Published in final edited form as:

Cancer. 2015 April 1; 121(7): 1118–1127. doi:10.1002/cncr.29148.

A Case-Matched Study of Toxicity Outcomes After Proton Therapy and Intensity-Modulated Radiation Therapy for Prostate Cancer

Penny Fang, MD¹, Rosemarie Mick, MS², Curtiland Deville, MD¹, Stefan Both, PhD¹, Justin E. Bekelman, MD¹, John P. Christodouleas, MD, MPH¹, Thomas J. Guzzo, MD, MPH³, Zelig Tochner, MD¹, Stephen M. Hahn, MD¹, and Neha Vapiwala, MD¹

¹Department of Radiation Oncology, University of Pennsylvania, Philadelphia, Pennsylvania

²Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, Pennsylvania

³Department of Urology, University of Pennsylvania, Philadelphia, Pennsylvania

Abstract

BACKGROUND—The authors assessed whether proton beam therapy (PBT) for prostate cancer (PCa) was associated with differing toxicity compared with intensity-modulated radiation therapy (IMRT) using case-matched analysis.

METHODS—From 2010 to 2012, 394 patients who had localized PCa received 79.2 Gray (Gy) relative biologic effectiveness (RBE) delivered with either PBT (181 patients) or IMRT (213 patients). Patients were case-matched on risk group, age, and prior gastrointestinal (GI) and genitourinary (GU) disorders, resulting in 94 matched pairs. Both exact matching (risk group) and nearest-neighbor matching (age, prior GI/GU disorders) were used. Residual confounding was adjusted for by using multivariable regression. Maximum acute and late GI/GU Common Terminology Criteria for Adverse Events-graded toxicities were compared using univariate and multivariable logistic and Cox regression models, respectively.

RESULTS—Bladder and rectum dosimetry variables were significantly lower for PBT versus IMRT ($P = .01$). The median follow-up was 47 months (range, 5–65 months) for patients who received IMRT and 29 months (range, 5–50 months) for those who received PBT. On multivariable analysis, which exploited case matching and included direct adjustment for confounders and independent predictors, there were no statistically significant differences between IMRT and PBT in the risk of grade 2 acute GI toxicity (odds ratio, 0.27; 95% confidence interval [CI], 0.06–1.24; $P = .09$), grade 2 acute GU toxicity (odds ratio, 0.69; 95% CI, 0.32–1.51; $P = .$

© 2014 American Cancer Society.

Corresponding author: Neha Vapiwala, MD, Perelman Center for Advanced Medicine, Department of Radiation Oncology, 3400 Civic Center Boulevard, TRC 2W, Philadelphia, PA 19104; Fax: (215) 349-5445; vapiwala@uphs.upenn.edu.

CONFLICT OF INTEREST DISCLOSURES

Dr. Christodouleas is an employee of Elekta, AB.

Additional Supporting Information may be found in the online version of this article.

36), grade 2 late GU toxicity (hazard ratio, 0.56; 95% CI, 0.22–1.41; $P = .22$), and grade 2 late GI toxicity (hazard ratio, 1.24; 95% CI, 0.53–2.94; $P = .62$).

CONCLUSIONS—In this matched comparison of prospectively collected toxicity data on patients with PCa who received treatment with contemporary IMRT and PBT techniques and similar dose-fractionation schedules, the risks of acute and late GI/GU toxicities did not differ significantly after adjustment for confounders and predictive factors.

Keywords

prostate cancer; proton therapy; intensity-modulated radiation therapy; gastrointestinal toxicity; genitourinary toxicity

INTRODUCTION

Intensity-modulated radiotherapy (IMRT) and proton beam therapy (PBT) are modalities used in definitive external beam radiotherapy for localized prostate cancer (PCa) that reportedly achieve similar rates of biochemical relapse-free and overall survival.^{1,2} IMRT is more commonly used,³ but PBT is becoming more prevalent based on dosimetric advantages in minimizing the radiation dose to organs at risk (OARs).^{4,5} In particular, PBT can achieve greater OAR sparing in the low-to-moderate dose range compared with IMRT, particularly with respect to the rectum and rectal wall.⁵ However, PBT has inherent technical challenges, such as range uncertainty, which can necessitate more conservative target volumes.

Despite dosimetric differences, there are few reports comparing acute and late clinical gastrointestinal (GI) and genitourinary (GU) toxicities in patients with PCa who received PBT versus IMRT. Reports comparing GI and GU morbidity in patients who received PBT and IMRT using population-based data identified small differences in toxicity, but the internal validity of those analyses suffered from substantial confounding as well as exposure and misclassification biases.^{6,7} The objective of the current study was to control for these factors by comparing toxicities between contemporary and comparable PBT and IMRT techniques through case-matching on features available in patients' medical records.

