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Comparative effectiveness of external beam radiation approaches for prostate cancer

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Abstract

Background—Intensity-modulated radiotherapy (IMRT) is increasingly used for treating localized prostate cancer. While allowing for the delivery of higher doses of radiation to the prostate, its effectiveness compared to the prior standard, 3-dimensional conformal therapy (3D-CRT), is uncertain.

Objective—To examine the comparative effectiveness of IMRT relative to 3D-CRT.

Design, setting, and participants—We performed a population-based cohort study using Surveillance, Epidemiology, and End Results (SEER)-Medicare data to identify men diagnosed with prostate cancer between 2001 and 2007 who underwent either 3D-CRT (n=6,976) or IMRT (n=11,039).

Measurements—We assessed our main outcomes (i.e., the adjusted use of salvage therapy with androgen deprivation therapy (ADT) and risk of a complication requiring an intervention) using Cox proportional-hazards models.

Results and limitations—The percentage of men receiving IMRT increased from 9% in 2001 to 93% in 2007. Compared to those treated with 3D-CRT, low-risk patients treated with IMRT had similar likelihoods of using salvage therapy with ADT and similar risks of having a complication requiring an intervention (all $p>0.05$). Conversely, a subset of higher-risk patients treated with IMRT who did not receive concurrent ADT were less likely to use salvage therapy ($p=0.02$), while maintaining similar complication rates. Since our cohort includes Medicare beneficiaries, our findings may not be generalizable to younger patients.

Conclusions—For a subset of higher-risk patients, IMRT appears to show a benefit in terms of reduced salvage therapy without an increase in complications. For other patients, the risks of salvage therapy and complications are comparable between the two modalities.

Keywords

complications; intensity-modulated radiotherapy; prostate cancer; radiation; salvage therapy

INTRODUCTION

Prostate cancer is the most common malignancy among men in the United States, accounting for approximately 200,000 new cases in 2011.[1] While there are several treatment options, radiation therapy is among the most frequently used, particularly for older men.[2] With the introduction of intensity-modulated radiation therapy (IMRT), treatment has evolved to deliver higher doses of radiation with improved precision.[3] As bowel, urinary, and sexual-related side effects are a concern with any prostate cancer treatment, enthusiasm for IMRT is largely based on the potential for translating this advance in targeting into better patient outcomes (i.e., improved cancer control and less toxicity).[4–6]

While IMRT's targeting capabilities afford the possibility of improved outcomes, its unfettered dissemination is not without potential trade-offs. First, relative to the prior standard of 3-dimensional conformal therapy (3D-CRT), evidence supporting IMRT's advantages in terms of lower toxicity[4, 5, 7] and improved cancer control[6, 8] is mixed. A comprehensive review noted that improvements in bowel toxicity were found in only half the studies comparing the two methods.[3] Another recent study demonstrated improved bowel morbidity but similar urinary morbidity and worse erectile dysfunction with IMRT.[9] Second, some worry that IMRT irradiates larger volumes of normal tissue, albeit at lower doses, which may increase the risk of secondary malignancies.[10] Third, IMRT carries a premium, approximately \$11,000 more per patient.[11] Thus, knowing the value of IMRT at the population level is important for optimally allocating spending for prostate cancer care.

For these reasons, we performed a study to better understand the associations between the radiation therapy delivery method and outcomes. Understanding the comparative effectiveness of alternative radiation approaches is paramount to improving the quality while limiting the costs of prostate cancer care, particularly in a climate of constrained economic resources.

MATERIALS AND METHODS

Data Source and Study Population

We used Surveillance, Epidemiology, and End Results (SEER)-Medicare data to identify men 66 years or older diagnosed with localized prostate cancer between 2001 and 2007. This nationally representative cancer registry comprises approximately 26% of the United States' population.[12] We excluded men 65 years old to ensure accurate comorbidity estimation using Medicare claims for the 12-month period prior to diagnosis.[13] Only men enrolled in Medicare Parts A and B throughout the study were included.

Using methods established by others that leverage both planning and delivery codes, we identified men undergoing IMRT and 3D-CRT using Healthcare Common Procedure

Coding System (HCPCS) codes in the outpatient and carrier files.[14] We included men treated within 12 months of diagnosis who had prostate cancer as their only cancer, and excluded those with unknown stage. Patients who received other treatments (e.g., prostatectomy, brachytherapy) between the time of diagnosis and radiation were excluded. Using these criteria, our study population consisted of 11,039 and 6,976 patients treated with IMRT and 3D-CRT, respectively.

Outcomes

Bowel, urinary, and sexual complications were identified using International Classification of Diseases, 9th Revision (ICD-9) diagnosis and procedure codes as well as HCPCS codes using well-defined algorithms.[14] We only assessed complications that required a procedure (appendix) because diagnosis codes alone lack specificity and may be underreported.[14, 15] We performed a sensitivity analysis to compare the odds ratios (IMRT vs. 3D-CRT) for each type of complication using the 2003 diagnosis cohort. We chose 2003 because nearly half these patients were treated with IMRT during that time. The odds ratios varied by as much as 25% between the two methods of identifying complications (procedure codes vs. procedure and diagnosis codes), which support the notion that diagnosis codes may be unreliable in measuring complications. To minimize the misclassification of pre-existing conditions as complications, we excluded patients with codes for the index complication present within 12-months prior to treatment.

