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ORIGINAL REPORT

Comparative Toxicities and Cost of Intensity-Modulated Radiotherapy, Proton Radiation, and Stereotactic Body Radiotherapy Among Younger Men With Prostate Cancer

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ABSTRACT

Purpose
To compare the toxicities and cost of proton radiation and stereotactic body radiotherapy (SBRT) with intensity-modulated radiotherapy (IMRT) for prostate cancer among men younger than 65 years of age with private insurance.

Methods
Using the MarketScan Commercial Claims and Encounters database, we identified men who received radiation for prostate cancer between 2008 and 2015. Patients undergoing proton therapy and SBRT were propensity score–matched to IMRT patients on the basis of clinical and sociodemographic factors. Proportional hazards models compared the cumulative incidence of urinary, bowel, and erectile dysfunction toxicities by treatment. Cost from a payer's perspective was calculated from claims and adjusted to 2015 dollars.

Results
A total of 693 proton therapy patients were matched to 3,465 IMRT patients. Proton therapy patients had a lower risk of composite urinary toxicity (33% *v* 42% at 2 years; $P < .001$) and erectile dysfunction (21% *v* 28% at 2 years; $P < .001$), but a higher risk of bowel toxicity (20% *v* 15% at 2 years; $P = .02$). Mean radiation cost was $115,501 for proton therapy patients and $59,012 for IMRT patients ($P < .001$). A total of 310 SBRT patients were matched to 3,100 IMRT patients. There were no significant differences in composite urinary, bowel, or erectile dysfunction toxicities between SBRT and IMRT patients ($P > .05$), although a higher risk of urinary fistula was noted with SBRT (1% *v* 0.1% at 2 years; $P = .009$). Mean radiation cost for SBRT was $49,504 and $57,244 for IMRT ($P < .001$).

Conclusion
Among younger men with prostate cancer, proton radiation was associated with significant reductions in urinary toxicity but increased bowel toxicity at nearly twice the cost of IMRT. SBRT and IMRT were associated with similar toxicity profiles; SBRT was modestly less expensive than IMRT.

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INTRODUCTION

From 2000 to 2010, intensity-modulated radiotherapy (IMRT) became the most common radiation treatment modality for localized prostate cancer.[1,2] Although more expensive than the historical standard of three-dimensional conformal radiation therapy, IMRT allowed for improved sparing of normal tissues that reduced treatment toxicity while facilitating modest dose escalation that improved biochemical disease-free survival.[3,4] Newer radiation techniques, such as proton radiation and stereotactic body radiotherapy (SBRT), seek to build on these gains. Specifically, proton therapy decreases low-dose radiation exposure to uninvolved organs, which potentially translates into lower risks of treatment toxicity and second malignancy.[5-7] Alternatively, SBRT decreases the number of treatment fractions to only five or fewer, thereby improving convenience and lowering cost.[8]

Recent studies have shown that prostate cancer is among the most common indications for treatment with these advanced radiation modalities.[9] Despite their potential benefits, high-level evidence supporting either modality as a replacement for IMRT has been difficult to

ASSOCIATED CONTENT

Appendix
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gather through randomized trials, which has prompted analyses of claims data to evaluate their comparative effectiveness. The current literature suggests that proton radiation costs more than IMRT, with no definite evidence of clinical benefit,[2,10] whereas SBRT provides cost savings at the expense of increased genitourinary (GU) toxicity.[11,12]

The available literature is derived almost exclusively from Medicare claims and limited to older men. However, patients younger than 65 years of age account for over 40% of prostate cancer diagnoses[13] and are unique because of smaller prostate volumes and fewer comorbidities.[14] Furthermore, reimbursement from private plans is considerably higher than Medicare. As such, it would be inappropriate to extrapolate existing comparative effectiveness and cost data to younger men. Thus, our goal was to evaluate the toxicity profile and cost of proton radiation and SBRT compared with IMRT in a cohort of younger men with incident prostate cancer using a contemporary private insurance claims database.

METHODS

Study Cohort

We used the MarketScan Commercial Claims and Encounter database (Truven Health Analytics, Ann Arbor, MI), a nationwide, employment-based convenience sample of medical claims data of employees and dependents younger than 65 years of age aggregated from over 100 payers.[15] Patients were included if they received IMRT, proton therapy, or SBRT (Appendix Table A1, online only) for a primary diagnosis of prostate cancer between 2008 and 2015 and had continuous coverage from 6 months before through 6 months after starting treatment. Patients were excluded if they received brachytherapy or combined radiation modalities, or if pretreatment claims indicated metastatic disease, radical prostatectomy, or other malignancy.

Defining Treatment

All time-to-event analyses were indexed to the start of treatment, defined as the date of first radiation treatment. Radiation treatment was defined as at least three fractions of SBRT or 20 fractions of IMRT or proton radiation within 90 days of starting radiation. Any androgen deprivation therapy (ADT) in claims from 6 months before through 3 months after starting radiation was considered treatment with concurrent ADT (Appendix Table A2, online only).

Covariables

Patient-level covariables extracted from MarketScan included age, metropolitan service area (MSA), geographic region, treatment year, insurer relation (employee *v* spouse/dependent), and insurance type (health maintenance organization or capitated *v* noncapitated plans). MSA-level median household income was obtained from the US Census Bureau[16] and divided into quartiles. Modified Charlson comorbidity index was determined using pretreatment claims.[17]

Outcomes

Treatment toxicity was defined a priori by the presence of specific diagnosis or procedure codes selected based on literature review[2,10-12,18,19] and expert opinion (Appendix Table A3, online only). Toxicity was initially divided into composite categories of urinary toxicity, bowel toxicity, and erectile dysfunction (ED). Urinary and bowel toxicities were further subcategorized for additional detail (Appendix Table A3). The most common diagnosis and procedure codes are listed in Appendix Table A4 (online only). The presence of each toxicity as a preradiation comorbidity was determined using pretreatment claims.

Costs were adjusted to 2015 US dollars using the Medical Care Consumer Price Index[20] and reported from a payer perspective unless otherwise noted. Radiation cost included treatment planning, treatment delivery, and patient management spanning 1 month before through 6 months after treatment. Out-of-pocket radiation costs were also computed. Complication cost was defined as the cost of all claims on days where toxicity was recorded. Total health care cost included all medical and pharmacy claims starting 1 month before treatment.

Statistical Analysis

Baseline covariables among the treatment groups of IMRT, proton radiation, and SBRT were compared using the χ^2 test. Propensity score-matched cohorts were created to account for differences in baseline covariables. Propensity scores were computed using logistic models with dependent variables of IMRT versus proton and IMRT versus SBRT and independent variables of age, residence type, median household income, geographic region, treatment year, employee relation, capitated insurance plan, medical comorbidity, baseline GU/bowel comorbidity, and concurrent ADT. Patients were matched using a greedy algorithm and a maximum allowed caliper distance of 0.1.[21] Covariable balance was assessed by postmatch standardized difference, with less than 10% indicating a similar distribution.[22] The number of matched IMRT patients was maximized while preserving the number of included proton and SBRT patients.

Within each matched cohort, separate Cox proportional hazards models stratified by matched pair were constructed to determine the hazard ratio of proton radiation or SBRT relative to IMRT for developing each toxicity. The proportional hazards assumption was confirmed by inspection of log (−log [survival]) curves. The modeled cumulative incidence of each toxicity at 6, 12, 24, and 36 months after the start of radiation is reported by treatment modality. Sensitivity analyses included (1) dividing the toxicity profile of treatment into early (up to 12 months) versus late (after 12 months) per existing literature,[2,10] (2) including only procedure codes (and excluding diagnosis codes) in toxicity assessment as a surrogate of severity, and (3) assessing toxicity as combinations of procedure and diagnosis codes previously validated for five severe toxicities (cystitis, rectal complications, urethral stricture, ureteral stricture, and urinary/rectal fistula) after pelvic radiation.[19] Toxicity analysis was performed using SAS, version 9.4 (SAS Institute, Cary, NC).