MATERIALS AND METHODS

We conducted an Institutional Review Board-approved, comparative analysis of patients with PCa who received PBT from January 2010 (when PBT first became available at our institution) to December 2012 versus a matched group of patients who received IMRT from July 2009 to December 2012. All patients had histologically confirmed prostatic adenocarcinoma with no clinical or pathologic evidence of extraprostatic disease or pelvic lymph node involvement. Patient allocation to PBT or IMRT was based on factors that included an assessment of oncologic and anatomic suitability for PBT determined by a multi-disciplinary proton triage committee as well as patient desire for PBT consideration, machine availability, and insurance coverage. Image-guided radiotherapy with an endorectal balloon was delivered as previously described.⁸ A passive scatter technique consisting of 2 parallel-opposed fields was used for the majority of patients who received PBT. The clinical

target volume (CTV) was contoured as the prostate plus 1 cm of the proximal seminal vesicle. Similar to the method described by Meyer et al,⁹ for purposes of optimization, a volume was defined as an ellipsoid expansion of the CTV with 0.5 cm in all directions, except that axial margins (along the beam direction) were defined as 3.5% of the water equivalent path length (skin to the distal edge of the CTV) plus 1 mm because of range uncertainty. For passive scattering treatments, another 2 mm were added to the axial margins, both proximally and distally, to further mitigate the impact on range uncertainty because of the presence of compensator and multileaf collimator blocks. The total prescribed dose to the CTV was 79.2 Gy/Gy (relative biologic effectiveness) delivered in 44 fractions. A planning target volume was created as a 5-mm, uniform expansion of the CTV for recording and reporting purposes.¹⁰

Clinical Assessment

Toxicities were prospectively scored by GU radiation oncology nurses who were trained and practicing in a joint-modality clinic using Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, weekly during treatment, 1 month after treatment, and at 3-month to 6-month intervals thereafter.¹¹ Patient-reported function was scored using the International Prostatic Symptom Scale (IPSS) and the Expanded Prostate Cancer Index Composite-derived Bowel Symptom Score.¹² Discrepancies in CTCAE scores and qualitative physician descriptions were investigated and resolved individually by 1 of the authors (P.F. and N.V.), and random audits of patients' visit notes were also performed (N.V.) to verify scoring accuracy. Follow-up was completed through June 2014. The median potential follow-up from initiation of treatment was 47 months (range, 5–65 months) for the IMRT group and 29 months (range, 5–50 months) for the PBT group.

Statistical Considerations

Study design and case matching—The primary study objective was to compare rates of acute and late GI and GU toxicity in patients with PCa who received either IMRT or PBT. In total, 394 consecutive patients (213 in the IMRT group and 181 in the PBT group) were identified. To reduce patient selection bias for a particular treatment, we conducted a matching study.¹³ The intent was to construct comparison groups comprised of patients who were matched for several key variables: PCa risk group, age at diagnosis, and prior GU or GI disorders, given the association of preradiation GU symptoms with early GU toxicity.¹⁴ We used exact matching for risk group (low, intermediate, and high according to D'Amico criteria) and nearest-neighbor matching for age and history of prior GU or GI disorders (absent/present). A 1-to-1 matching without replacement was performed using the *MatchIt* routine in the R software program (R Foundation for Statistical Computing, Vienna, Austria). There were 94 matches (total, 188 patients) in the statistical analysis. The statistician (R.M.) was blinded to toxicity outcomes during the matching process.

Statistical analysis—Treatment groups were compared using the chi-square test for categorical variables and the Student *t* test for continuous variables. All *P* values were 2-sided. Regardless of differences (or lack thereof) between groups, all remaining (nonmatched) baseline variables were evaluated as possible predictors, including androgen-deprivation therapy (ADT), hypertension, hemorrhoids, diabetes, Eastern Cooperative

Oncology Group performance status, IPSS score, and Bowel Symptom Score. Acute GI and GU toxicities were scored within 90 days from the start of radiation, graded from 0 to 5, and then dichotomized as grades 0 and 1 versus grade 2 for correlative analyses. Mixed effects logistic regression (Supporting Statistical Analysis; see online supporting information) was used to identify predictors of acute toxicity and to assess associations (ie, odds ratios [ORs]) between the risk of acute GI or GU toxicities and treatment, allowing us to exploit the case matching. Unadjusted and adjusted associations between the risk of acute GI or GU toxicities and treatment were estimated using univariate and multivariable logistic models. Predictive variables with a univariate significance of $P \leq .10$ were tested in the multivariable models. Backward elimination was used to guide in the selection of independent predictors and to construct parsimonious multivariable models, as appropriate for the modest number of events being modeled. Predictive variables included hypertension for acute GI toxicity and ADT and IPSS for acute GU toxicity. To adjust for residual confounding of differences between treatment groups in toxicities experienced just before the acute toxicity period (ie, baseline susceptibility), multivariable models included the preradiation toxicity grade regardless of its univariate significance. These confounders, although they may not be statistically significant on their own, modify the association between acute toxicity and treatment when included in the model.

