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OUTCOMES AFTER INTENSITY-MODULATED VERSUS CONFORMAL RADIOTHERAPY IN OLDER MEN WITH NONMETASTATIC PROSTATE CANCER

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Abstract

Purpose—There is little evidence comparing complications after intensity-modulated (IMRT) vs. three-dimensional conformal radiotherapy (CRT) for prostate cancer. The study objective was to test the hypothesis that IMRT, compared with CRT, is associated with a reduction in bowel, urinary, and erectile complications in elderly men with nonmetastatic prostate cancer.

Methods and Materials—We undertook an observational cohort study using registry and administrative claims data from the SEER-Medicare database. We identified men aged 65 years or older diagnosed with nonmetastatic prostate cancer in the United States between 2002 and 2004 who received IMRT ($n = 5,845$) or CRT ($n = 6,753$). The primary outcome was a composite measure of bowel complications. Secondary outcomes were composite measures of urinary and erectile complications. We also examined specific subsets of bowel (proctitis/hemorrhage) and urinary (cystitis/hematuria) events within the composite complication measures.

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The interpretation and reporting of these data are the sole responsibility of the authors. Dr. Bekelman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest: Dr. Bekelman reports serving as a consultant for the Riverside Company and receiving grants to his institution from the American Cancer Society and philanthropic sources. Dr. Armstrong reports receiving grants to her institution from the National Institutes of Health, the Department of Defense, the American Cancer Society, and the RobertWood Johnson Foundation. All other authors report no potential conflicts of interest.

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Results—IMRT was associated with reductions in composite bowel complications (24-month cumulative incidence 18.8% vs. 22.5%; hazard ratio [HR] 0.86; 95% confidence interval [CI], 0.79–0.93) and proctitis/hemorrhage (HR 0.78; 95% CI, 0.64–0.95). IMRT was not associated with rates of composite urinary complications (HR 0.93; 95% CI, 0.83–1.04) or cystitis/hematuria (HR 0.94; 95% CI, 0.83–1.07). The incidence of erectile complications involving invasive procedures was low and did not differ significantly between groups, although IMRT was associated with an increase in new diagnoses of impotence (HR 1.27, 95% CI, 1.14–1.42).

Conclusion—IMRT is associated with a small reduction in composite bowel complications and proctitis/hemorrhage compared with CRT in elderly men with nonmetastatic prostate cancer.

Keywords

Prostate cancer; Comparative effectiveness research; IMRT

INTRODUCTION

Policy makers, clinicians, and the media have highlighted the need for rigorous comparative evaluation of prostate cancer treatments (1, 2). Attention has focused particularly on intensity-modulated radiotherapy (IMRT), given its potential to minimize radiation morbidity and its higher cost in comparison to three-dimensional conformal radiotherapy (CRT).

IMRT is an evolution of CRT. CRT uses customized blocks to shape radiation beams to a tumor volume while minimizing dose to nearby normal organs. IMRT uses beams of nonuniform radiation intensity to deliver radiation dose distributions that better conform to targets with irregular shapes (3). Because the prostate gland is adjacent to both the rectum and the bladder, restricting the volume of surrounding tissue irradiated is particularly important in reducing the morbidity of prostate cancer treatment, including bowel, urinary, and erectile complications (4, 5).

There is little evidence comparing IMRT with CRT for prostate cancer (6). Studies to date have been limited to single institution series (7). Despite calls for a randomized trial comparing IMRT to CRT for prostate cancer, such a trial has not been undertaken. The challenges in conducting a randomized trial likely arise from several factors, including reluctance on the part of clinicians and patients to participate and the rapid adoption of IMRT in the United States (8, 9). Thus, the clinical efficacy of IMRT in terms of limiting bowel, urinary, and erectile morbidity remains unknown.

Under conditions in which randomization is not likely feasible, nonrandomized evidence may provide insights into the effectiveness of therapeutic interventions (10, 11). Therefore, we conducted an observational cohort study to test the hypothesis that IMRT compared to CRT is associated with fewer posttreatment complications in men with nonmetastatic prostate cancer.