Mean radiation cost within matched cohorts was compared using the Wilcoxon rank sum test. Mean values of complication and total health care cost were estimated at various time points while accounting for censored data using the general representation theorem for missing data processes and were compared as asymptotically normally distributed values.[23] Cost analysis was conducted using Stata software, version 14 (STATA, College Station, TX) using the hcost module.[24]

RESULTS

Patient Characteristics

A total of 12,128 patients met the study selection criteria (Table 1), which included 11,123 IMRT patients (92%), 693 proton therapy patients (6%), and 312 SBRT patients (3%). The median number of treatment fractions was 42 for IMRT (interquartile range [IQR], 38 to 44), 39 for proton radiation (IQR, 39 to 44), and five for SBRT (IQR, 5 to 5). IMRT patients were more likely to reside in MSAs with lower median household income, have greater medical comorbidity, and receive concurrent ADT. Proton therapy patients were younger and more likely to participate in a noncapitated insurance plan. SBRT patients were more likely to be

Table 1. Patient Characteristics

Covariable	Proton (n = 693) No.	%	SBRT (n = 312) No.	%	IMRT (n = 11,123) No.	%	Total) (n = 12,128) No.	%	*P*
Age, years									< .001
≤ 55	198	29	72	23	2,233	20	2,503	21	
56-60	270	39	104	33	4,033	36	4,407	36	
61-64	225	32	136	44	4,857	44	5,218	43	
Residence									< .001
Rural	92	13	22	7	1,448	13	1,562	13	
Urban	578	83	288	92	9,476	85	10,342	85	
Unknown	23	3	2	1	199	2	224	2	
Median household income									< .001
Lowest quartile	41	6	14	4	799	7	854	7	
2nd quartile	86	12	29	9	1,369	12	1,484	12	
3rd quartile	127	18	67	21	2,724	24	2,918	24	
Highest quartile	323	47	177	57	4,580	41	5,080	42	
Unknown	116	17	25	8	1,651	15	1,792	15	
Region									< .001
Northeast	52	8	90	29	2,528	23	2,670	22	
North central	115	17	56	18	2,186	20	2,357	19	
South	353	51	107	34	4,722	42	5,182	43	
West	150	22	57	18	1,485	13	1692	14	
Unknown	23	3	2	1	202	2	227	2	
Treatment year									< .001
2008-2011	407	59	109	35	6,653	60	7,169	59	
2012-2015	286	41	203	65	4,470	40	4,959	41	
Employee relation									.86
Self	548	79	243	78	8,634	78	9,425	78	
Dependent	145	21	69	22	2,483	22	2,697	22	
HMO or PPO with capitation									< .001
No	642	93	277	89	9,756	88	10,675	88	
Yes	51	7	35	11	1,367	12	1,453	12	
Comorbidity									< .001
None	604	87	259	83	8,685	78	9,548	79	
1	68	10	40	13	1,805	16	1,913	16	
≥ 2	21	3	13	4	633	6	667	6	
Concurrent ADT									< .001
No	563	81	289	93	7,793	70	8,645	71	
Yes	130	19	23	7	3,330	30	3,483	29	

Abbreviations: ADT, androgen deprivation therapy; HMO, health maintenance organization; IMRT, intensity-modulated radiotherapy; PPO, preferred provider organization; SBRT, stereotactic body radiotherapy.

treated in the latter half of the study period and reside in urban locations. Pretreatment urinary comorbidity was lower among proton therapy patients, bowel comorbidity was similar among treatment groups, and ED was higher among IMRT patients (Appendix Table A5, online only).

A total of 693 proton therapy patients (median follow-up, 23 months) were matched to 3,465 IMRT patients (median follow-up, 23 months), and 310 SBRT patients (median follow-up, 18 months) were matched to 3,100 IMRT patients (median follow-up, 21 months). Postmatch baseline covariables, including pretreatment urinary, bowel, and ED comorbidity, were similar between treatment groups (Appendix Table A6, online only).

Proton-IMRT Comparison

Comparative toxicities of patients receiving proton therapy and IMRT are listed in Table 2. Proton therapy patients had a lower risk of composite urinary toxicity (33% *v* 42% at 2 years; $P < .001$), which was persistent on sensitivity analysis when assessed as early, late, or procedure-only toxicity (Appendix Tables A7 and A8, online only). This urinary benefit with proton radiation was seen across multiple domains, including incontinence, bleeding/irritation, obstruction, and stricture (Figs 1A to 1E). Sensitivity analysis demonstrated reduction in urinary bleeding/irritation and obstruction/retention in the early period, stricture in the late period, and incontinence in both periods (Appendix Table A7). Additional sensitivity analysis using previously validated pelvic radiation severe toxicity criteria also demonstrated a lower risk of urethral stricture with proton radiation (0% *v* 1% at 2 years; $P = .03$; Appendix Table A9, online only). Bowel toxicity was higher among proton therapy patients (20% *v* 15% at 2 years; $P = .02$), which was principally late bleeding/proctitis (Figs 1F to 1G; Appendix Table A7) and confirmed on procedure-only sensitivity analysis (Appendix Table A8). ED was less common among proton therapy patients (21% *v* 28% at 2 years; $P < .001$; Fig 1H), but the difference did not persist when assessed as procedure-only toxicity (Appendix Table A8).

The mean radiation cost for protons and IMRT to the payer was $115,501 and $59,012 ($P < .001$), respectively, and to the patient was $2,269 and $1,714 ($P < .001$), respectively. Proton

Table 2. Toxicities for Propensity Score-Matched IMRT and Proton Cohort

Toxicity	Proton (reference, IMRT) HR (95% CI)	*P*	6- month Incidence (%) IMRT (n = 3,465)	6- month Incidence (%) Proton (n = 693)	12-month Incidence (%) IMRT (n = 2,862)	12-month Incidence (%) Proton (n = 572)	24-month Incidence (%) IMRT (n = 1,718)	24-month Incidence (%) Proton (n = 341)	36-month Incidence (%) IMRT (n = 1,003)	36-month Incidence (%) Proton (n = 205)
Any urinary toxicity	0.72 (0.63 to 0.83)	< .001	21.5	12.1	31.6	23.1	42.2	33.3	48.3	39.1
Incontinence	0.36 (0.21 to 0.60)	< .001	1.4	0.0	3.0	0.5	5.9	2.1	7.5	3.5
Bleeding/irritation	0.79 (0.68 to 0.91)	.002	17.7	10.9	26.4	21.2	36.0	31.1	42.4	36.0
Obstruction/retention	0.69 (0.53 to 0.90)	.006	5.8	2.7	8.8	5.0	12.7	8.7	15.7	10.0
Stricture	0.21 (0.08 to 0.58)	.002	0.4	0.1	1.1	0.5	2.6	0.7	3.3	0.7
Fistula	—	—	0.1	0.0	0.1	0.0	0.2	0.0	0.4	0.0
Any bowel toxicity	1.27 (1.05 to 1.55)	.02	3.2	1.6	7.7	7.4	15.4	19.5	19.2	24.9
Bleeding/proctitis	1.34 (1.10 to 1.63)	.004	3.1	1.4	7.3	7.0	14.6	19.5	18.0	24.8
Ulcer/stricture/fistula	0.94 (0.42 to 2.12)	.89	0.1	0.1	0.4	0.6	1.1	0.6	1.4	1.0
Incontinence	0.77 (0.17 to 3.40)	.73	0.1	0.0	0.2	0.2	0.3	0.3	0.4	0.3
Proctectomy/hyperbaric oxygen	0.72 (0.22 to 2.41)	.59	0.1	0.0	0.3	0.0	0.6	0.6	0.9	0.6
Erectile dysfunction	0.71 (0.59 to 0.84)	< .001	9.7	5.0	18.1	10.6	27.8	20.7	34.3	28.6

NOTE. Separate proportional hazards model for each toxicity. (—) Hazard ratios cannot be estimated when a treatment group has no events.
Abbreviations: HR, hazard ratio; IMRT, intensity-modulated radiotherapy.

therapy patients had a lower mean complication cost ($1,737 *v* $2,730 at 2 years; $P = .008$; Fig 2A) but higher mean total health care cost ($133,220 *v* $79,209 at 2 years; $P < .001$; Fig 2B).