Late GI and GU toxicities were scored beyond 90 days after the start of radiation, graded from 0 to 3, and then dichotomized as grades 0 and 1 versus grades 2 and 3 for correlative analyses. Because the window is open-ended for late toxicity, survival analysis methods were used. The time to late toxicity was computed as the time from day 90 to either the first date of grade 2 or 3 toxicity (an event) or the last follow-up without grade 2 or 3 toxicity (censored). The median potential follow-up from the day-90 landmark was 41 months (range, 2–62 months) for the IMRT group and 24 months (range, 2–47 months) for the PBT group. This discrepancy was because of the limited start-up capacity of our PBT facility in 2010, resulting in notably lower volumes of patients with PCa undergoing PBT early in the study period. Because only 2 of 188 matched patients died during the follow-up period, and estimation using Kaplan-Meier and cumulative incidence methods would have yielded virtually identical results, we used the Kaplan-Meier method to estimate the 1-year and 2-year toxicity-free rates. A shared-frailty Cox regression (Supporting Statistical Analysis; see online supporting information) was used to identify predictors of late toxicity and to assess associations (ie, hazard ratios [HRs]) between the time to late GI or GU toxicities and treatment, taking advantage of the case matching. The proportional hazards assumption was verified on the basis of Schoenfeld residuals. Unadjusted and adjusted associations between the time to late GI or GU toxicities and treatment were estimated using univariate and multivariable Cox models. For multivariable testing, predictive variables with univariate significance of $P \leq .10$ were tested. Parsimonious multivariable models were constructed as described above. The IPSS score was a predictor for late GU toxicity. To adjust for residual confounding of differences between treatment groups in toxicities experienced before the late toxicity period, multivariable models included both preradiation and acute toxicity grade (ie, baseline and acquired susceptibility, respectively), regardless of univariate significance. Statistical analyses were performed using either Stata/MP 13 (StataCorp, College Station, Tex) or SPSS 20 (IBM Corporation, Armonk, NY).

RESULTS

Baseline Clinical Characteristics for Prematched and Matched Study Populations

There were expected differences between patients who received IMRT and those who received PBT in the pre-matched study population (Table 1). The patients who received PBT were younger, had a lower risk, and were less likely to receive ADT or to have a history of GU disorders or existing comorbidities (eg, hypertension, diabetes). In the matched study population, there were no statistically significant differences between the IMRT and PBT groups with regard to matching variables (all $P > .27$). Moreover, the age difference *within* matched pairs was 5 years in 81% of pairs.

Significant differences between the IMRT and PBT groups did exist for several nonmatching variables, but most were not associated with the risk of toxicities (Tables 2 and 3). The imbalance in the distribution of preradiation GU toxicity in the matched population was attributed to the matching of relatively few intermediate-risk ($n = 35$ of 74) and high-risk ($n = 7$ of 87) patients in the IMRT group. Thus, the 7 patients who had grade 2 preradiation GU toxicity in the IMRT group were unlikely to have been selected for the matched population because of their intermediate-risk ($n = 2$) or high-risk ($n = 5$) grouping. Nonetheless, because preradiation GU toxicity (ie, baseline susceptibility for toxicity) was considered a confounder, it was included in all GU toxicity models. The mean $\pm$ standard error and median prostate volumes did not differ significantly between groups ($P = .65$) and were 44.9 ± 2.9 mL (median, 44.1 mL; range, 9–142 mL) for the PBT group and 47.0 ± 3.7 mL (median, 41.0 mL; range, 17–187 mL) for the IMRT group.

Dosimetry

All patient plans met predefined, stringent target-dose constraints. In the matched study population, as expected, bladder and rectum dosimetry variables (eg, mean/total dose to the target, 5 Gy [V5], V20, V40, V65, and V70) were statistically significantly lower for the PBT group compared with the IMRT group ($P = .01$) (Supporting Table 1; see online supporting information).

Acute GI and GU Toxicities

The majority of patients in the IMRT (86.2%) and PBT (95.7%) groups reported maximum grade 1 acute GI toxicity (Supporting Table 2; see online supporting information). Grade 2 acute GI toxicity was recorded in 13 IMRT patients (13.8%) and 4 PBT patients (4.3%). No patients had grade 3 acute GI toxicity. In univariate analysis, there was a statistically significant reduction in the risk of acute GI toxicity in the PBT group (OR, 0.25; 95% confidence interval [CI], 0.07–0.89; $P = .03$) (Table 2). In patients who had a history of hypertension, the risk of acute GI toxicity was significantly increased (OR, 8.62; 95% CI, 1.29–57.40; $P = .03$). This association was partly a reflection of comorbidities in the IMRT group.

Similarly, most patients in the IMRT (71.2%) and PBT (78.7%) groups reported maximum grade 1 acute GU toxicity. Grade 2 acute GU toxicity was recorded in 27 IMRT patients (28.7%) and 20 PBT patients (21.3%), and none experienced grade 3 acute GU toxicity. The

risk of acute GU toxicity did not differ between groups (OR, 0.63; 95% CI, 0.31–1.30; $P = .21$) (Table 2) but was significantly increased in patients who received ADT (OR, 3.02; 95% CI, 1.10–8.34; $P = .03$) and in those who had higher IPSS scores (OR, 1.08; 95% CI, 1.01–1.15; $P = .03$). The IPSS score was an independent predictor of GU toxicity but had no association with treatment group ($P = .99$) (Table 1).

Late GI and GU Toxicities

Grade 2 late GI toxicity was recorded in 10 IMRT patients (10.8%) and 12 PBT (12.8%) patients (Supporting Table 2; see online supporting information). Two IMRT patients experienced late grade 3 hematochezia. One patient was receiving dabigatran for atrial fibrillation and developed trace hematochezia, which progressed to 3 days of spontaneous rectal bleeding, 2.5 years postradiation; colonoscopy demonstrated radiation proctopathy. The second patient, who was receiving clopidogrel for atrial fibrillation, was admitted for large-volume hematochezia 2 years postradiation; colonoscopy and rectal biopsy revealed angioectasias consistent with radiation colitis. Both patients had resolution of hematochezia after Argon beam coagulation.