METHODS AND MATERIALS

Study design

The study was an observational cohort study designed to compare rates of complications after IMRT versus CRT using registry and administrative claims data from the Surveillance, Epidemiology and End Results (SEER)-Medicare database. The study was approved by the institutional review board at the University of Pennsylvania.

Data sources

The SEER-Medicare database links patient demographic and tumor-specific data collected by SEER cancer registries to longitudinal health care claims for Medicare enrollees in the United States and has been used extensively for observational research (12). Medicare claims result from physician documentation of medical diagnoses and procedures in billing records and can be used to assess the complications of cancer treatments (13). The Medicare program provides healthcare benefits to 97% of the U.S. population aged 65 years old. Approximately 94% of patients in SEER aged 65 years have been successfully linked with their Medicare claims.

Study population

We identified patients with non-metastatic prostate cancer age 65 years or older diagnosed between January 1, 2002 and December 31, 2004 in SEER with follow-up through December 31, 2006 in Medicare (eAppendix Supplementary Fig. 1). IMRT was not widely used before 2002, and we allowed for enough follow-up for both IMRT and CRT patients to report 24-month complication outcomes. The primary analytic cohort comprised 5,845 men who received IMRT and 6,753 men who received CRT.

Definition of variables

Treatment—External beam radiotherapy was identified from Medicare inpatient, outpatient, and physician/supplier component files as described previously (14, 15). Delivery of IMRT was identified by the presence of Healthcare Common Procedure Coding System (HCPCS) codes 77418 and G1074 (16). Delivery of CRT was identified by the presence of code 77295 (conformal simulation) or a combination of 77290 (complex simulation) and 76370 (computed tomography guidance for placement of radiotherapy portals).

Outcomes—We identified complications in Medicare claims data by searching for ICD-9 diagnosis codes consistent with possible radiotherapy injury and related ICD-9 or HCPCS/CPT-4 invasive procedure codes according to previously published literature (13, 17–23). We included updated codes through 2006 on the basis of review by clinical experts. Because of concern about the lack of specificity of diagnostic codes alone, we required the presence of both a diagnostic and corresponding procedural code to classify a patient as experiencing the complication in our primary analysis. This approach confined our analyses to what were likely to be the more serious outcomes, comparable to Grade 3 toxicity as measured by the NCI Common Toxicity Criteria for Adverse Events scoring system (*i.e.*, requiring hospital

admission or surgical intervention) (24). In sensitivity analyses, we also evaluated diagnoses independent of invasive procedures.

To reduce the possibility that preexisting morbidity would be misclassified as associated with IMRT or CRT, we focused our investigation on new complications from the start of radiotherapy through death or December 31, 2006. Men with codes for complications in the 12 months before the start of radiotherapy were considered to have persistent morbidity and were not included in the analysis of new complications. We performed an analysis in which we included patients with prior codes for the complication of interest, and results did not differ substantially from our main findings.

The primary outcome was a composite measure of bowel complications, selected because bowel injury is the limiting toxicity of prostate radiotherapy, and evidence suggests that improvements in radiotherapy technique may lessen bowel morbidity (25, 26). Secondary outcomes were a composite measure of urinary complications and a composite measure of erectile complications. In addition, we examined specific subsets of bowel (proctitis/hemorrhage) and urinary (cystitis/hematuria) events within the composite complication measures because of their clinical relevance.

Composite bowel complications were defined as diagnoses of proctitis or hemorrhage, ulceration, stricture, or fistula of the rectum or anus, intestinal obstruction, pain or incontinence of feces with invasive diagnostic or repair procedures of the anus or rectum. Composite urinary complications were defined as diagnoses of cystitis or hematuria, obstruction, stricture, retention, incontinence or sphincter deficiency, and fistula with invasive urinary diagnostic or repair procedures of the urethra or bladder. Composite erectile complications were defined as diagnoses of impotence and invasive procedures including penile prostheses and intracavernosal injections. Measures of proctitis/hemorrhage and cystitis/hematuria consisted of diagnoses and invasive procedures for these specific conditions. eAppendix Supplementary Table 1 shows Medicare codes used to define complication diagnoses and invasive procedures, and eAppendix Supplementary Table 2 shows the five most common diagnosis and procedure codes for bowel and urinary complications.