SBRT-IMRT Comparison

Comparative toxicities of SBRT and IMRT patients are listed in Table 3. There were no statistically significant differences between SBRT and IMRT patients in composite urinary, composite bowel, or ED toxicities. SBRT was associated with a higher risk of urinary toxicity within the specific domains of obstruction/retention (21% *v* 15% at 2 years; $P = .003$) and fistula (1% *v* 0.1% at 2 years; $P = .009$). Sensitivity analysis demonstrated that the increased risk of obstruction/retention was limited to the early period, whereas the increased risk of fistula was limited to the late period (Appendix Table A10, online only). There were no differences between SBRT and IMRT when toxicity evaluation was conducted using only procedure codes (Appendix Table A11, online only) or previously validated pelvic radiation severe toxicity criteria (Appendix Table A12, online only).

The mean radiation cost for SBRT and IMRT was $49,504 and $57,244 ($P < .001$) to the payer, respectively, and $1,015 and $1,560 ($P < .001$) to the patient, respectively. SBRT and IMRT patients had a similar mean complication cost ($3,084 *v* $2,079 at 2 years; $P = .25$; Fig 3A) and mean total health care cost ($80,786 *v* $77,539 at 2 years; $P = .36$; Fig 3B).

DISCUSSION

Given its high economic burden[25] and multiple effective treatment options, localized prostate cancer is a high-priority area for comparative effectiveness research.[26] As randomized trials of proton radiation accrue[27] and trials of SBRT mature,[28] large cohort studies provide key evidence to evaluate these modalities. To our knowledge, this study is the first to report comparative toxicities and private insurance cost of these treatment options in younger men.

The recent rapid expansion of proton centers in the United States has been driven by a combination of medical promise and competitive market pressures.[29] Although proton prostate radiation offers a theoretical benefit of lower delivered dose to normal pelvic structures,[6,7] controversy remains around its continued use in the absence of demonstrable clinical benefit within existing comparative effectiveness literature. A Medicare study of early toxicity found a transient reduction in GU toxicity at 6 months and no difference in bowel toxicity,[10] whereas a SEER-Medicare study of late toxicity found no difference in GU toxicity and an increase in bowel toxicity with proton radiation.[2]

A strength of this study was further a priori refinement of toxicity criteria from prior studies to maximize the specificity of our measured result for radiation toxicity, such as inclusion of irritative bladder symptoms and exclusion of endoscopies that did not include modifiers of bleeding control. Although the prior SEER-Medicare study was conducted when only a single proton center was located within the SEER catchment area,[30] this study has increased generalizability because of its inclusion of nationwide proton facilities. Within this context, our finding of increased late bowel toxicity of bleeding/proctitis among proton therapy patients within a younger, private insurance data set corroborated the prior observation among older men.

To our knowledge, this study is the first to identify possible benefit associated with proton radiation compared with IMRT for prostate cancer, with results suggesting decreased multidomain urinary toxicity. To put in perspective the effect size of proton radiation in this study, the magnitude of the decreased risk of urinary toxicity (33% *v* 43% at 2 years) compares favorably with population-based studies showing a reduction in bowel complications (19% *v* 23% at 2 years) between patients with prostate cancer treated with three-dimensional conformal radiation therapy and IMRT.[18]

The observed toxicity differences may be partially explained by the dose-volume characteristics of each technology. The available evidence suggests that the high dose volume to the rectum is correlated with late toxicity,[31] whereas there is no clearly established bladder dose-volume relationship with GU toxicity.

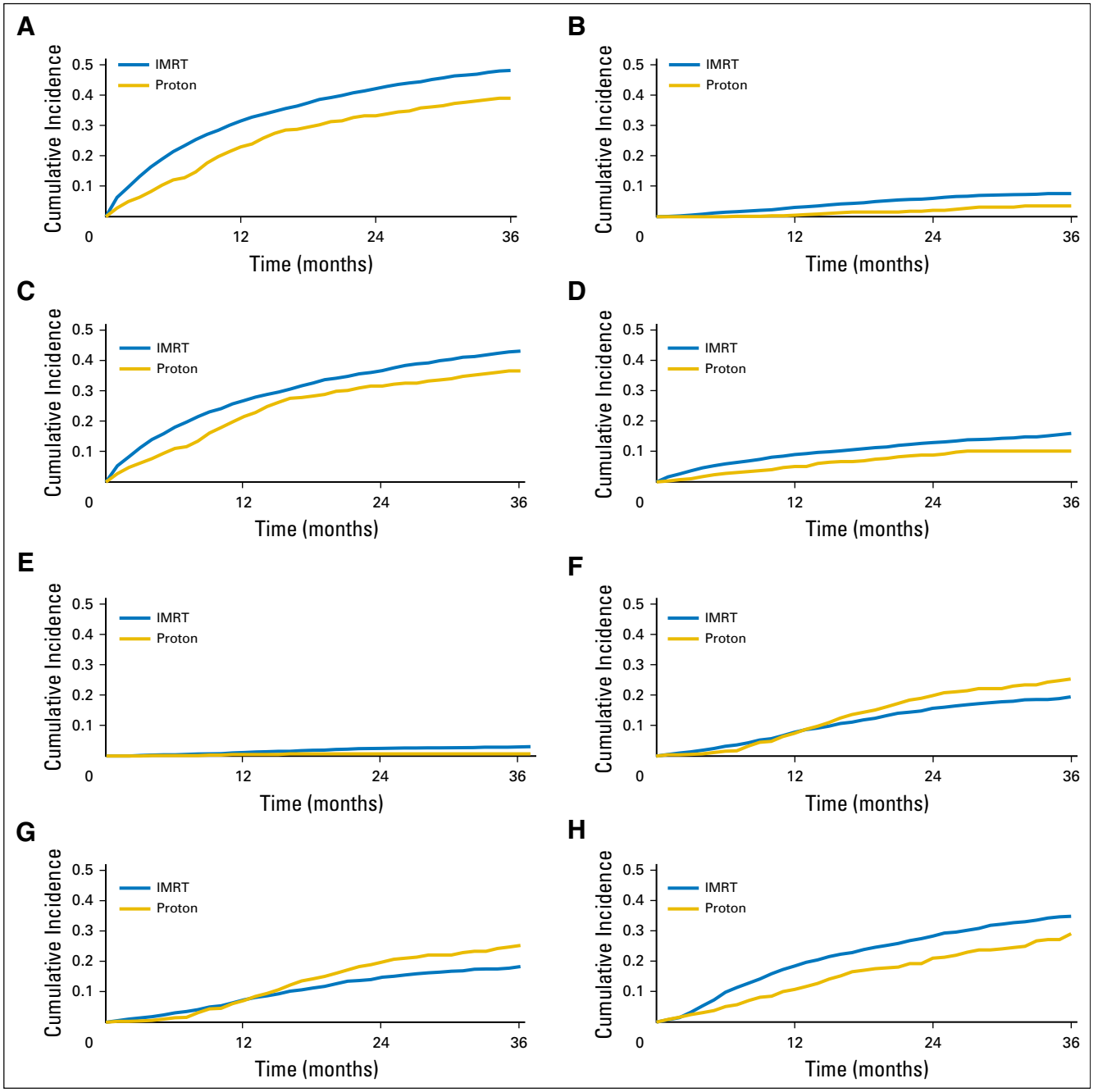

Fig 1. Cumulative incidence of genitourinary and bowel toxicities among propensity score-matched intensity-modulated radiotherapy (IMRT) and proton cohort: (A) any urinary toxicity; (B) urinary incontinence; (C) urinary bleeding/irritation; (D) urinary obstruction; (E) urinary stricture; (F) any bowel toxicity; (G) bowel bleeding/irritation; and (H) erectile dysfunction.