From the day-90 landmark, the 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 (Fig. 1A). In univariate analysis, the risk of late GI toxicity did not differ between groups (HR, 1.28; 95% CI, 0.55–2.99; $P = .57$) (Table 3). The risk of late GI toxicity was increased in patients who had grade 1 and 2 preradiation GI toxicity but did not reach statistical significance (HR, 2.65; 95% CI, 0.71–9.85; $P = .15$).

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. One patient who had a history of fulguration for a low-grade bladder tumor had new-onset weak stream 4 months postradiation. Cystoscopy revealed urinary stricture, and urethral dilation was performed with subsequent relief of retention. The second patient, who had a history of marked benign prostatic hyperplasia, presented to the emergency room 1 year postradiation with sudden urinary retention requiring intermittent catheterization.

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 (Fig. 1B). The risk of late GU toxicity did not differ between groups (HR, 0.81; 95% CI, 0.38–1.74; $P = .59$) (Table 3) but was significantly increased with higher IPSS scores (HR, 1.14; 95% CI, 1.06–1.23; $P < .001$) and in patients who had grade 2 acute GU toxicity (HR, 3.21; 95% CI, 1.52–6.76; $P = .002$). The association with grade 2 preradiation GU toxicity also was statistically significant (HR, 3.78; 95% CI, 1.18–12.09; $P = .03$).

Multivariable Models of Acute and Late Toxicity

In multivariable analysis, which exploited case matching and included direct adjustment for confounders (ie, previously experienced toxicity) and significant independent predictors (ie, $P < .05$), there were no statistically significant differences between IMRT and PBT (Table 4). After adjusting for hypertension, the risk of acute GI toxicity was not significantly

different (OR, 0.27; 95% CI, 0.06–1.24; $P = .09$), and the confidence limits indicated that the true risk of acute GI toxicity could be reduced by as much as 94% or increased by as much as 24% with protons. The risk of acute GU toxicity was not different (OR, 0.69; 95% CI, 0.32–1.51; $P = .36$) when adjusting for ADT and IPSS score and confounding by preradiation GU toxicity. The risk of late GI toxicity was not significantly different (HR, 1.24; 95% CI, 0.53–2.94; $P = .62$) when adjusting for confounding by preradiation and acute GI toxicities. After adjusting for IPSS score and confounding by preradiation and acute GU toxicities, the risk of late GU toxicity was not different (HR, 0.56; 95% CI, 0.22–1.41; $P = .22$); and, again, the confidence limits indicated that the true late GU toxicity risk could be reduced or increased with protons. The IPSS score was a strong, independent predictor of late GU toxicity in this model ($P = .002$), with the risk increasing by 13% for each unit increase in IPSS score.

DISCUSSION

To our knowledge, this study examining differences in clinical toxicity between patients with PCa who received image-guided IMRT versus PBT is the first to report a patient-level, matched comparison of these modalities using prospectively collected outcome data. Although proton dose distributions to the bladder and rectum were markedly lower, these differences did not translate to a demonstrable clinical benefit in acute or late GI or GU toxicity.

Acute Toxicity

The current data are consistent with and expand upon previously published toxicity studies (Supporting Table 3; see online supporting information).^{1,6,7,14–20} Yet, in multivariable analysis adjusting for confounders and predictive variables, the risk of neither acute GI toxicity nor acute GU toxicity differed significantly between treatment groups. ADT and IPSS scores were associated with a higher risk of acute GU toxicity. Although ADT was predictive of grade 2 GU toxicity in previous multi-institutional series,^{15,21} mechanisms for urinary effects were not clearly elucidated or consistently observed. Higher IPSS scores were associated with a striking increase in the risk of acute GU toxicity, supporting the relevance of IPSS scores for predicting acute GU toxicity and meriting further investigation.

Gray et al reported worse acute GU/GI toxicity with IMRT versus PBT based on quality-of-life decrements over time derived from patient-reported outcomes.²² However, Hoppe et al reported no difference between IMRT and PBT patient-reported changes in bowel, urinary, and sexual summary scores within 2 years after treatment.²³ Our provider-reported outcomes from “blended-modality” clinics should complement such studies, because the latter are subject to patient-perceived biases in addition to inherent imbalances in the populations compared, including age, treatment-seeking behavior, and underlying risk factors.

Late Toxicity

Our overall rates of GU and GI toxicities with PBT were consistent with prior reports (Supporting Table 3; see online supporting information), although we observed a slightly

higher GI toxicity rate, which may be partially because of higher baseline GI morbidity in our matched PBT group. In our IMRT group, the grade 2 late GI toxicity rate was 3.4% by 1 year, with 2 late grade 3 GI toxicities noted overall, and the 1-year grade 2 GU toxicity rate was 11.1%, which, again, was within range of other institutional series.