Other variables—Patient characteristics were categorized from SEER-Medicare data and analyzed according to the variables shown in Table 1. Patient comorbidities were identified by classifying all available inpatient and outpatient Medicare claims for the 12-month interval preceding prostate cancer diagnosis into 46 categories (27–29). Neither PSA nor radiotherapy dose are reported in SEER-Medicare data.

Statistical analysis

We used chi-square tests to compare baseline characteristics between patients receiving IMRT vs. CRT. To balance observed covariates between the IMRT and CRT groups in regression analyses, we used propensity score methods. Propensity scores reflect the probability that a patient will receive therapy on the basis of his observed covariates and can help adjust for selection bias when comparing groups of patients in observational studies (30, 31). For example, patients given CRT may have more severe comorbid disease that may

be associated with bowel or urinary complications than those given IMRT. Bowel or urinary complications in these patients may reflect differences in underlying characteristics rather than treatment effects. Propensity score methods try to construct a randomized trial–like comparison between treatment groups that are comparable across observed characteristics. We calculated propensity scores using multivariable logistic regression with receipt of IMRT as the outcome of interest, adjusting for age at diagnosis, race, ethnicity, marital status, T-stage, Gleason sum, history of transurethral resection of the prostate or androgen suppression, comorbidity, diagnosis year, SEER registry, area population, and median income (32). We used chi-square tests to determine whether the covariates were balanced within propensity score quintiles and found that diagnosis year and population size in the county of residence were still not balanced (Table 1).

The Kaplan-Meier method was used to compare estimates of the unadjusted, cumulative incidence of primary and secondary complication outcomes between IMRT and CRT. The observation time for follow-up was calculated as the time from the start date of radiotherapy (determined by the first code for radiotherapy delivery) until either the occurrence of the complication outcome being analyzed or censorship. Patients were censored at death or end of follow-up (December 31, 2006).

To adjust for potential measured confounders, we constructed Cox proportional hazard models to compare complication outcomes between IMRT and CRT, adjusting for propensity score as a continuous variable as well as diagnosis year and area population, which were not balanced after propensity score adjustment. To assess the proportional hazards assumption, we used the Schoenfeld residuals test and complementary log-log plots, and demonstrated that this assumption was not violated in our models (33). In sensitivity analysis, we limited the cohort to men with a minimum follow-up period of 2 years, and results were similar (data not shown).

In observational data sets, it is not always clear why certain patients receive particular treatments. Treatment decisions may be made on the basis of baseline differences between patients that may be prognostically important and that may be measured or unmeasured. When unknown or unmeasured patient characteristics (sometimes called “hidden bias”) potentially affect both the decision to treat and the outcome of treatment, bias between patient groups cannot be removed using propensity score methods. To examine the effects of unknown or unmeasured confounders, we performed a sensitivity analysis to assess the potential influence an unmeasured covariate might have on the hazard ratio (HR) estimates of the association between IMRT and complications (29, 34, 35). We varied both the prevalence of the unmeasured covariate in the CRT group and the relative hazard of complications associated with the confounder. Propensity score calculations and survival analyses were performed using SAS version 9.2 (Cary, NC), and sensitivity analyses were performed using R version 2.7.2 (Vienna, Austria). Statistical significance was set at 0.05, and all tests were two-tailed.

RESULTS

Patient baseline characteristics

The analytic cohort consisted of 12,598 patients diagnosed between 2002 and 2004, of whom 5,845 received IMRT and 6,753 received CRT. Table 1 presents the baseline characteristics of the two groups. Patients who received IMRT were more likely to reside in areas with larger populations or higher median income and to have earlier stage and lower grade tumors. During the study period, IMRT use increased dramatically.