One dosimetric study comparing proton radiation with IMRT showed that proton radiation had increased high-dose rectal exposure, improved target/prostate dose homogeneity, and increased low-dose bladder sparing.[32] These dosimetric findings could correspond to our respective observations of increased late rectal bleeding/proctitis, decreased urethral stricture, and decreased other urinary toxicity with protons. However, other dosimetric studies suggest either decreased[7] or similar[6] rectal high-dose exposure with protons compared with IMRT. In addition, other treatment-related factors, such as stricter prostate immobilization in proton radiation due to the increased sensitivity of proton dosimetry through varying tissue densities, may contribute to our observed toxicity differences. Given the conflicting dosimetric studies and potential nondosimetric factors affecting dose delivered to organs at risk, the empiric findings in this study provide valuable observational toxicity data.

With the current emphasis on cost-effective health care, our toxicity findings must be considered in the context of differing cost profiles. Although there was a durable statistically significant reduction in complication cost for proton therapy patients,

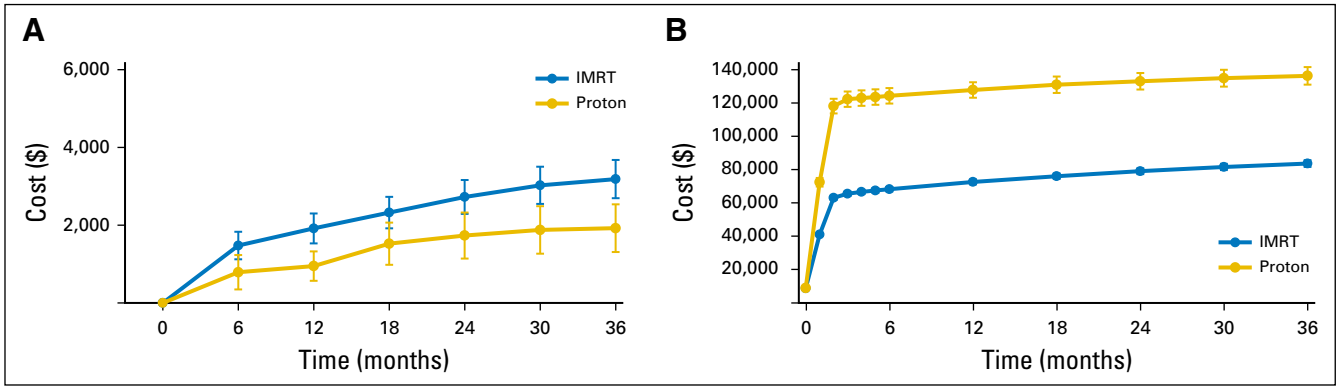

Fig 2. Complication and total health care cost comparison between propensity score–matched intensity-modulated radiotherapy (IMRT) and proton cohort: (A) complication cost and (B) total cost. $P < .05$ at all time points.

differences in overall health care expenditure were driven by private insurance reimbursing nearly twice the amount for proton radiation compared with IMRT. It is important to note that these radiation cost differences represent national averages that can differ significantly from reimbursement rates negotiated between individual treatment centers and specific payers, and some institutions offer proton radiation as a cost-neutral option to IMRT.[33] The reported toxicity risks and cost can facilitate the design of models to evaluate the likelihood that proton radiation is cost-effective across a spectrum of societal willingness to pay or of proton-IMRT cost differences.[34] Ultimately, innovative delivery strategies to reduce the cost of proton radiation are likely necessary for it to be considered cost effective while balancing its potential for reduced GU toxicity with increased bowel toxicity.

Alongside the adoption of proton radiation, there has been longstanding interest in hypofractionated radiation in the treatment of prostate cancer.[35] Multiple randomized trials have recently published initial results demonstrating the noninferiority of moderately hypofractionated prostate radiation regimens compared with conventional fractionation.[36-38] SBRT represents an extreme form of hypofractionation that recently became possible with improved radiation technology. As such, there is less robust follow-up with SBRT, and published comparative effectiveness research is limited to population-based studies from Medicare and SEER-Medicare showing greater GU toxicity, including urethritis, obstruction, and incontinence[11,12] with SBRT compared with IMRT.

Although our study did not show differences in composite urinary or bowel toxicity between SBRT and IMRT, it similarly demonstrated additional early toxicity within the specific urinary domain obstruction/retention among younger men. Given the concern for the late toxicity of fistula with SBRT, we notably also found a statistically significant higher risk of urinary fistula. However, it was a small absolute risk detected based on diagnosis codes alone without associated procedure codes and was comparable to the risk of grade 3+ urinary/bowel toxicity reported in prospective SBRT studies.[39] It is reassuring that 2-year toxicity data from a randomized trial comparing SBRT with conventionally fractionated IMRT recently reported in abstract form showed no long-term difference in physician- or patient-reported bowel or GU toxicity.[28] While we await final publication of these data, the currently available comparative effectiveness data suggest that it is appropriate to counsel patients on the potential of increased urinary toxicity with SBRT and to reduce the risk of post-treatment obstructive symptoms with appropriate patient selection.

Table 3. Toxicities for Propensity Score-Matched IMRT and SBRT Cohort

	SBRT (reference, IMRT)		6-month Incidence (%)		12-month Incidence (%)		24-month Incidence (%)		36-month Incidence (%)	
Toxicity	HR (95% CI)	*P*	IMRT (n = 3,100)	SBRT (n = 310)	IMRT (n = 2,522)	SBRT (n = 234)	IMRT (n = 1,316)	SBRT (n = 113)	IMRT (n = 619)	SBRT (n = 43)
Any urinary toxicity	1.08 (0.91 to 1.29)	.37	25.0	27.5	35.1	36.1	46.5	48.4	53.0	50.7
Incontinence	0.75 (0.42 to 1.35)	.34	1.5	2.3	2.9	3.3	6.1	4.3	8.2	4.3
Bleeding/irritation	1.15 (0.96 to 1.38)	.14	21.1	22.2	30.1	31.1	41.0	46.1	47.0	50.0
Obstruction/retention	1.50 (1.15 to 1.97)	.003	6.8	10.5	10.6	17.6	14.8	20.7	17.4	22.6
Stricture	0.70 (0.28 to 1.73)	.44	0.7	0.0	1.3	1.2	2.6	2.3	3.5	2.3
Fistula	6.68 (1.60 to 28.0)	.009	0.0	0.0	0.1	0.0	0.1	1.3	0.2	2.6
Any bowel toxicity	1.11 (0.81 to 1.53)	.51	2.8	3.9	7.4	8.6	15.4	14.9	18.2	22.7
Bleeding/proctitis	1.08 (0.77 to 1.51)	.65	2.6	3.9	7.0	8.0	14.6	13.8	17.4	21.6
Ulcer/stricture/fistula	2.27 (0.87 to 5.95)	.09	0.2	0.0	0.3	1.4	0.8	1.9	1.0	1.9
Incontinence	2.04 (0.45 to 9.21)	.35	0.1	0.0	0.2	0.0	0.3	0.9	0.4	0.9
Proctectomy/hyperbaric oxygen	2.70 (0.57 to 12.7)	.21	0.1	0.0	0.1	0.8	0.4	0.8	0.4	0.8
Erectile dysfunction	0.82 (0.64 to 1.05)	.11	10.0	9.9	19.0	16.8	29.1	21.9	36.2	28.8

NOTE. Separate proportional hazards model for each toxicity.
Abbreviations: HR, hazard ratio; IMRT, intensity-modulated radiotherapy; SBRT, stereotactic body radiotherapy.

