would not benefit from dose escalation using PR [49] as a high FFBF rate can already be obtained using less costly current photon modalities [21,81,82]. Others found that the median reimbursement for prostate RT in the USA was >$32,000 for PR, but only $18,000 for IMRT. This retrospective study also found no difference between short term GI or GU toxicities at 12 months,

despite the increase in cost, illustrating that PR is not cost effective within that short time frame [21]. In their review article, Muralidhar et al. [109] et al concluded that for low and intermediate risk cases, shorter course and simpler radiation therapy techniques, such as brachytherapy and SBRT were more cost efficient than IMRT or PR. A similar review by Schroek et al. [110] has concluded that the quality of available evidence to ascertain the cost effectiveness of PR relative to IMRT to be 'very low'. Yu et al. [111] report that based on 2008 and 2009 data the median Medicare reimbursement in the US for Pr was $32,428 and for IMRT was $18,575.

Limitations

Using the Downs and Black's checklist [112], a methodological quality testing of both of randomised and non-randomised studies of health care interventions which consists of 27 questions examining reporting, external and internal validity, the scores obtained were from 12 to 24, meaning that the internal and external validities were moderate to good. Those at the lower end of this range included mainly single armed studies as there is currently a paucity of comparative PT versus PR trials. Variations in sample sizes in studies between those treated with PR and PT also existed. A limited number of studies reported on cost per QALY data; making it difficult to assess cost effectiveness for patients treated with PR.

Conclusion

At present, a vast amount of evidence exists in favour of PR offering improved bladder and rectal dosimetry compared to PT. However, these dose metrics do not automatically translate to clinically improved GI/GU toxicities. The robustness of PR plans are acceptable when specific corrections and protocols are adhered to. Evidence regarding the cost efficiency of PR for Pca patients is limited and somewhat conflicting. However from that which is available, PR is not cost effective for all Pca patients when comparing the QALY results of PR compared to the less costly PT. However PR may be cost effective for younger presenting or high risk patients when costs pertaining to acute and late toxicities and lifetime costs are taken into consideration.

Declaration of Competing Interest

Michelle Leech has the following conflict of interest to declare: Co-editor in chief of Technical Innovations and Patient Support in Radiation Oncology.

Sophie Mangan has no conflicts of interest to declare.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tipsro.2019.08.001.