Unadjusted cumulative incidence of complication outcomes after IMRT vs. CRT

Because of differences in median length of follow-up between men in the IMRT and CRT groups, we evaluated rates of complications over time accounting for censoring. The Kaplan-Meier curve for the estimated cumulative incidence of the primary outcome is shown in Fig. 1a. The incidence of composite bowel complications requiring invasive procedures was less in the IMRT group vs. the CRT group (24-month cumulative incidence of 18.8% vs. 22.5%, Table 2). The incidence of composite urinary complications was lower in the IMRT group (Fig. 1b). The incidence of composite erectile complications involving procedural intervention was low and did not differ significantly between groups. The incidence of proctitis/hemorrhage and cystitis/ hematuria were also lower with IMRT than CRT (Fig. 1c).

Adjusted hazard of complication outcomes after IMRT vs. CRT

After adjusting for propensity score, diagnosis year, and area population in Cox models, IMRT was associated with a significant reduction in composite bowel complications (hazard ratio [HR] 0.86; 95% confidence interval [CI], 0.79–0.93) and proctitis/hemorrhage (HR 0.78; 95% CI, 0.64–0.95; Table 3). In contrast, the associations between IMRT and reductions in composite urinary complications and cystitis/hematuria were no longer significant.

Cumulative incidence and hazard of complication diagnoses

We performed a sensitivity analysis to evaluate differences in rates of complication diagnoses independent of invasive procedures. Not surprisingly, complication diagnoses were more frequent than complications with invasive procedures (eAppendix Supplementary Fig. 2). The incidence of bowel diagnoses was less in the IMRT group than the CRT group, whereas the incidence of urinary diagnoses did not differ significantly between the groups. The incidence of new impotence diagnoses was higher in the IMRT group vs. the CRT group (24-month cumulative incidence of 15.6% vs. 12.6%). In Cox models adjusted for propensity score, diagnosis year, and area population, hazards of complication diagnoses associated with IMRT vs. CRT were very similar to the main analysis of complications with invasive procedures (eAppendix Supplementary Table 2). IMRT was associated with a significant increase in impotence diagnoses in unadjusted (HR 1.28, 95% CI, 1.16–1.41) and adjusted (HR 1.27, 95% CI, 1.14–1.42) proportional hazards models.

Effect of an unmeasured confounder

In nonrandomized studies, an observed association between treatment and outcome may reflect the effects of unmeasured confounders. Poor functional status is an example of an unmeasured confounder that may be relevant to the cohort and outcomes under study that is not recorded in SEER-Medicare data. The strength of the association between IMRT and complications is affected by (1) the prevalence of the unmeasured confounder in the IMRT group, (2) the prevalence of the unmeasured confounder in the CRT group, and (3) the hazard associated with the unmeasured confounder (which is assumed to be the same in the IMRT and CRT groups).

The sensitivity analysis for the primary outcome is shown in Table 4 and is based on the estimated adjusted hazard ratio for composite bowel complications for IMRT vs. CRT (0.86, 95% CI, 0.79–0.93). We set the prevalence of the unmeasured confounder in the IMRT group at 10%, which is in the range, for example, of prevalence estimates of poor functional status or disability among the elderly (36). We then varied the prevalence of the unmeasured confounder in the CRT group to determine the extent to which its distribution would need to be imbalanced between the groups to influence the statistical significance of the results (*i.e.*, the upper bound of the 95% CI crosses 1.0). For example, if the unmeasured confounder were a moderate confounder, increasing the risk of complications by 50% (HR 1.50), the estimated hazard ratio would be significantly affected if the prevalence of the unmeasured confounder in the IMRT and CRT groups were threefold different (*i.e.*, 30% prevalence in the CRT group but only 10% prevalence in the IMRT group). Under these conditions, our results would no longer be significant.

DISCUSSION

We conducted this study to compare complications after IMRT vs. CRT in a population-based cohort of men with nonmetastatic prostate cancer. Analyzing administrative claims data from patients diagnosed between 2002 and 2004 in the United States, we found that IMRT was associated with a small reduction in a composite measure of bowel complications as well as the specific complications of proctitis/hemorrhage. Measures of urinary complications did not differ significantly between patients treated with IMRT vs. CRT. Although erectile complications involving invasive procedures were rare in both treatment groups, IMRT was associated with a moderate increase in new diagnoses of impotence compared with CRT.