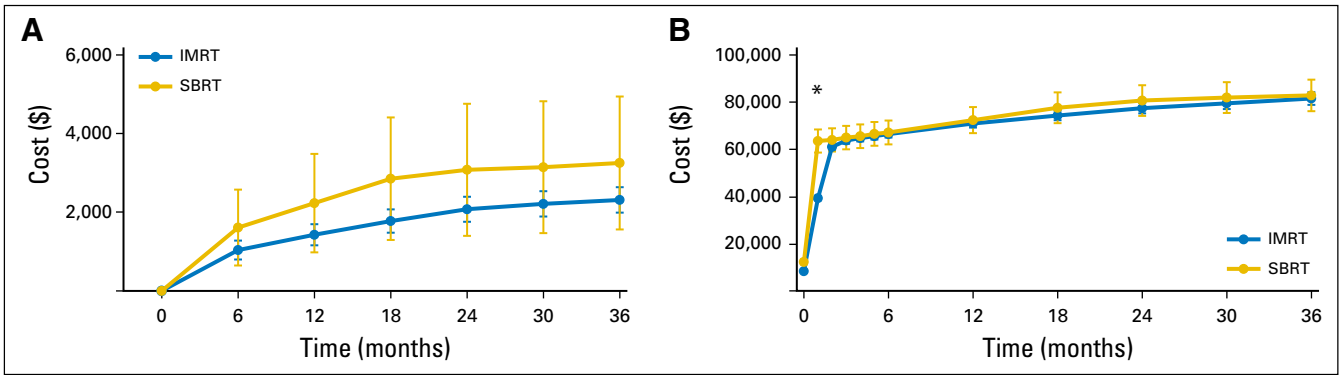

Fig 3. Complication and total health care cost comparison between propensity score–matched intensity-modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT) cohort: (A) complication cost and (B) total cost. (*) Denotes $P < .05$ at measured time point.

In our study, private insurance reimbursement for SBRT was 14% less than IMRT, and out-of-pocket cost was 35% less. Despite this upfront cost savings, overall long-term health care expenditures between the two patient groups were similar. However, other potential cost savings from the reduced treatment time of SBRT, including less patient time away from work and improved radiotherapy resource use are unaccounted for in this comparison. The combined toxicity and cost comparison between SBRT and IMRT suggest that SBRT is a well-tolerated and good-value treatment alternative to conventionally fractionated or moderately hypofractionated radiation in appropriately selected patients.

The strengths of using claims data for comparative effectiveness research include the assessment of real-world cost and outcomes that are externally valid and representative. However, there are also limitations to this approach. Although patients with metastatic disease were excluded, other prognostic information, including Gleason score, prostate-specific antigen level, and clinical stage, and treatment information, such as radiation field and dose, were unavailable. Importantly, propensity score matching thus could not account for these and other potential unmeasured confounders that could differ between treatment groups and influence measured outcomes. In addition, median follow-up was relatively short, reflecting frequent changes in insurance coverage endemic to the private insurance market. Reassuringly, however, follow-up did not vary by type of treatment, indicating that informative censoring bias was unlikely a concern. Claims data do not distinguish between passive scatter proton radiation and more modern intensity-modulated proton therapy, which may have differing toxicity profiles.[40] Determination of toxicity grade is limited by the lack of physician- and patient-reported outcomes, and there are few validated algorithms for claims-based toxicity assessment of pelvic radiation.[19,41,42] Differences in the proportion of hospital-based versus freestanding treatment facility between radiation modalities cannot be assessed and may partially account for cost differences. Alternative treatment options, including surveillance, brachytherapy, and surgery, were not included in this study, but comparative toxicities have been previously reported.[43-46] Finally, follow-up within a private insurance cohort is less robust than Medicare, which limits the ability to study long-term toxicity or efficacy.

Nevertheless, to our knowledge, this study is unique in its assessment of the toxicity and cost of prostate radiation treatment options in the previously understudied but significant patient population of younger men with private insurance. Our findings include sustained reductions in urinary toxicity but increased bowel toxicity with proton therapy and modestly increased domain-specific urinary toxicity with SBRT. These key findings, coupled with the real-world private insurance cost reported herein, will be useful for patients selecting the most appropriate treatment and for researchers designing cost-effectiveness models to guide treatment decisions in prostate cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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REFERENCES

1. Nguyen PL, Gu X, Lipsitz SR, et al: Cost implications of the rapid adoption of newer technologies for treating prostate cancer. J Clin Oncol 29: 1517-1524, 2011

2. Sheets NC, Goldin GH, Meyer AM, et al: Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. JAMA 307:1611-1620, 2012

3. Kuban DA, Tucker SL, Dong L, et al: Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys 70:67-74, 2008

4. Spratt DE, Pei X, Yamada J, et al: Long-term survival and toxicity in patients treated with high-dose intensity modulated radiation therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 85:686-692, 2013

5. Slater JD, Rossi CJ Jr, Yonemoto LT, et al: Proton therapy for prostate cancer: The initial Loma Linda University experience. Int J Radiat Oncol Biol Phys 59:348-352, 2004

6. Trofimov A, Nguyen PL, Coen JJ, et al: Radiotherapy treatment of early-stage prostate cancer with IMRT and protons: A treatment planning comparison. Int J Radiat Oncol Biol Phys 69:444-453, 2007

7. 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 70:744-751, 2008

8. King CR, Freeman D, Kaplan I, et al: Stereotactic body radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials. Radiother Oncol 109:217-221, 2013

9. Pan HY, Jiang J, Shih YT, et al: Adoption of radiation technology among privately insured nonelderly patients with cancer in the United States, 2008 to 2014: A claims-based analysis. J Am Coll Radiol 14:1027-1033.e2, 2017

10. 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 105:25-32, 2013

11. Halpern JA, Sedrakyan A, Hsu WC, et al: Use, complications, and costs of stereotactic body radiotherapy for localized prostate cancer. Cancer 122:2496-2504, 2016

12. Yu JB, Cramer LD, Herrin J, et al: Stereotactic body radiation therapy versus intensity-modulated radiation therapy for prostate cancer: Comparison of toxicity. J Clin Oncol 32:1195-1201, 2014

13. Howlader N, Noone A, Krapcho M, et al: SEER Cancer Statistics Review, 1975-2014. Bethesda, MD, National Cancer Institute, 2017

14. Salinas CA, Tsodikov A, Ishak-Howard M, et al: Prostate cancer in young men: An important clinical entity. Nat Rev Urol 11:317-323, 2014

15. IBM: Putting research data into your hands with the MarketScan Database. http://truvenhealth.com/markets/life-sciences/products/data-tools/marketscan-databases

16. United States Census Bureau: American FactFinder. https://factfinder.census.gov/

17. Klabunde CN, Potosky AL, Legler JM, et al: Development of a comorbidity index using physician claims data. J Clin Epidemiol 53:1258-1267, 2000

18. Bekelman JE, Mitra N, Efstathiou J, et al: Outcomes after intensity-modulated versus conformal radiotherapy in older men with nonmetastatic prostate cancer. Int J Radiat Oncol Biol Phys 81:e325-e334, 2011

19. Sewell JM, Rao A, Elliott SP: Validating a claims-based method for assessing severe rectal and urinary adverse effects of radiotherapy. Urology 82:335-340, 2013

20. Bureau of Labor Statistics: Measuring price change for medical care in the CPI. https://www.bls.gov/cpi/factsheets/medical-care.htm

21. Austin PC: An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 46:399-424, 2011

22. Austin PC: A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. Stat Med 27:2037-2049, 2008

23. Zhao H, Tian L: On estimating medical cost and incremental cost-effectiveness ratios with censored data. Biometrics 57:1002-1008, 2001

24. Chen S, Rolfes J, Zhao HW: Estimation of mean health care costs and incremental cost-effectiveness ratios with possibly censored data. Stata J 15:698-711, 2015