References

[1] Verma M, Patel P, Verma M. Biomarkers in prostate cancer epidemiology. Cancers 2011;3:3773–98.
[2] Mouw K, Trofimov A, Zietman A, Efstathiou J. Clinical controversies: proton therapy for prostate cancer. Seminars Radiat Oncol 2013;23(2):109–14.
[3] St. Clair W, Adams J, Bues M, Fullerton B, La Shell S, Kooy H, et al. Advantage of protons compared to conventional X-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. Int J Radiat Oncol Biol Phys 2004;58(3):727–34.
[4] Matloob S, Nasir H, Choi D. Proton beam therapy in the management of skull base chordomas: systematic review of indications, outcomes, and implications for neurosurgeons. Br J Neurosurg 2016;30(4):382–7.
[5] Boyer AL, Goitein G, Lomax AJ, Pedroni E. Radiation in the treatment of cancer. Phys Today 2002:34–6.
[6] Lomax A. Charged particle therapy: the physics of interaction. Cancer J 2009;15(4):285–91.
[7] Brown ASuit H. The centenary of the discovery of the Bragg peak. Radiother Oncol 2004;73(3):265–8.
[8] Schulz-Ertner D. The clinical experience with particle therapy in adults. Cancer J 2009;15(4):306–11.
[9] Greco C. Particle therapy in prostate cancer: a review. Prostate Cancer Prostatic Diseases 2007;10(4):323–30.
[10] Wilson RR. Radiological use of fast protons. Radiology 1946;47:487–91.
[11] Goozner M. The proton beam debate: are facilities outstripping the evidence? JNCI J Natl Cancer Inst 2010;102(7):450–3.
[12] StatBite: particle beam therapy facilities worldwide. JNCI J Natl Cancer Inst 2010;102(7):451–451.
[13] Zietman A. The titanic and the iceberg: prostate proton therapy and health care economics. J Clin Oncol 2007;25(24):3565–6.
[14] Goitein M. Radiation oncology: a physicist's-eye view. New York: Springer Science and Business Media; 2008.
[15] Rana S, Cheng C, Zheng Y, Risalvato D, Cersonsky N, Ramirez E, et al. Proton therapy vs. VMAT for prostate cancer: a treatment planning study. Int J Particle Therapy 2014;1(1):22–33.
[16] Chera B, Vargas C, Morris C, 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(4):994–1002.
[17] Proton Therapy vs. IMRT for Low or Intermediate Risk Prostate Cancer- Full Text View - ClinicalTrials.gov [Internet]. Clinicaltrials.gov. 2016 [cited 19 November 2016]. Available from: https://clinicaltrials.gov/ct2/show/NCT01617161.
[18] Goitein M. A technique for calculating the influence of thin inhomogeneities on charged particle beams. Med Phys 1978;5(4):258.
[19] Goitein M. Measurements and calculations of the influence of thin inhomogeneities on charged particle beams. Med Phys 1978;5(4):265.
[20] Efstathiou J, Gray P, Zietman A. Proton beam therapy and localised prostate cancer: current status and controversies. Br J Cancer 2013;108(6):1225–30.
[21] Verma V, Mishra M, Mehta M. A systematic review of the cost and cost-effectiveness studies of proton radiotherapy. Cancer 2016;122(10):1483–501.
[22] Lievens Y, Pijls-Johannesma M. Health economic controversy and cost-effectiveness of proton therapy. Seminars Radiat Oncol 2013;23(2):134–41.
[23] Chen A. Comparative effectiveness research in radiation oncology: assessing technology. Seminars Radiat Oncol 2014;24(1):25–34.
[24] Sheets N. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. JAMA 2012;307(15):1611.
[25] Yu J, Soulos P, Herrin J, Cramer L, Potosky A, Roberts K, et al. Proton versus intensity-modulated radiotherapy for prostate cancer: patterns of care and early toxicity. JNCI J Natl Cancer Inst 2012;105(1):25–32.
[26] Scobioala S, Kittel C, Wissmann N, Haverkamp U, Channaoui M, Habibeh O, et al. A treatment planning study comparing tomotherapy, volumetric modulated arc therapy, Sliding Window and proton therapy for low-risk prostate carcinoma. Radiat Oncol 2016;11(1).
[27] Hoppe B, Michalski J, Mendenhall N, Morris C, Henderson R, Nichols R, et al. Comparative effectiveness study of proton therapy versus IMRT for definitive treatment of prostate cancer based on patient-reported outcomes. Int J Radiat Oncol Biol Phys 2013;87(2):346.
[28] Fang P, Mick R, Deville C, Both S, Bekelman J, Christodouleas J, et al. A case-matched study of toxicity outcomes after proton therapy and intensity-modulated radiation therapy for prostate cancer. Cancer 2014;121(7):1118–27.
[29] Rana Suresh, Cheng ChihYao, Zheng Yuanshui, Hsi Wen, Zeidan Omar, Schreuder Niek, Vargas Carlos, Larson Gary. Dosimetric study of uniform scanning proton therapy planning for prostate cancer patients with a metal hip prosthesis, and comparison with volumetric-modulated arc therapy. J Appl Clin Med Phys 2014;15(3):335–48. https://doi.org/10.1120/jacmp.v15i3.4611.
[30] Doyle L, Studenski M, Harvey A, Dicker A, Xiao Y, Yu Y, et al. Dosimetric comparison of VMAT, IMRT and proton therapy for post-prostatectomy radiation therapy for prostate Cancer. Int J Radiat Oncol Biol Phys 2010;78(3):806.
[31] Zheng Y, Keole S, Liu Y, Ding X, Aust C, Campbell J, et al. Dosimetric comparison between IMRT and uniform scanning proton therapy for prostate cancer Treatment. Int J Radiat Oncol Biol Phys 2012;84(3):844.
[32] 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(3):744–51.
[33] Trofimov A, Nguyen P, Coen J, Doppke K, Schneider R, Adams J, 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(2):444–53.
[34] Mendenhall N, Wong W, Bryant C, Vora S, Henderson R, Keole S, et al. Potential improved outcomes with proton therapy in prostate cancer: a comparison of IMRT and proton cohorts. Int J Radiat Oncol Biol Phys 2017;99(2):E254.
[35] Pan H, Jiang J, Hoffman K, Tang C, Choi S, Nguyen Q, 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;18(36):1823–30. JCO.2017.75.537.