The lower rate of bowel complications we observed is consistent with the reduced proportion of rectum exposed to higher doses of radiation with IMRT (25). Minimal differences in urinary side effects between IMRT and CRT may be explained because a portion of bladder neck and prostatic urethra are included in the irradiated target volume regardless of radiotherapy technique (37).

Our findings are consistent with and extend those of previous studies examining technological improvements in radiotherapy delivery. The only randomized comparison between different radiotherapy techniques for patients with prostate cancer compared CRT to conventional radiation therapy, a two-dimensional technique employed before the

introduction of CRT that used rectangular irradiation fields rather than three-dimensional imaging to shape the radiation beam to the prostate (26). Fewer patients developed radiation-induced proctitis in the CRT group vs. the conventional group, whereas there were no significant differences in rates of cystitis. The proportion of patients experiencing Grade 3 proctitis (*i.e.*, requiring hospital admission or procedural intervention) in this study and other controlled trials of CRT, using radiation doses ranging from 64 to 78 Gy, has ranged from 0% to 7% (26, 38–40).

A recent systematic review of IMRT identified five published studies in which late toxicity data was compared between IMRT and CRT, and we identified one additional study based on a comprehensive search (7, 41–46). Table 5 summarizes these studies and compares results to our findings. Although differences exist between patient characteristics in the IMRT and CRT groups and several studies used historical controls from the previous decade (42, 44, 47), the limited evidence available shows that IMRT is generally associated with lower rates of Grade 3 proctitis (range, 1%–6%), compared with CRT (range, 2%–21%). Taken together, the magnitude and direction of the IMRT treatment effect from these studies is very similar to the rates of proctitis/hemorrhage (the most comparable endpoint) in our population-based cohort. This evidence provides some external validity of our outcome measures but also highlights the fact that any improvement with IMRT, although perhaps measurable and important, will be modest in absolute terms. Our study augments the existing literature by examining a large and broad population of patients and adjusting for known confounders, including an extensive set of comorbidities ascertained from Medicare data.

The finding that IMRT is associated with increased new diagnoses of impotence raises several important questions. Although a growing literature describes the use of IMRT to limit the dose of radiation to presumed erectile structures, the etiology of erectile dysfunction after radiotherapy remains poorly established (48, 49). Because IMRT increases radiation dose heterogeneity (*e.g.*, “hot spots”) compared with CRT (50), IMRT may result in higher doses of radiation to erectile structures and higher rates of subsequent impotence. In addition, radiotherapy dose escalation has been facilitated by IMRT, and it is possible that men in the IMRT group were treated with higher overall doses of radiation than men in the CRT group. Systematic differences in radiotherapy dose, which are not recorded in SEERMedicare data, may contribute to the observed differences in erectile dysfunction. However, the measurement of impotence from Medicare claims data is well known to be challenging and to underestimate actual rates of erectile dysfunction (13). Moreover, men who were early adopters of IMRT may be intrinsically more likely to pursue medical care than those who received CRT. This bias may result in a higher rate of claims-based detection of impotence among men undergoing IMRT, thereby inflating the association between IMRT and impotence.

Because our study design was observational rather than randomized, our results must be interpreted within the context of the limitations of observational research (51). The propensity score approach reasonably adjusts for potential bias due to measured confounders and revealed little material change in the IMRT treatment effect across study endpoints. However, residual bias due to unmeasured confounders remains a challenge for

observational research (52). In addition, the statistically significant treatment effect we report for the primary outcome is of moderate strength and thus possibly sensitive to systematic bias (53, 54). In the sensitivity analysis, we found that the statistical significance of the observed association between IMRT and reduced bowel complications could be eliminated under what would be considered extreme scenarios (i.e., an unmeasured confounder, such as poor functional status, would need to have an increased risk of bowel complications of 1.5- and a 3-fold difference in prevalence between the CRT and IMRT groups); however, such situations are plausible in a broadly representative population-based cohort.

Given the challenges in conducting randomized trials in this area, complementary observational studies with more extensive clinical data, including clinician- or patient-reported toxicity measures, would be helpful, particularly for disentangling the possible relationship between IMRT and erectile dysfunction. For example, cancer cooperative groups could retrospectively analyze prospective clinical trials in which both IMRT and CRT were used. The creation of registries with patient-reported outcomes would also be an important contribution. Moreover, the gap in randomized evidence for new medical technology that is highlighted by the case of IMRT underscores the need and opportunity to design efficient, pragmatic clinical trials as new therapies are developed (55).