25. Mariotto AB, Yabroff KR, Shao Y, et al: Projections of the cost of cancer care in the United States: 2010-2020. J Natl Cancer Inst 103:117-128, 2011

26. Institute of Medicine: Initial national priorities for comparative effectiveness research. Washington, DC, National Academies Press, 2009

27. US National Institute of Health: Proton therapy vs. IMRT for low of intermediate risk prostate cancer (PARTIQoL). https://clinicaltrials.gov/ct2/show/NCT01617161

28. Widmark A, Gunnlaugsson A, Beckman L, et al: Extreme hypofractionation versus conventionally fractionated radiotherapy for intermediate risk prostate cancer: Early toxicity results from the Scandinavian Randomized Phase III Trial "HYPO-RT-PC." Int J Radiat Oncol Biol Phys 96:938-939, 2016

29. Steinberg ML, Konski A: Proton beam therapy and the convoluted pathway to incorporating emerging technology into routine medical care in the United States. Cancer J 15:333-338, 2009

30. International Cancer Institute: About the SEER registries. https://seer.cancer.gov/registries/

31. Michalski JM, Gay H, Jackson A, et al: Radiation dose-volume effects in radiation-induced rectal injury. Int J Radiat Oncol Biol Phys 76:S123-S129, 2010 (3, suppl)

32. Zhang X, Dong L, Lee AK, et al: Effect of anatomic motion on proton therapy dose distributions in prostate cancer treatment. Int J Radiat Oncol Biol Phys 67:620-629, 2007

33. Bekelman JE, Hahn SM: Reference pricing with evidence development: A way forward for proton therapy. J Clin Oncol 32:1540-1542, 2014

34. Konski A, Speier W, Hanlon A, et al: Is proton beam therapy cost effective in the treatment of adenocarcinoma of the prostate? J Clin Oncol 25:3603-3608, 2007

35. Fowler JF: The radiobiology of prostate cancer including new aspects of fractionated radiotherapy. Acta Oncol 44:265-276, 2005

36. Catton CN, Lukka H, Gu CS, et al: Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. J Clin Oncol 35:1884-1890, 2017

37. Dearnaley D, Syndikus I, Mossop H, et al: Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol 17:1047-1060, 2016

38. Lee WR, Dignam JJ, Amin MB, et al: Randomized phase III noninferiority study comparing two radiotherapy fractionation schedules in patients with low-risk prostate cancer. J Clin Oncol 34:2325-2332, 2016

39. King CR, Collins S, Fuller D, et al: Health-related quality of life after stereotactic body radiation therapy for localized prostate cancer: Results from a multi-institutional consortium of prospective trials. Int J Radiat Oncol Biol Phys 87:939-945, 2013

40. 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 87:946-953, 2013

41. Meyer AM, Kuo TM, Chang Y, et al: Using procedure codes to define radiation toxicity in administrative data: The devil is in the details. Med Care 55:e36-e43, 2017

42. Potosky AL, Warren JL, Riedel ER, et al: Measuring complications of cancer treatment using the SEER-Medicare data. Med Care 40:IV62-IV68, 2002 (8, suppl)

43. Frank SJ, Pisters LL, Davis J, et al: An assessment of quality of life following radical prostatectomy, high dose external beam radiation therapy and brachytherapy iodine implantation as monotherapies for localized prostate cancer. J Urol 177:2151-2156, 2007; discussion 2156

44. Resnick MJ, Koyama T, Fan KH, et al: Long-term functional outcomes after treatment for localized prostate cancer. N Engl J Med 368:436-445, 2013

45. Sanda MG, Dunn RL, Michalski J, et al: Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med 358:1250-1261, 2008

46. Donovan JL, Hamdy FC, Lane JA, et al: Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. N Engl J Med 375:1425-1437, 2016

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Comparative Toxicities and Cost of Intensity-Modulated Radiotherapy, Proton Radiation, and Stereotactic Body Radiotherapy Among Younger Men With Prostate Cancer

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Appendix

Table A1. Inclusion and Exclusion Criteria Procedure and Diagnosis Codes

Criteria	CPT/HCPCS/ICD9 Procedure Codes	ICD9 Diagnosis Codes
Stereotactic body radiotherapy	77371-77373, G0173, G0251, G0339, G0340	
Proton radiotherapy	77520, 77522-77523, 77525	
Intensity-modulated radiotherapy	77418, 0073T, G6015, G6016, 77385, 77386	
Brachytherapy	77761-77789, 0182T, G0458	
Metastatic disease		196-198
Radical prostatectomy	55810, 55812, 55815, 55840, 55842, 55845, 55866, 60.5	V45.77
Other malignancy		140-184, 186-195, 199-209, V10

Abbreviations: CPT, Current Procedural Terminology; HCPCS, Healthcare Common Procedure Coding System; ICD9, International Classification of Disease (9th revision, clinical modification).

Table A2. Androgen Deprivation Therapy Procedure Codes

Treatment Type	CPT/ICD9 Codes
Hormone injection	99.24, J1950, J9202, J9217, J9218, J9219, J3315, J0128, C9430, C9216, S0165, S9560, J1675, Q2020, S0133, J9225, J9155
Orchiectomy	62.4, 62.41, 62.42, 54520, 54690

Abbreviations: CPT, Current Procedural Terminology; ICD9, International Classification of Disease (9th revision, clinical modification).

Table A3. Treatment Toxicity Diagnosis and Procedure Codes

Toxicity Group	Diagnosis Codes	Procedure Codes
Urinary		
Incontinence	599.82, 788.3, 788.30, 788.31, 788.32, 788.33, 788.34, 788.35, 788.36, 788.37, 788.38, 788.39	51715, 51840, 51841, 51990, 51992, 53431, 53440, 53442, 53444, 53445, 53446, 53447, 53448, 53449, 58.93, 58.99, 59.3, 59.4, 59.5, 59.6, 59.7, 59.71, 59.72, 59.79
Bleeding/irritation	595.82, 596.7, 597.80, 597.81, 599.0, 599.7, 599.70, 599.71, 599.72, 788.1, 788.4, 788.41, 788.42, 788.43, 788.63	52001, 52214, 52224
Obstruction/retention	596.0, 599.6, 599.60, 599.69, 788.2, 788.20, 788.21, 788.29, 788.61, 788.62, 788.64, 788.65	51701, 51702, 51703, 51040, 51520, 51800, 52601, 52612, 52614, 52620, 52630, 52640, 53850, 53852, 57.1, 57.11, 57.12, 57.17, 57.18, 57.19, 57.2, 57.21, 57.22, 57.94, 60.2, 60.21, 60.29
Stricture	598, 598.0, 598.00, 598.01, 598.1, 598.2, 598.8, 598.9	52275, 52276, 52281, 52282, 52283, 52290, 53010, 53020, 53410, 53415, 53420, 53425, 53600, 53601, 53605, 53620, 53621, 57.85, 57.93, 58.0, 58.1, 58.3, 58.31, 58.39, 58.46, 58.47, 58.5, 58.6, 60.95
Fistula	596.1, 596.2, 599.1	44660, 44661, 53400, 53405, 53520, 57.84, 58.43, 58.44
Bowel		
Bleeding/proctitis	558.1, 569.3, 569.42, 569.49, 578.9, 578.1	48.31, 48.32, 45317, 45334, 45382, 46614
Ulcer/stricture/fistula	565.1, 569.2, 569.41, 560.1	49.73, 96.22, 96.23, 45150, 45303, 45327, 45340, 45386, 45387, 45500, 45562, 45563, 45800, 45805, 45820, 45825, 45905, 45910, 46270, 46275, 46280, 46285, 46604, 46700, 48.91, 48.93, 49.1, 49.11, 49.12, 57.83
Incontinence	787.6, 787.60, 787.61, 787.62, 787.63	49.72
Proctectomy/hyperbaric oxygen		93.95, 45110, 45111, 45112, 45113, 45114, 45116, 45119, 45123, 45395, 45397, 48.5, 48.50, 48.51, 48.52, 48.59, 99183, G0167
Erectile dysfunction	607.84	54231, 54235, 54400, 54401, 54405, 54406, 54408, 54410, 54411, 54415, 54416, 54417, 64.95, 64.96, 64.97, C1813, C2622, J0270, J0275, J2440, J2760, L7900

NOTE. Although hyperbaric oxygen is not specific to bowel versus urinary toxicity, it was categorized as bowel toxicity for consistency with published literature.