[36] Soukup M, Söhn M, Yan D, Liang J, Alber M. Study of robustness of IMPR and IMRT for prostate cancer against organ movement. Int J Radiat Oncol Biol Phys 2009;75(3):941–9.
[37] Zhang X, Dong L, Lee A, Cox J, Kuban D, Zhu R, et al. Effect of anatomic motion on proton therapy dose distributions in prostate cancer treatment. Int J Radiat Oncol Biol Phys 2007;67(2):620–9.
[38] Yoon M, Kim D, Shin D, Park S, Lee S, Kim D, et al. Inter- and Intrafractional movement-induced dose reduction of prostate target volume in proton beam treatment. Int J Radiat Oncol Biol Phys 2008;71(4):1091–102.
[39] Sejpal S, Amos R, Bluett J, Levy L, Kudchadker R, Johnson J, et al. Dosimetric changes resulting from patient rotational setup errors in proton therapy prostate plans. Int J Radiat Oncol Biol Phys 2009;75(1):40–8.
[40] Trofimov A, Nguyen P, Efstathiou J, Wang Y, Lu H, 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(3):928–37.
[41] Wang Y, Efstathiou J, Sharp G, Lu H, Frank Ciernik I, Trofimov A. Evaluation of the dosimetric impact of interfractional anatomical variations on prostate proton therapy using daily in-room CT images. Med Phys 2011;38(8):4623.
[42] Thörnqvist S, Muren L, Bentzen L, Hysing L, Høyer M, Grau C, et al. Degradation of target coverage due to inter- fraction motion during intensity-modulated proton therapy of prostate and elective targets. Acta Oncol 2013;52(3):521–7.
[43] Pugh T, Amos R, John Bapriste S, Choi S, Nhu Nguyen Q, Ronald Zhu X, et al. Multifield optimization intensity- modulated proton therapy (MFO-IMPR) for prostate cancer: robustness analysis through simulation of rotational and translational alignment errors. Med Dosim 2013;38(3):344–50.
[44] Tang S, Deville C, McDonough J, Tochner Z, Wang K, Vapiwala N, et al. Effect of intrafraction prostate motion on proton pencil beam scanning delivery: a quantitative assessment. Int J Radiat Oncol Biol Phys 2013;87(2):375–82.
[45] Kirk M, Tang S, Zhai H, Vapiwala N, Deville C, James P, et al. Comparison of prostate proton treatment planning technique, interfraction robustness, and analysis of single-field treatment feasibility. Pract Radiat Oncol 2015;5(2):99–105.
[46] Tang S, Deville C, Tochner Z, Wang K, McDonough J, Vapiwala N, et al. Impact of intrafraction and residual interfraction effect on prostate proton pencil beam scanning. Int J Radiat Oncol Biol Phys 2014;90(5):1186–94.
[47] Wang Y, Efstathiou J, Lu H, Sharp G, Trofimov A. Hypofractionated proton therapy for prostate cancer: dose delivery uncertainty due to interfractional motion. Med Phys 2013;40(7):071714.
[48] Moteabbed M, Trofimov A, Sharp G, Wang Y, Zietman A, Efstathiou J, 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(1):444–53.
[49] Konski A, Speier W, Hanlon A, Beck J, Pollack A. Is proton beam therapy cost effective in the treatment of adenocarcinoma of the prostate? J Clin Oncol 2007;25(24):3603–8.
[50] Lundkvist J, Ekman M, Ericsson S, Jönsson B, Glimelius B. Proton therapy of cancer: potential clinical advantages and cost-effectiveness. Acta Oncol 2005;44(8):850–61.
[51] Parthan A, Pruttivarasin N, Davies D, Taylor D, Pawar V, Bijlani A, et al. Comparative cost-effectiveness of stereotactic body radiation therapy versus intensity-modulated and proton radiation therapy for localized prostate cancer. Front Oncol 2012;2.
[52] Raju M. Proton radiobiology, radiosurgery and radiotherapy. Int J Radiat Biol 1995;67(3):237–59.
[53] Yonemoto L, Slater J, Rossi C, Antoine J, Loredo L, Archambeau J, et al. Combined proton and photon conformal radiation therapy for locally advanced carcinoma of the prostate: preliminary results of a phase study. Int J Radiat Oncol Biol Phys 1997;37(1):21–9.