Using Medicare claims data to study the complications of cancer treatment has limitations. Medicare billing codes are an imperfect measure of complications, particularly when the complication does not involve further procedures. Although we assume that new, posttreatment Medicare claims related to bowel, urinary, or erectile morbidity reflect complications from radiotherapy, there may be several reasons for these claims, possibly leading to higher complication estimates (18). For example, physicians may be particularly diligent about documenting diagnoses of morbidity for billing purposes, even though the incidence of serious complications requiring procedural intervention is lower. In the primary analysis, our outcome measures required the presence of both a procedure and diagnosis billing code, thereby maximizing the specificity of the measure for serious complications. Although this approach underestimates the rates of less severe complications that do not involve a procedure, the results of sensitivity analyses using diagnoses alone were very similar to the primary analyses for both bowel and urinary complications. Furthermore, any misclassification of Medicare claims is likely to be nondifferential (e.g., equal among men in the IMRT and CRT groups) or potentially biased in favor of the CRT group (men who are early adopters of IMRT are also more likely to seek medical attention for their complications) (13). It is important to note as well that we are unable to ascertain more minor complications consistent with clinician-reported Grade 1 or 2 toxicity.

Although IMRT was associated with a small reduction in composite bowel complications (our primary endpoint), our results show that approximately one in five patients experienced such complications requiring an invasive procedure at 24 months. When used to assess complications of cancer treatment, Medicare claims measure the incidence of interventions rather than the prevalence of adverse function (12). The incidence of interventions after radiotherapy among this U.S. population-based cohort may reflect, in part, U.S.-specific practice patterns consistent with health services overutilization (2). In addition, although we

adjusted for known covariates that may increase the likelihood of complications after treatment, we could not characterize baseline bowel, urinary, or erectile function on the basis of Medicare billing codes. Also, early vs. late or transient vs. chronic radiotherapy complications cannot be reliably ascertained from SEERMedicare data.

In conclusion, our study demonstrates that IMRT is associated with a small reduction in composite bowel complications and proctitis/hemorrhage compared to CRT in elderly men with nonmetastatic prostate cancer. Our results have both internal and external validity. They are biologically plausible based on established dose–volume–outcome principles of radiotherapy. The selected outcomes are confined to diagnoses consistent with radiotherapy injury and associated with invasive procedures likely to be well documented in claims data (13). Although restricted to men aged 65 years and older, findings from this population-based cohort are generalizable to the great majority of men who receive radiotherapy for prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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Fig. 1.

(a) Cumulative incidence of composite bowel complications requiring an invasive procedure after intensitymodulated (IMRT) and three-dimensional conformal (CRT) radiotherapy. (b) Cumulative incidence of composite urinary complications requiring invasive procedures after IMRT and CRT. (c). Cumulative incidence of subsets of bowel and urinary complications requiring invasive procedures after IMRT and CRT

Table 1

Baseline characteristics of study cohort

	IMRT		CRT		p Value	
	n (%)	n (%)	n (%)	Before adjustment	After propensity adjustment	
All patients	5,845 (46)	6,753 (53.6)				
Patient characteristics						
Age at diagnosis						
65–74 years	3,204 (55)	3,684 (55)				
75 years or older	2,641 (45)	3,069 (45)		0.778	0.616	
Race						
White	4,851 (83)	5,707 (85)				
Black	521 (9)	708 (10)				
Other	371 (6)	249 (4)				
Unknown	102 (2)	89 (1)		<0.0001	0.805	
Hispanic ethnicity						
Not Hispanic	5,384 (92)	6,207 (92)				
Hispanic	311 (5)	384 (6)				
Unknown	150 (3)	162 (2)		0.569	0.903	
Marital status						
Married	4,153 (71)	4,789 (71)				
Not married	1,154 (20)	1,418 (21)				
Unknown	538 (9)	546 (8)		0.030	0.908	
Clinical characteristics						
Tumor stage (AJCC 6th ed.)						
T1	2,511 (43)	2,547 (38)				
T2	3,081 (51)	3,908 (58)				
T3	215 (4)	230 (3)				
T4	38 (1)	68 (1)		<0.0001	0.824	
Gleason sum						
8–10	1,590 (27)	1,937 (29)				