Table A4. Most Common Toxicity Codes

Code	Definition	Proportion of Complication Codes (%)
Urinary diagnoses		
788.41	Urinary frequency	12
788.43	Nocturia	11
599.0	Urinary tract infection	11
599.70	Hematuria, NOS	9
788.1	Dysuria	8
	Total	51
Bowel diagnoses		
569.3	Anorectal hemorrhage	31
569.49	Other anorectal disorders, including proctitis NOS	21
578.1	Blood in stool	20
578.9	GI hemorrhage, NOS	9
558.1	Gastroenteritis and colitis due to radiation	7
	Total	87
Erectile dysfunction diagnoses		
607.84	Impotence	100
	Total	100
Urinary procedures		
51702	Foley, simple	17
52281	Cystourethroscopy with stricture dilation	16
52224	Cystourethroscopy with fulguration of minor lesions	7
52276	Cystourethroscopy with urethrotomy	6
52601	Transurethral resection of prostate	5
	Total	51
Bowel procedures		
45382	Colonoscopy with bleeding control	40
45334	Sigmoidoscopy with bleeding control	19
99183	Hyperbaric oxygen	18
45317	Proctoscopy with bleeding control	4
46280	Surgical treatment of anal fistula	4
	Total	84
Erectile dysfunction procedures		
54235	Injection of corpora cavernosa	35
L7900	Male vacuum erection system	22
54405	Insertion of multicomponent inflatable penile prosthesis	13
C1813	Inflatable penile prosthesis	8
J0270	Injection, alprostadil	7
	Total	85

Abbreviation: NOS, not otherwise specified.

Table A5. Preradiation Genitourinary and Bowel Comorbidity in Unmatched Cohort

	SBRT (n = 312)		Proton (n = 693)		IMRT (n = 11,123)		Total (n = 12,128)		
Comorbidity	No.	%	No.	%	No.	%	No.	%	*P*
Any urinary comorbidity	93	30	171	25	3386	30	3650	30	.006
Incontinence	2	1	6	1	387	3	395	3	< .001
Bleeding/irritation	68	22	136	20	2384	21	2588	21	.52
Obstruction/retention	35	11	66	10	1263	11	1364	11	.33
Stricture	5	2	5	1	195	2	205	2	.12
Fistula	0	0	0	0	5	0	5	0	.80
Any bowel comorbidity	11	4	28	4	403	4	442	4	.85
Bleeding/proctitis	9	3	27	4	361	3	397	3	.60
Ulcer/stricture/fistula	2	1	2	0	41	0	45	0	.69
Incontinence	0	0	0	0	8	0	8	0	.70
Proctectomy/hyperbaric oxygen	0	0	0	0	0	0	0	0	—
Erectile dysfunction	32	10	64	9	1496	13	1592	13	.002

Abbreviations: IMRT, intensity modulated radiotherapy; SBRT, stereotactic body radiotherapy.

Table A6. Baseline Characteristics of Propensity Score-Matched Cohorts

Covariable	IMRT-SBRT (n = 3,410)			IMRT-Proton (n = 4,158)		
	IMRT (%)	SBRT (%)	SD (%)	IMRT (%)	Proton (%)	SD (%)
Age, years						
≤ 55	22	23	1.4	29	29	0.0
56-60	33	33	0.2	39	39	0.5
61-64	45	44	−1.4	33	32	−0.5
Residence						
Rural	6	7	3.1	12	13	5.2
Urban	93	92	−2.7	86	83	−6.3
Median household income						
Lowest quartile	5	5	−0.6	5	6	2.0
2nd quartile	9	9	0.4	12	12	0.6
3rd quartile	24	22	−5.5	19	18	−1.8
Highest quartile	55	57	3.3	49	47	−4.8
Unknown	7	8	2.6	14	17	6.7
Region						
Northeast	27	29	4.0	9	8	−5.9
North central	17	18	0.9	17	17	−0.1
South	38	35	−7.8	51	51	−1.0
West	16	18	4.4	20	22	3.8
Treatment year						
2008-2011	36	35	−0.7	59	59	−1.4
2012-2015	64	65	0.7	41	41	1.4
Employee relation						
Self	80	78	−4.1	79	79	0.8
Dependent	20	22	4.1	21	21	−0.8
HMO or PPO with capitation						
No	90	89	−3.8	93	93	−3.2
Yes	10	11	3.8	7	7	3.2
Medical comorbidity						
None	83	83	−0.9	89	87	−6.6
1	13	13	0.1	9	10	4.1
≥ 2	4	4	1.5	2	3	6.0
ADT						
No	92	93	1.7	81	81	0.1
Yes	8	7	−1.7	19	19	−0.1
Urinary comorbidity						
Any	34	35	1.4	24	27	6.7
Incontinence	1	1	−3.9	1	1	1.6
Bleeding/irritation	28	28	0.2	20	23	6.3
Obstruction/retention	12	11	−2.7	8	10	5.1
Stricture	1	1	−1.1	1	1	−1.9
Fistula	0	0	−3.6	0	0	—
Bowel comorbidity						
Any	3	3	0.4	3	4	6.7
Bleeding/proctitis	3	3	−2.2	3	4	4.6
Ulcer/stricture/fistula	0	1	5.8	0	0	3.9
Incontinence	0	0	—	0	0	−2.4
Proctectomy/hyperbaric oxygen	0	0	—	0	0	—
Erectile dysfunction						
Yes	10	10	0.5	7	9	6.9

Abbreviations: ADT, androgen deprivation therapy; HMO, health maintenance organization; IMRT, intensity modulated radiotherapy; PPO, preferred provider organization; SBRT, stereotactic body radiotherapy; SD, standard difference.

Table A7. Sensitivity Analysis of Early Versus Late Toxicity of Propensity Score-Matched IMRT and Proton Cohort

	Early (0-12 months)				Late (≥ 13 months)			
	Proton (reference, IMRT)		1-year Incidence (%)		Proton (reference, IMRT)		2-year Incidence (%)	
Description	HR (95% CI)	*P*	IMRT	Proton	HR (95% CI)	*P*	IMRT	Proton
Any urinary toxicity	0.66 (0.56 to 0.78)	< .001	31.6	23.1	0.81 (0.67 to 0.96)	.02	25.8	20.4
Incontinence	0.15 (0.05 to 0.47)	.001	3.0	0.5	0.40 (0.22 to 0.72)	.002	4.4	1.5
Bleeding/irritation	0.74 (0.62 to 0.89)	.001	26.4	21.2	0.86 (0.71 to 1.05)	.13	20.7	17.7
Obstruction/retention	0.54 (0.38 to 0.78)	< .001	8.8	5.0	0.87 (0.63 to 1.19)	.37	7.6	6.2
Stricture	0.41 (0.13 to 1.31)	.13	1.1	0.5	0.08 (0.01 to 0.54)	.01	1.8	0.2
Fistula	—	—	0.1	0.0	—	—	0.0	0.0
Any bowel toxicity	0.93 (0.68 to 1.27)	.65	7.7	7.4	1.60 (1.27 to 2.00)	< .001	9.7	15.3
Bleeding/proctitis	0.94 (0.69 to 1.30)	.72	7.3	7.0	1.69 (1.35 to 2.13)	< .001	9.1	15.2
Ulcer/stricture/fistula	1.54 (0.50 to 4.73)	.45	0.4	0.6	0.60 (0.18 to 1.98)	.40	0.8	0.0
Incontinence	0.72 (0.09 to 5.82)	.75	0.2	0.2	1.10 (0.24 to 5.11)	.90	0.1	0.3
Proctectomy/hyperbaric oxygen	—	—	0.3	0.0	0.95 (0.28 to 3.24)	.93	0.4	0.6
Erectile dysfunction	0.56 (0.43 to 0.71)	< .001	18.1	10.6	0.87 (0.71 to 1.06)	.16	18.9	16.1

NOTE. Separate proportional hazards model for each toxicity. (—) Hazard ratios cannot be estimated when a treatment group has no events.
Abbreviations: HR, hazard ratio; intensity-modulated radiotherapy.