In multivariable analysis adjusting for confounders and predictive variables, the risk of neither late GI toxicity nor late GU toxicity was significantly different between treatment groups. In our study, acute GI morbidity was not predictive of late GI morbidity, whereas acute GU toxicity did predict a risk of late GU toxicity. Furthermore, patient-reported IPSS scores were strongly predictive of late GU toxicity, underscoring its radiation modality-independent relevance to clinical outcomes. Matched PBT patients had shorter follow-up duration than IMRT patients, which may have imposed a bias toward lower rates of late GI toxicity in the PBT group; however, higher 1-year and 2-year GI toxicity rates actually were observed in the PBT group. It appeared that most late GI toxicities occurred by 24 months, but additional follow-up is needed to verify this early observation. The 1-year and 2-year GU toxicity rates were similar between groups, but additional late events after 2 years were observed in the IMRT group, underscoring the importance of continued toxicity surveillance of patients. This finding is consistent with that observed in the claims-based analysis performed by Yu et al,⁷ although another claims-based, propensity score-matched comparison between IMRT and PBT reported a lower rate of GI morbidity with IMRT.⁶ Although claims-based reports offer the enticing power of numbers, there are multiple well described limitations to substituting insurance codes for primary source data, because only the latter can accurately provide and control for radiation dose, treatment volume, and actual clinical events.²⁴

Limitations of this report include its retrospective analysis of a nonrandomized, mixed cohort of patients. However, we rigorously matched patients in an attempt to minimize the effect of confounding factors. We chose to match patients exactly on risk group. This was critical given the dramatic difference between the IMRT and PBT groups in the prematched study population, and forcing balance in the risk distribution would allow for greater clarity in the interpretation of results. Our approach to testing was also rigorous, because our mixed effects models both exploited case matching and included direct adjustment for confounders and independent predictive factors. Because of the modest numbers of patients and events in the study, we avoided model over-fitting and sought parsimonious, multivariable models. Nonetheless, our analyses may have been underpowered to detect clinically important differences in treatment. Moreover, the confidence intervals for the true relative risks were wide and included zero, indicating that the true risks may have been decreased or increased with protons. Finally, this is a preliminary report with relatively limited follow-up to characterize the late GI and GU toxicities that occur beyond 2 years. Continued surveillance could reveal meaningful differences in clinical and patient-reported toxicity over time. Ultimately, however, our current findings suggest that, over the first few years of follow-up, clinical benefits from improved dosimetry may not manifest in provider-reported toxicity assessments.

Conclusions

This study provides a rigorous comparative analysis of acute and late toxicity rates in patients with PCa who receive definitive radiotherapy using IMRT and PBT modalities. Although dosimetric differences in the bowel, bladder, and rectum were evident between patients in the PBT and IMRT groups, we did not observe significant differences in the risks of acute or late GI and GU toxicity after controlling for known confounders. Careful prospective evaluation of the rapidly evolving technology of PBT is needed to better characterize the merit of its apparent dosimetric advantages.

Acknowledgments

FUNDING SUPPORT

This work was supported by the University of Pennsylvania. Dr. Bekelman was supported by National Cancer Institute grant K07-CA163616: Effectiveness of Radiotherapy for Prostate Cancer.

References

1. Slater JD, Rossi CJ, Yonemoto LT, et al. Conformal proton therapy for early-stage prostate cancer. *Urology*. 1999; 4295:978–984. [PubMed: 10223493]
2. Hoppe B, Henderson R, Mendenhall WM, Nichols RC, Li Z, Mendenhall NP. Proton therapy for prostate cancer. *Oncology (Williston Park)*. 2011; 25:644–650. 652. [PubMed: 21888265]
3. Dinan M, Robinson T, Zagar T. Changes in initial treatment for prostate cancer among Medicare beneficiaries, 1999–2007. *Int J Radiat Oncol Biol Phys*. 2012; 82:e781–e786. [PubMed: 22331001]
4. Fowler J. What can we expect from dose escalation using proton beams? *Clin Oncol*. 2003; 15:S10–S15.
5. Vargas C, Fryer A, Mahajan C, et al. Dose-volume comparison of proton therapy and intensity-modulated radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2008; 70:744–751. [PubMed: 17904306]
6. Sheets NC, Goldin GH, Meyer A, et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. *JAMA*. 2012; 307:1611–1620. [PubMed: 22511689]
7. Yu JB, Soulos PR, Herrin J, et al. Proton versus intensity-modulated radiotherapy for prostate cancer: patterns of care and early toxicity. *J Natl Cancer Inst*. 2013; 105:25–32. [PubMed: 23243199]
8. Deville C, Both S, Bui V, et al. Acute gastrointestinal and genitourinary toxicity of image-guided intensity modulated radiation therapy for prostate cancer using a daily water-filled endorectal balloon [serial online]. *Radiat Oncol*. 2012; 7:76. [PubMed: 22621764]
9. Meyer J, Bluett J, Amos R, et al. Spot scanning proton beam therapy for prostate cancer: treatment planning technique and analysis of consequences of rotational and translational alignment errors. *Int J Radiat Oncol Biol Phys*. 2010; 78:428–434. [PubMed: 20100641]
10. Jones, D.; Suit, H.; Akine, Y. International Commission on Radiation Units and Measurements Report 78: Prescribing, Recording, and Reporting Proton-Beam Therapy. Bethesda, MD: International Commission on Radiation Units and Measurements; 2007.
11. Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol*. 2003; 13:176–181. [PubMed: 12903007]
12. Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG. Development and validation of the Expanded Prostate Cancer Index Composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. *Urology*. 2000; 56:899–905. [PubMed: 11113727]