	IMRT		CRT		p Value	
	n (%)		n (%)		Before adjustment	After propensity adjustment
5-7	4,091 (70)	4,603 (68)				
2-4	61 (1)	107 (2)				
Unknown	103 (2)	106 (2)			0.009	0.971
History of TURP						
No	5,617 (96)	6,432 (95)				
Yes	228 (4)	321 (5)			0.019	0.683
Adjuvant androgen suppression						
No	2,225 (38)	2,526 (37)				
Yes	3,620 (62)	4,227 (63)			0.445	0.909
Comorbidity index *						
0	1,470 (25)	1,669 (24)				
1	1,759 (30)	2,065 (31)				
2	2,616 (45)	3,019 (45)			0.786	0.921
Demographic characteristics						
Year of diagnosis						
2002	1,183 (20)	3,278 (49)				
2003	1,911 (33)	2,172 (32)				
2004	2,751 (47)	1,303 (19)			<0.0001	<0.0001
SEER registry **						
San Francisco	200 (3)	239 (3)				
Connecticut	474 (8)	599 (9)				
Detroit	642 (11)	890 (13)				
Hawaii	156 (3)	75 (1)				
Iowa	214 (4)	589 (9)				
New Mexico	203 (3)	176 (3)				
Seattle	157 (3)	387 (6)				
Utah	39 (1)	109 (2)				
Atlanta	97 (2)	103 (1)				

	IMRT		CRT		p Value	
	n (%)		n (%)		Before adjustment	After propensity adjustment
San Jose	109 (2)		153 (2)			
Los Angeles	619 (11)		250 (4)			
Greater California	1,065 (18)		1,072 (16)			
Kentucky	175 (3)		801 (12)			
Louisiana	510 (9)		376 (6)			
New Jersey	1,178 (20)		922 (14)		<0.0001	0.418
Population of county of residence						
1,000,000 or more	3,700 (63)		3,326 (49)			
250,000 to 999,999	1,091 (19)		1,317 (20)			
0 to 249,999	1,054 (18)		2,110 (31)		<0.0001	0.025
Median household income in census tract of residence (US\$)						
34,000 or less	1,225 (21)		1,828 (27)			
> 34,000 to 44,000	992 (17)		1,493 (22)			
> 44,000 to 60,000	1,437 (25)		1,741 (26)			
> 60,000	2,191 (37)		1,691 (25)		<0.0001	0.123

Abbreviations: AJCC = American Joint Committee on Cancer; CRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; SEER = Surveillance, Epidemiology, and End Results; TURP = transurethral resection of the prostate.

* Comorbidity score of 2 represents highest level of comorbidity.

** Data not shown for 19 patients in the SEER Rural Georgia registry, according to SEER-Medicare guidelines.

24-Month cumulative incidence of complications requiring an invasive procedure after intensity-modulated (IMRT) and three-dimensional conformal (CRT) radiotherapy

Table 2

	IMRT			CRT		
	Median follow-up (months)*	Cohort at risk (24 months)	24-month estimate, % (95% CI)	Median follow-up (months)*	Cohort at risk (24 months)	24-month estimate, % (95% CI)
Primary outcome						
Bowel complications	28	3,727	18.8 (17.8–19.9)	34	4,614	22.5 (21.5–23.5)
Secondary outcomes						
Urinary complications	29	3,997	10.4 (9.6–11.1)	37	5,145	11.2 (10.4–12.0)
Erectile complications	32	4,586	1.0 (0.8–1.3)	41	5,946	0.7 (0.5–0.9)
Subsets of bowel and urinary complications						
Proctitis, hemorrhage	31	4,472	3.5 (3.0–4.0)	40	5,723	4.5 (4.0–5.0)
Cystitis, hematuria	30	4,226	7.7 (7.0–8.4)	39	5,433	8.3 (7.6–9.0)

Abbreviation: CI = confidence interval.