[54] Viswanathan A, Yorke E, Marks L, Eifel P, Shipley W. Radiation dose-volume effects of the urinary bladder. Int J Radiat Oncol Biol Phys 2010;76(3):S116–22.
[55] Fiorino C, Valdagni R, Rancati T, Sanguineti G. Dose–volume effects for normal tissues in external radiotherapy: pelvis. Radiother Oncol 2009;93(2):153–67.
[56] Durante M, Loeffler J. Charged particles in radiation oncology. Nat Rev Clin Oncol 2009;7(1):37–43.
[57] Mock U, Bogner J, Georg D, Auberger T, Pötter R. Comparative treatment planning on localized prostate carcinoma. Strahlenther Onkol 2005;181(7):448–55.
[58] Hamstra D, Stenmark M, Ritter T, Litzenberg D, Jackson W, Johnson S, et al. Age and comorbid illness are associated with late rectal toxicity following dose-escalated radiation therapy for prostate cancer. Int J Radiat Oncol Biol Phys 2013;85(5):1246–53.
[59] Kim S, Shen S, Moore D, Shih W, Lin Y, Li H, et al. Late gastrointestinal toxicities following radiation therapy for prostate cancer. Eur Urol 2011;60(5):908–16.
[60] Vargas C, Wagner M, Indelicato D, et al. Image guidance based on prostate position for prostate cancer proton therapy. Int J Radiat Oncol Biol Phys 2008;71(5):1322–8.
[61] Cella L, Lomax A, Miralbell R. Potential role of intensity modulated proton beams in prostate cancer radiotherapy. Int J Radiat Oncol Biol Phys 2001;49(1):217–23.
[62] Fagundes M, Robison B, Price S, Hsi R, Sylvester J, Beyer D, et al. High-Dose rectal sparing with transperineal injection of hydrogel spacer in intensity modulated proton therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2015;93(3):E230.
[63] Mock U, Bogner J, Georg D, et al. Comparative treatment planning on localized prostate carcinoma conformal photon-versus proton-based radiotherapy. Strahlenther Onkol 2005;181:448–545.
[64] Teh B, Mai W, Uhl B, Augspurger M, Grant W, Lu H, et al. Intensity-modulated radiation therapy (IMRT) for prostate cancer with the use of a rectal balloon for prostate immobilization: acute toxicity and dose–volume analysis. Int J Radiat Oncol Biol Phys 2001;49(3):705–12.
[65] Chan T, Tan P, Tang J. Proton therapy for early stage prostate cancer: is there a case? OncoTargets Therapy 2016;9:5577–86.
[66] Yan X, Titt U, Koehler A, Newhauser W. Measurement of neutron dose equivalent to proton therapy patients outside of the proton radiation field. Nucl Instrum Methods Phys Res, Sect A 2002;476(1–2):429–34.
[67] Gottschalk B. Neutron dose in scattered and scanned proton beams: In regard to Eric J. Hall (Int J Radiat Oncol Biol Phys 2006;65:1–7). Int J Radiat Oncol Biol Phys 2006;66(5):1594.
[68] Mendenhall N, Li Z, Hoppe B, Marcus R, Mendenhall W, Nichols R, et al. Early outcomes from three prospective trials of image-guided proton therapy for prostate cancer. Int J Radiat Oncol Biol Phys 2012;82(1):213–21.
[69] Mayahara H, Murakami M, Kagawa K, Kawaguchi A, Oda Y, Miyawaki D, et al. Acute morbidity of proton therapy for prostate cancer: the hyogo ion beam medical center experience. Int J Radiat Oncol Biol Phys 2007;69(2):434–43.
[70] Nihei K, Ogino T, Onozawa M, Murayama S, Fuji H, Murakami M, et al. Multi-institutional phase II study of proton beam therapy for organ-confined prostate cancer focusing on the incidence of late rectal toxicities. Int J Radiat Oncol Biol Phys 2011;81(2):390–6.
[71] Zelefsky M, Levin E, Hunt M, Yamada Y, Shippy A, Jackson A, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2008;70(4):1124–9.