13. Rubin, DB. Matched Sampling for Causal Effects. Cambridge, UK: Cambridge University Press; 2006.
14. Mendenhall NP, Li Z, Hoppe BS, et al. Early outcomes from 3 prospective trials of image-guided proton therapy for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2012; 82:213–221. [PubMed: 21093164]
15. Mayahara H, Murakami M, Kagawa K, et al. Acute morbidity of proton therapy for prostate cancer: the Hyogo Ion Beam Medical Center experience. *Int J Radiat Oncol Biol Phys*. 2007; 69:434–443. [PubMed: 17482768]
16. Nihei K, Ogino T, Onozawa 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; 81:390–396. [PubMed: 20832180]
17. Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinary toxicities after 3-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2008; 70:1124–1129. [PubMed: 18313526]
18. Pugh TJ, Munsell MF, Choi S, 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; 87:946–953. [PubMed: 24139077]
19. Eade TN, Horwitz EM, Ruth K, et al. A comparison of acute and chronic toxicity for men with low-risk prostate cancer treated with intensity-modulated radiation therapy or (125)I permanent implant. *Int J Radiat Oncol Biol Phys*. 2008; 71:338–345. [PubMed: 18207665]
20. De Meerleer GO, Fonteyne VH, Vakaet L, et al. Intensity-modulated radiation therapy for prostate cancer: late morbidity and results on biochemical control. *Radiother Oncol*. 2007; 82:160–166. [PubMed: 17222931]
21. Feng M, Hanlon AL, Pisansky TM, 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; 68:1417–1423. [PubMed: 17418972]
22. Gray PJ, Paly JJ, Yeap BY, et al. Patient-reported outcomes after 3-dimensional conformal, intensity-modulated, or proton beam radio-therapy for localized prostate cancer. *Cancer*. 2013; 119:1729–1735. [PubMed: 23436283]
23. Hoppe B, Michalski J, Mendenhall N. Comparative effectiveness study of patient reported outcomes after proton therapy or intensity-modulated radiotherapy for prostate cancer. *Cancer*. 2014; 120:1076–1082. [PubMed: 24382757]
24. Deville C, Ben-Josef E, Vapiwala N. Radiation therapy modalities for prostate cancer [letter]. *JAMA*. 2012; 308:450. author reply 451–452.

Figure 1.

From 90 days after the start of radiation (the day-90 landmark), time to Grade 2 late GI and GU Toxicity in IMRT patients (blue lines) and PBT patients (green lines). (A) Late GI toxicity. IMRT versus PBT treatment comparison adjusted HR = 1.24, $P = 0.62$. (B) Late GU toxicity. IMRT versus PBT treatment comparison adjusted HR = 0.56, $P = 0.22$.

TABLE 1

Baseline Variables of All Patients and Patients Included in the Matching Study

Variable	All Patients Identified			Patients Included in the Matching Study		
	No. (%)		P	No. (%)		P
	IMRT, n = 213	PBT, n = 181		IMRT, n = 94	PBT, n = 94	
Risk group						
Low	52 (24.4)	139 (76.8)	<.001	52 (55.3)	52 (55.3)	1.00
Intermediate	74 (34.7)	35 (19.3)		35 (37.2)	35 (37.2)	
High	87 (40.8)	7 (3.9)		7 (7.4)	7 (7.4)	
Prior GI disorders						
No	196 (92)	159 (87.8)	.17	80 (85.1)	83 (88.3)	.52
Yes	17 (8)	22 (12.2)		14 (14.9)	11 (11.7)	
Prior GU disorders						
No	154 (72.3)	157 (86.7)	<.001	73 (77.7)	79 (84)	.27
Yes	59 (27.7)	24 (13.3)		21 (22.3)	15 (16)	
Age, y						
40–49	1 (0.5)	3 (1.7)	.001	0 (0)	0 (0)	.38
50–59	42 (19.7)	48 (26.5)		18 (19.1)	25 (26.6)	
60–69	87 (40.8)	94 (51.9)		44 (46.8)	47 (50)	
70–79	71 (33.3)	33 (18.2)		29 (30.9)	20 (21.3)	
80	12 (5.6)	3 (1.7)		3 (3.2)	2 (2.1)	
ADT						
No	91 (42.9)	164 (90.6)	<.001	66 (71)	79 (84)	.03
Yes	121 (57.1)	17 (9.4)		27 (29)	15 (16)	
Hypertension						
No	78 (36.6)	101 (55.8)	<.001	31 (33)	51 (54.3)	.003
Yes	135 (63.4)	80 (44.2)		63 (67)	43 (45.7)	
Hemorrhoids						
No	196 (92)	154 (85.1)	.03	85 (90.4)	81 (86.2)	.36
Yes	17 (8)	27 (14.9)		9 (9.6)	13 (13.8)	
Diabetes mellitus						