* Median follow-up for surviving patients.

Table 3

Association between intensity-modulated radiotherapy and complications requiring an invasive procedure

	Univariate HR for complication	Multivariable HR for complication *
	(95% CI)	(95% CI)
Primary outcomes		
Bowel complications	0.86 (0.76–0.88)	0.86 (0.79–0.93)
Secondary outcomes		
Urinary complications	0.87 (0.79–0.97)	0.93 (0.83–1.04)
Erectile complications	1.30 (0.91–1.88)	1.50 (1.00–2.24)
Subsets of bowel and urinary complications		
Proctitis, Hemorrhage	0.78 (0.66–0.93)	0.78 (0.64–0.95)
Cystitis, Hematuria	0.86 (0.77–0.96)	0.94 (0.83–1.07)

Abbreviations: CI = confidence interval; HR = hazard ratio.

* Adjusted for propensity score, year of diagnosis, and area population

Table 4

Sensitivity analysis estimating the effect of an unmeasured confounder on the hazard ratio of bowel complications after intensity-modulated radiotherapy (IMRT)

Prevalence of UC in IMRT group	Prevalence of UC in CRT group	UC HR	Treatment HR adjusted for UC (95% CI)
0.10	0.3	1.25	0.90 (0.83, 0.98)
0.10	0.4	1.25	0.92 (0.85, 0.99)
0.10	0.5	1.25	0.94 (0.87, 1.02)
0.10	0.2	1.50	0.90 (0.83, 0.97)
0.10	0.3	1.50	0.94 (0.86, 1.02)
0.10	0.2	1.75	0.92 (0.85, 0.99)
0.10	0.3	1.75	0.98 (0.90, 1.06)
0.10	0.2	2.0	0.94 (0.86, 1.01)

Abbreviations: CRT = three-dimensional conformal radiotherapy; HR = hazard ratio; UC = unmeasured confounder.

The rows in bold highlight situations in which the unmeasured confounder is strong enough to influence the significance of the results (e.g., the upper bound of the 95% CI crosses 1).

Summary of studies comparing late rectal and urinary toxicity after intensity-modulated (IMRT) and three-dimensional conformal (CRT) radiotherapy

Table 5

Study	Follow-up median/ reported (months)	Definition	IMRT		CRT		Late rectal toxicity			Late urinary toxicity			P value
			n	Dose	n	Dose	IMRT	CRT	pvalue	IMRT	CRT	pvalue	
Shu 2001 ⁴³	23/10	RTOG Gr. 2	18	85 Gy	26	84 Gy	NR	NR	0.163	NR	NR	NR	0.025
Kupelian 2002 ⁴¹	25/30	RTOG Gr. 3	166	70 Gy/2.5 Gy	116	78 Gy	2%	8%	0.059	0	0	NA	NA
Sanguineti 2006 ⁴²	26/24	RTOG Gr. 2	45	76 Gy	68	76 Gy	6%	21%	0.06	NR	NR	NR	NR
Vora 2007 ⁴⁴	60/60	RTOG Gr. 3	145	75.6 Gy	271	68.4 Gy	1%	2%	0.24	6%	5%	0.33	0.33
Zelefsky 2008 ⁴⁵	96/120	CTC Gr. 2	472	81 Gy	358	75.6 Gy	5%	13%	<0.001	20%	12%	0.01	0.01
Odratzka 2010 ⁴⁶	53/36	RTOG Gr. 3	112	78 Gy	228	70 Gy	2%	5%	0.20	5%	16%	0.01	0.01
Bekelman 2011	36/24	Medicare claims*	5,845	NA	6,753	NA	3.5%	4.5%	0.01**	7.7%	8.3%	0.19**	0.19**

Abbreviations: CTC = Common Toxicity Criteria; Gr = Grade; NA = not applicable; NR = not reported; RTOG = Radiation Therapy Oncology Group.

* Based on Medicare claims for diagnoses and procedures consistent with proctitis/hemorrhage or cystitis/hematuria

** Adjusted p.