[72] Eade T, Horwitz E, Ruth K, Buyyounouski M, D'Ambrosio D, Feigenberg S, et al. A comparison of acute and chronic toxicity for men with low-risk prostate cancer treated with intensity-modulated radiation therapy or 125I permanentimplant. Int J Radiat Oncol Biol Phys 2008;71(2):338–45.
[73] De Meerleer G, Fonteyne V, Vakaet L, Villeirs G, Denoyette L, Verbaeys A, et al. Intensity-modulated radiation therapy for prostate cancer: late morbidity and results on biochemical control. Radiother Oncol 2007;82(2):160–6.
[74] Pugh T, Munsell M, Choi S, Nguyen Q, Mathai B, Zhu X, et al. Quality of life and toxicity from passively scattered and spot-scanning proton beam therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2013;87(5):946–53.
[75] Feng M, Hanlon A, Pisansky T, Kuban D, Catton C, Michalski J, et al. Predictive factors for late genitourinary and gastrointestinal toxicity in patients with prostate cancer treated with adjuvant or salvage radiotherapy. Int J Radiat Oncol Biol Phys 2007;68(5):1417–23.
[76] Lin L, Vargas C, Hsi W, Indelicato D, Slopsema R, Li Z, et al. Dosimetric uncertainty in prostate cancer proton radiotherapy. Med Phys 2008;35(11):4800.
[77] Nakamura N, Hatanaka S, Takahashi O, Mizuno N, Endo H, Tamaki S, et al. Gas in the rectum tends to reduce during radical external beam radiotherapy for localised prostate cancer. J Med Imag Radiat Oncol 2013;58(2):253–6.
[78] Slater J, Rossi C, Yonemoto L, Reyes-Molyneux N, Bush D, Antoine J, et al. Conformal proton therapy for prostate carcinoma. Eur J Cancer 1999;35:341.
[79] Wang K, Vapiwala N, Bui V, Deville C, Plastaras J, Bar-Ad V, et al. The impact of stool and gas volume on intrafraction prostate motion in patients undergoing radiotherapy with daily endorectal balloon. Radiother Oncol 2014;112(1):89–94.
[80] Lomax A. Intensity modulated proton therapy and its sensitivity to treatment uncertainties 2: the potential effects of inter-fraction and inter-field motions. Phys Med Biol 2008;53(4):1043–56.
[81] Schiffner D, Gottschalk A, Lometti M, Aubin M, Pouliot J, Speight J, et al. Daily electronic portal imaging of implanted gold seed fiducials in patients undergoing radiotherapy after radical prostatectomy. Int J Radiat Oncol Biol Phys 2007;67(2):610–9.
[82] Wu J, Haycocks T, Alasti H, Ottewell G, Middlemiss N, Abdolell M, et al. Positioning errors and prostate motion during conformal prostate radiotherapy using on-line isocentre set-up verification and implanted prostate markers. Radiother Oncol 2001;61(2):127–33.
[83] Chen J, Lee R, Handrahan D, Sause W. Intensity-modulated radiotherapy using implanted fiducial markers with daily portal imaging: assessment of prostate organ motion. Int J Radiat Oncol Biol Phys 2007;68(3):912–9.
[84] Schallenkamp J, Herman M, Kruse J, Pisansky T. Position of the prostate relative to pelvic bony anatomy based on intraprostatic gold fiducial markers and electronic portal imaging. Int J Radiat Oncol Biol Phys 2004;60(1):437.
[85] Pugh T, Amos R, John Baptiste S, Choi S, Nhu Nguyen Q, Ronald Zhu X, et al. Multifield optimization intensity- modulated proton therapy (MFO-IMPT) for prostate cancer: Robustness analysis through simulation of rotational and translational alignment errors. Med Dosim 2013;38(3):344–50.
[86] Urie M, Goitein M, Wagner M. Compensating for heterogeneities in proton radiation-therapy. Phys Med Biol 1984;29:553–66.
[87] Wong J, Gao Z, Merrick S, Wilson P, Uematsu M, Woo K, et al. Potential for higher treatment failure in obese patients: correlation of elevated body mass index and increased daily prostate deviations from the radiation beam isocenters in an analysis of 1,465 computed tomographic images. Int J Radiat Oncol Biol Phys 2009;75(1):49–55.