Variable	All Patients Identified			Patients Included in the Matching Study		
	IMRT, n = 213	PBT, n = 181	P	IMRT, n = 94	PBT, n = 94	P
No	161 (75.6)	163 (90.1)	<.001	72 (76.6)	81 (86.2)	.09
Yes	52 (24.4)	18 (9.9)		22 (23.4)	13 (13.8)	
ECOG PS						
0	195 (92)	174 (96.1)	.16	87 (92.6)	91 (96.8)	.19
1	15 (7.1)	7 (3.9)		7 (7.4)	3 (3.2)	
2	2 (0.9)	0 (0)		0 (0)	0 (0)	
Preradiation GI toxicity grade						
0	194 (91.5)	165 (91.2)	.38	88 (93.6)	86 (91.5)	.36
1	18 (8.5)	14 (7.7)		6 (6.4)	6 (6.4)	
2	0 (0)	2 (1.1)		0 (0)	2 (2.1)	
Preradiation GU toxicity grade						
0	115 (54.2)	99 (54.7)	.28	63 (67)	53 (56.4)	.004
1	90 (42.5)	69 (38.1)		31 (33)	31 (33)	
2	7 (3.3)	12 (6.6)		0 (0)	10 (10.6)	
3	0 (0)	1 (0.6)		0 (0)	0 (0)	
IPSS			.56			.99
No.	201	181		91	94	
Mean $\pm$ SD	7.7 $\pm$ 6.5	7.3 $\pm$ 6.2		6.9 $\pm$ 6.0	6.9 $\pm$ 5.8	
Range	0–34	0–25		0–31	0–23	
BSS			.05			.003
No.	108	139		54	76	
Mean $\pm$ SD	94.8 $\pm$ 7.5	92.9 $\pm$ 7.9		96.6 $\pm$ 5.4	92.7 $\pm$ 9.3	
Range	60.7–100	53.6–100		71–100	53.6–100	

Abbreviations: ADT, androgen-deprivation therapy; BSS, Bowel Symptom Score; ECOG PS, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; GU, genitourinary; IMRT, intensity-modulated radiotherapy; IPSS, International Prostate Symptom Score; PBT, proton beam therapy; SD, standard deviation.

TABLE 2

Univariate Analyses of Acute Gastrointestinal and Genitourinary Toxicity

Variable	Acute GI Toxicity: No. (%)			Logistic Regression Models ^a			Acute GU Toxicity: No. (%)			Logistic Regression Models ^a			
	Grade 0–1	Grade 2–3		OR	95% CI	P	Grade 0–1	Grade 2–3		OR	95% CI	P	
Treatment group													
IMRT	81 (86.2)	13 (13.8)		1.00			67 (71.3)	27 (28.7)		1.00			
PBT	90 (95.7)	4 (4.3)		0.25	0.07–0.89	.03	74 (78.7)	20 (21.3)		0.63	0.31–1.30	0.21	
ADT													
No	132 (91)	13 (9.)		1.00			114 (78.6)	31 (21.4)		1.00			
Yes	38 (90.5)	4 (9.5)		1.09	0.32–3.78	.88	26 (61.9)	16 (38.1)		3.02	1.10–8.34	.03	
Hypertension													
No	80 (97.6)	2 (2.4)		1.00			64 (78)	18 (22)		1.00			
Yes	91 (85.8)	15 (14.2)		8.62	1.29–57.40	.03	77 (72.6)	29 (27.4)		1.49	0.67–3.32	.33	
Hemorrhoids													
No	152 (91.6)	14 (8.4)		1.00			123 (74.1)	43 (25.9)		1.00			
Yes	19 (86.4)	3 (13.6)		1.81	0.43–7.68	.42	18 (81.8)	4 18.2		0.72	0.20–2.62	.62	
Diabetes mellitus													
No	140 (91.5)	13 (8.5)		1.00			115 (75.2)	38 (24.8)		1.00			
Yes	31 (88.6)	4 (11.4)		1.39	0.41–4.73	.60	26 (74.3)	9 (25.7)		1.11	0.43–2.87	.84	
ECOG PS													
0	161 (90.4)	17 (9.6)		1.00			134 (75.3)	44 (24.7)		1.00			
1	10 (100)	0 (0)		NE	NE	NE	7 (70)	3 (30)		1.42	0.29–6.93	.67	
Preradiation GI or GU toxicity grade ^b													
0	157 (90.2)	17 (9.8)		1.00			89 (76.7)	27 (23.3)		1.00			
1–2	14 (100)	0 (0)		NE	NE	NE	45 (72.6) 7 (70)	17 (27.4) 3 (30)		1.33 1.33	0.59–2.98 0.26–6.77	.49 .73	
IPSS													
No.	169	16					139	46					
Mean ± SD	7.0 ± 6.0	6.4 ± 4.2		0.98	0.89–108	.74	6.4 ± 5.7	8.6 ± 6.0		1.08	1.01–1.15	.03	
Range	0–31	0–15					0–31	1–24					
BSS													

Variable	Acute GI Toxicity: No. (%)			Logistic Regression Models ^a			Acute GU Toxicity: No. (%)			Logistic Regression Models ^a		
	Grade 0-1	Grade 2-3	No.	OR	95% CI	P	Grade 0-1	Grade 2-3	No.	OR	95% CI	P
No.	122	8					102	28				
Mean ± SD	94.3 ± 8.0	95.1 ± 9.5		1.04	0.90–1.19	.60	94.4 ± 8.0	93.7 ± 8.5		.99	0.93–1.04	.62
Range	53.6–100	75–100					53.6–100	71–100				

Abbreviations: ADT, androgen-deprivation therapy; BSS, Bowel Symptom Score; ECOG PS, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; GU, genitourinary; IMRT, intensity-modulated radiotherapy; NE, not estimable; PBT, proton beam therapy; SD, standard deviation.