Table A8. Sensitivity Analysis of Procedure-Only Toxicity of Propensity Score-Matched IMRT and Proton Cohort

	Procedure Only			
	Proton (reference, IMRT)		2-year Incidence (%)	
Description	HR (95% CI)	*P*	IMRT (%)	Proton (%)
Any urinary toxicity	0.24 (0.12 to 0.48)	< .001	4.7	1.3
Incontinence	—	—	0.3	0.0
Bleeding/irritation	0.13 (0.02 to 0.91)	.04	1.0	0.0
Obstruction/retention	0.29 (0.12 to 0.70)	.006	2.5	0.9
Stricture	0.15 (0.04 to 0.62)	.009	1.9	0.3
Fistula	—	—	0.0	0.0
Any bowel toxicity	1.50 (0.91 to 2.47)	.11	2.3	2.5
Bleeding/proctitis	2.25 (1.29 to 3.92)	.004	1.5	1.9
Ulcer/stricture/fistula	0.51 (0.07 to 3.97)	.52	0.3	0.1
Incontinence	—	—	0.0	0.0
Proctectomy/hyperbaric oxygen	0.72 (0.22 to 2.41)	.59	0.6	0.6
Erectile dysfunction	0.63 (0.36 to 1.10)	.10	3.1	2.0

NOTE. Separate proportional hazards model for each toxicity. (—) Hazard ratios cannot be estimated when a treatment group has no events.
Abbreviations: HR, hazard ratio; IMRT, intensity-modulated radiotherapy.

Table A9. Sensitivity Analysis of Previously Validated Severe Toxicity Criteria After Pelvic Radiation of Propensity Score-Matched IMRT and Proton Cohort

	Proton (reference, IMRT)		24-month Incidence (%)	
Toxicity	HR (95% CI)	*P*	IMRT	Proton
Cystitis	0.32 (0.04 to 2.38)	.26	0.4	0.0
Rectal complications	1.19 (0.62 to 2.30)	.60	1.5	2.0
Urethral stricture	0.12 (0.02 to 0.86)	.03	1.3	0.0
Ureteral stricture	—	—	0.1	0.0
Urinary/rectal fistula	—	—	0.0	0.0

NOTE. Separate proportional hazards model for each toxicity. (—) Hazard ratios cannot be estimated when a treatment group has no events.
Abbreviations: HR, hazard ratio; IMRT, intensity-modulated radiotherapy.

Table A10. Sensitivity Analysis of Early Versus Late Toxicity of Propensity Score-Matched IMRT and SBRT Cohort

	Early (0-12 months)				Late (≥ 13 months)			
	SBRT (reference, IMRT)		11-year Incidence (%)		SBRT (reference, IMRT)		2-year Incidence (%)	
Description	HR (95% CI)	*P*	IMRT	SBRT	HR (95% CI)	*P*	IMRT	SBRT
Any urinary toxicity	1.10 (0.90 to 1.33)	.36	35.1	36.1	1.03 (0.81 to 1.32)	.80	29.9	30.2
Incontinence	1.19 (0.62 to 2.29)	.60	2.9	3.3	0.41 (0.15 to 1.11)	.08	4.2	1.7
Bleeding/irritation	1.09 (0.88 to 1.34)	.45	30.1	31.1	1.13 (0.87 to 1.47)	.36	25.3	26.6
Obstruction/retention	1.75 (1.31 to 2.35)	< .001	10.6	17.6	0.95 (0.60 to 1.50)	.84	9.1	10.6
Stricture	—	.65	1.3	1.2	0.49 (0.12 to 2.01)	.32	1.7	1.2
Fistula	—	—	0.1	0.0	11.4 (2.30 to 56.5)	.003	0.1	1.3
Any bowel toxicity	1.21 (0.81 to 1.84)	.88	7.4	8.6	0.89 (0.62 to 1.51)	.89	9.6	8.5
Bleeding/proctitis	1.18 (0.77 to 1.82)	.45	7.0	8.0	0.87 (0.54 to 1.41)	.58	9.1	7.3
Ulcer/stricture/fistula	4.06 (1.27 to 12.9)	.02	0.3	1.4	0.80 (0.11 to 6.06)	.83	0.5	0.5
Incontinence	—	—	0.2	0.0	3.30 (0.68 to 15.9)	.14	0.1	0.6
Proctectomy/hyperbaric oxygen	5.23 (0.96 to 28.6)	.06	0.1	0.8	4.25 (0.82 to 21.9)	.08	0.3	0.6
Erectile dysfunction	0.89 (0.67 to 1.19)	.45	19.0	16.8	0.67 (0.47 to 0.96)	.03	20.0	10.8

NOTE. Separate proportional hazards model for each toxicity. (—) Hazard ratios cannot be estimated when a treatment group has no events.
Abbreviations: HR, hazard ratio; IMRT, intensity-modulated radiotherapy; SBRT, stereotactic body radiotherapy.

Table A11. Sensitivity Analysis of Procedure-Only Toxicity of Propensity Score-Matched IMRT and SBRT Cohort

	Procedure Only			
	SBRT (reference, IMRT)		2-year Incidence (%)	
Description	HR (95% CI)	*P*	IMRT	SBRT
Any urinary toxicity	0.83 (0.42 to 1.63)	.59	4.0	3.5
Incontinence	—	—	0.2	0.0
Bleeding/irritation	0.50 (0.07 to 3.70)	.50	0.7	0.3
Obstruction/retention	1.70 (0.84 to 3.42)	.14	2.0	3.5
Stricture	0.76 (0.28 to 2.10)	.60	2.1	1.9
Fistula	—	—	0.0	0.0
Any bowel toxicity	0.38 (0.09 to 1.56)	.18	2.4	0.8
Bleeding/proctitis	—	—	1.8	0.0
Ulcer/stricture/fistula	—	—	0.2	0.0
Incontinence	—	—	0.0	0.0
Proctectomy/hyperbaric oxygen	2.70 (0.57 to 12.7)	.21	0.4	0.8
Erectile dysfunction	1.03 (0.50 to 2.12)	.94	3.0	2.7

NOTE. Separate proportional hazards model for each toxicity. (—) Hazard ratios cannot be estimated when a treatment group has no events.
Abbreviations: HR, hazard ratio; IMRT, intensity-modulated radiotherapy; SBRT, stereotactic body radiotherapy.

Table A12. Sensitivity Analysis of Previously Validated Severe Toxicity Criteria After Pelvic Radiation of Propensity Score-Matched IMRT and SBRT Cohort

	SBRT (reference, IMRT)		24-month Incidence (%)	
Toxicity	HR (95% CI)	*P*	IMRT	SBRT
Cystitis	0.85 (0.11 to 6.51)	.88	0.4	0.4
Rectal complications	—	—	1.6	0.0
Urethral stricture	0.72 (0.17 to 3.02)	.65	1.1	0.7
Ureteral stricture	—	—	0.1	0.0
Urinary/rectal fistula	—	—	0.0	0.0

NOTE. Separate proportional hazards model for each toxicity. (—) Hazard ratios cannot be estimated when a treatment group has no events.
Abbreviations: HR, hazard ratio; IMRT, intensity-modulated radiotherapy; SBRT, stereotactic body radiotherapy.