[88] Yoon W, Yang D, Lee J, Lee S, Park Y, Kim C. Risk factors related to interfractional variation in whole pelvic irradiation for locally advanced pelvic malignancies. Strahlenther Onkol 2012;188(5):395–403.
[89] Li H, Zhang X, Park P, Liu W, Chang J, Liao Z, et al. Robust optimization in intensity-modulated proton therapy to account for anatomy changes in lung cancer patients. Radiother Oncol 2015;114(3):367–72.
[90] Unkelbach J, Chan T, Bortfeld T. Accounting for range uncertainties in the optimization of intensity modulated proton therapy. Phys Med Biol 2007;52 (10):2755–73.
[91] Moul JW. The evolving definition of advanced prostate cancer. Rev Urol 2004;6(Suppl 8):S10–7.
[92] Un S, Turk H, Koca O, Divrik R, Zorlu F. Factors determining biochemical recurrence in low-risk prostate cancer patients who underwent radical prostatectomy. Türk Üroloji Dergisi/Turkish J Urol 2015;41(2):61–6.
[93] Eaton B, MacDonald S, Yock T, Tarbell N. Secondary malignancy risk following proton radiation therapy. Front Oncol 2015;5.
[94] Hall E. Intensity-modulated radiation therapy, protons, and the risk of second cancers. Int J Radiat Oncol Biol Phys 2006;65(1):1–7.
[95] Salinas C, Tsodikov A, Ishak-Howard M, Cooney K. Prostate cancer in young men: an important clinical entity. Nat Rev Urol 2014;11(6):317–23.
[96] Konski A, Watkins-Bruner D, Brereton H, Feigenberg S, Hanks G. Long-term hormone therapy and radiation is cost-effective for patients with locally advanced prostate carcinoma. Cancer 2006;106(1):51–7.
[97] Konski A, Watkins-Bruner D, Feigenberg S, Hanlon A, Kulkarni S, Beck J, et al. Using decision analysis to determine the cost-effectiveness of intensity-modulated radiation therapy in the treatment of intermediate risk prostate cancer. Int J Radiat Oncol Biol Phys 2006;66(2):408–15.
[98] Chang AJ, Autio KA, Roach 3rd M, Scher HI. High-risk prostate cancer-classification and therapy. Nat Rev Clin Oncol 2014;11:308–23.
[99] Proton Therapy for High Risk Prostate Cancer- Full Text View - ClinicalTrials.gov [Internet]. Clinicaltrials.gov. 2016 [cited 11 November 2016]. Available from: https://clinicaltrials.gov/ct2/show/NCT01811810.
[100] Owens D. Interpretation of cost-effectiveness analyses. J Gen Intern Med 1998;13(10):716–7.
[101] Peeters A, Grutters J, Pijls-Johannesma M, Reimoser S, De Ruysscher D, Severens J, et al. How costly is particle therapy? Cost analysis of external beam radiotherapy with carbon-ions, protons and photons. Radiother Oncol 2010;95(1):45–53.
[102] Study of Hypo-fractionated Proton Radiation for Low Risk Prostate Cancer - Full Text View - ClinicalTrials.gov [Internet]. Clinicaltrials.gov. 2016 [cited 11 November 2016]. Available from: https://clinicaltrials.gov/ct2/show/NCT01230866.
[103] Muralidhar, Vinayak, Nguyen, Paul L. Maximizing resources in the local treatment of prostate cancer: A summary of cost-effectiveness studies. Urologic Oncol: Seminars Original Invest 10.1016/j.urolonc.2016.06.003.
[104] Kole T, Nichols R, Lei S, Wu B, Huh S, Morris C, 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 2014;54(6):825–31.
[105] Zietman A, DeSilvio M, Slater J, Rossi C, Miller D, Adams J, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate. JAMA 2005;294(10):1233.
[106] Leonhardt D. In health reform, a cancer offers an acid test. The New York Times. July 8, 2009;A1.
[107] Yu J, Cramer L, Herrin J, Soulos P, Potosky A, Gross C. Stereotactic body radiation therapy versus intensity- modulated radiation therapy for prostate cancer: comparison of toxicity. J Clin Oncol 2014;32(12):1195–201.
[108] Ollendorf DA, Hayes JH, McMahon P. Management options for low-risk prostate cancer: a report on comparative effectiveness and value. Inst Clin Econ Rev 2009.
[109] Muralidhar V, Nguyen P. Maximising resources in the local treatment of prostate cancer: a summary of cost-effectiveness studies. Urol Oncol 2017;35:76–85.
[110] Schroeck F, Jacobs B, Bhayani S, Nguyen P, Penson D, Hu J. Cost of new technologies in prostate cancer treatment: systematic review of costs and cost effectiveness of robotic-assisted laparoscopic prostatectomy, intensity modulated radiotherapy and proton beam therapy. Eur Urol 2017;72 (5):712–35.
[111] Yu J, Soulos P, Herrin J, Cramer L, Potosky A, Roberts K, et al. Proton versus intensity-modulated radiotherapy for prostate cancer: patterns of care and early toxicity. J Natl Cancer Inst 2013;105:25–32.
[112] Downs S, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998;52 (6):377–84.