^aThe mixed-effects models accounted for patient matching.

^bFor GI toxicity, preradiation grade 0 toxicity was tested versus grade 1 and 2 toxicity. For GU toxicity, preradiation grade 0 versus grade 1 versus grade 2 was tested. Not all values could be evaluated (NE), because all patients who had either an ECOG PS of 1 or grade 1 or 2 preradiation GI toxicity had grade 0 or 1 acute toxicity.

TABLE 3

Univariate Analyses of Late Gastrointestinal and Genitourinary Toxicity

Treatment group														
Variable	No.	No. of Events	Late GI Toxicity			Cox Regression Models ^a			Late GU Toxicity			Cox Regression Models ^a		
			No. of Events	1-Year Toxicity-Free Rate, % ^b	HR	95% CI	P	No. of Events	No.	1-Year Toxicity-Free Rate, % ^b	HR	95% CI	P	
IMRT	93	10		96.6	1.00		93	17		88.9	1.00			
PBT	94	12		90.3	1.28	0.55–2.99	.57	94	12		88.2	0.81	0.38–1.74	.59
ADT														
No	145	21		92.2	1.00		145	21		88.8	1.00			
Yes	41	1		97.1	0.18	0.02–1.35	.10	41	7		87	1.35	0.55–3.30	.51
Hypertension														
No	81	10		91.1	1.00		81	13		88.6	1.00			
Yes	106	12		95.1	0.83	0.35–1.98	.67	106	16		88.4	0.88	0.41–1.88	.75
Hemorrhoids														
No	165	19		93.7	1.00		165	27		88.1	1.00			
Yes	22	3		90.9	1.18	0.33–4.22	.80	22	2		90.9	0.54	0.12–2.32	.41
Diabetes mellitus														
No	152	18		94.5	1.00		152	21		89.2	1.00			
Yes	35	4		87.9	1.03	0.33–3.15	.96	35	8		85.3	1.63	0.70–3.78	.26
ECOG PS														
0	178	21		93	1.00		178	26		88.5	1.00			
1	9	1		100	0.90	0.11–7.15	.92	9	3		87.5	2.20	0.65–7.49	.21
Preradiation GI or GU toxicity grade ^c														
0	174	19		94	1.00		116	17		89.3	1.00			
1–2	13	3		84.6	2.65	0.71–9.85	.15	61	8		90	0.91	0.39–2.15	.91
							10	4		70	3.78	1.18–12.09	0.3	
Acute GI or GU toxicity grade ^d														
0–1	170	20		92.7	1.00		141	16		92.7	1.00			
2–3	17	2		100	0.98	0.22–4.49	.98	46	13		75	3.21	1.52–6.76	.002
IPSS	184	21			0.98	0.91–1.06	.64	184	27			1.14	1.06–1.23	<.001
BSS	129	16			1.02	0.95–1.09	.67	129	17			0.97	0.93–1.00	.08

Abbreviations: ADT, androgen-deprivation therapy; BSS, Bowel Symptom Score; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; GU, genitourinary; HR, hazard ratio; IMRT, intensity-modulated radiotherapy; IPSS, International Prostate Symptom Score; PBT, proton beam therapy.

^p Shared-frailty models accounted for patient matching.

^q The 1-year toxicity-free rate was calculated from 90 days after the initiation of radiation therapy.

^c For GI toxicity, preradiation grade 0 toxicity was tested versus grade 1 and 2 toxicity. For GU toxicity, preradiation grade 0 versus grade 1 versus grade 2 toxicity was tested.

^d Acute toxicity was evaluated as a confounder for the risk of late toxicity.

TABLE 4
Multivariable Analyses of Acute and Late Gastrointestinal and Genitourinary Toxicity

Toxicity Outcome	Univariate Models ^a				Multivariable Models ^a			
	OR	HR	95% CI	P	OR	HR	95% CI	P
Acute GI toxicity								
IMRT	1.00					1.00		
PBT	0.25 ^b		0.07–0.89	.03	0.27 ^c		0.06–1.24	.09
Acute GU toxicity								
IMRT	1.00					1.00		
PBT	0.63 ^b		0.31–1.30	.21	0.69 ^d		0.32–1.51	.36
Late GI toxicity								
IMRT		1.00					1.00	
PBT		1.28 ^b	0.55–2.99	.57		1.24 ^e	0.53–2.94	.62
Late GU toxicity								
IMRT		1.00					1.00	
PBT		0.81 ^b	0.38–1.74	.59		0.56 ^f	0.22–1.41	.22

Abbreviations: CI, confidence interval; GI, gastrointestinal; GU, genitourinary; HR, hazard ratio; IMRT, intensity-modulated radiotherapy; OR, odds ratio; PBT, proton beam therapy.

^aBoth models accounted for patient matching.

^bThese are unadjusted ORs and HRs.

^cThis OR was adjusted for confounding by hypertension.

^dThis OR was adjusted for confounding by preradiation GU toxicity and by the independent predictors androgen-deprivation therapy and International Prostate Symptom Score.

^eThis HR was adjusted for confounding by preradiation and acute GI toxicity.

^fThis HR was adjusted for confounding by preradiation and acute GU toxicity and by the independent predictor International Prostate Symptom Score.