Because of concerns related to attribution of cause-of-death,[16] prostate cancer's protracted clinical course, and the intermediate maturity of our cohort (mean follow-up: 36 months, IMRT and 62 months, 3D-CRT), we assessed the use of salvage androgen deprivation therapy (ADT) as a measure of cancer control as opposed to overall or cancer-specific mortality. Based on evidence from randomized trials, clinical guidelines recommend 2–3 years of ADT when radiation therapy is administered for high-risk prostate cancer.[17] Because some patients are treated with hormones during radiation (concurrent ADT) and others are not (no concurrent ADT), we implemented separate definitions of salvage accordingly. Among patients treated with concurrent ADT, salvage therapy was assigned to those treated with hormones beyond 36 months after the start of radiation. Conversely, among patients not receiving concurrent ADT, the use of ADT beyond 6 months of radiation was classified as salvage. We assessed all-cause mortality as a secondary outcome.

Statistical Analysis

We compared patient characteristics using chi-square tests. For each outcome, we fit Cox proportional-hazards models. By implementing a survival analysis framework, we accounted for differences in follow-up between the two cohorts. Models were back-transformed to generate 5-year predicted probabilities and were adjusted for age, race/ethnicity, comorbidity, socioeconomic status, tumor grade and stage, and treatment year. Socioeconomic class was ascertained at the zip code level.[18] There was some indication of a decreasing trend in complications for IMRT over time. To help alleviate this concern, we adjusted for treatment year. For our primary outcomes, models were risk-stratified. As defined previously,[2] low-risk patients included men of any age with well-differentiated tumors or men 70 or older with moderately-differentiated tumors; all others were considered

to have higher-risk disease. Due to the timeframe of our study (2001–2009), we could not use the more conventional D'Amico classification to assign risk groups. However, we have previously shown good agreement between these two definitions of low-risk disease.[19] Analyses were performed using SAS v9.2 (Cary, NC). The probability of a type I error was set at 0.05 and all testing was two-sided. The University of Michigan's Institutional Review Board approved the study protocol.

RESULTS

Among men treated with external beam radiation, the percentage undergoing IMRT, as opposed to 3D-CRT, increased from 9% in 2001 to 93% in 2007 ($p<0.01$ for trend) (Figure 1). While we noted statistically different compositions of race/ethnicity and socioeconomic class, these differences (1–2%) did not appear to be clinically significant (Table 1). Compared with those treated with 3D-CRT, patients undergoing IMRT were more likely to have poorly differentiated (38% versus 53%, $p<0.01$) and non-palpable (39% versus 52%, $p=0.01$) tumors and less likely to receive concurrent ADT (54% versus 39%, $p<0.01$).

Figure 2 illustrates the adjusted percentage of men with low-risk disease having a complication and undergoing salvage therapy at 5 years. For these patients, the likelihood of having a complication requiring an intervention or needing salvage therapy was similar between the two approaches (all $p>0.05$).

The 5-year probabilities of a complication and salvage therapy for men with higher-risk disease are shown in Figure 3. Again, the risks of a complication were similar for IMRT and 3D-CRT. However, among higher-risk patients who did not receive concurrent ADT, those treated with IMRT were less likely to undergo salvage therapy compared to those treated with 3D-CRT (16% vs. 20%, $p=0.02$). The 5-year adjusted percentage of overall mortality for 3DCRT compared to IMRT was 20% versus 22%, respectively ($p<0.01$).

DISCUSSION

Over the last decade, there has been a significant change in how men with prostate cancer are treated with external beam radiation. The use of IMRT, as opposed to 3D-CRT, grew from 9% of Medicare beneficiaries in 2001 to 93% in 2007. This sea change toward IMRT was associated with declines in the subsequent use of salvage therapy with ADT for a subset of men with higher-risk disease who were not treated with hormones concurrently at the time radiation. In addition, men treated with IMRT and 3D-CRT had similar risks of complications requiring an intervention despite that, on average, higher doses of radiation were likely administered with IMRT.

Enthusiasm for IMRT stems from its precise targeting capability to deliver radiation, thereby enabling higher dose delivery to cancerous sites while limiting exposure to normal tissues. [3] The notion that higher radiation dose with better targeting enhances patient outcomes (i.e., lower toxicity, improved cancer control) is strongly supported by randomized clinical trials involving 3D-CRT. In these trials, the use of 3D-CRT reduced toxicity compared to its prior alternative, conventional radiation therapy,[20] and resulted in lower rates of biochemical recurrence with the administration of higher doses.[21] Based on these data, it

is generally believed that patients would gain similar benefits in both toxicity and effectiveness with IMRT.

However, results from head-to-head trials comparing efficacy of IMRT with 3D-CRT for prostate cancer are lacking, although one study (NCT 00326638) is currently recruiting patients and expects to provide answers to this question by mid-2014.[22] Observational data from single institutions have yielded mixed findings with respect to toxicity, with IMRT providing a benefit in some studies,[4] but not in others.[7] A recent population-based study comparing IMRT with 3D-CRT demonstrated that IMRT was associated with lower bowel morbidity, similar urinary morbidity, worse erectile dysfunction, and improved cancer control.[9]

Our study differs from this one in a few important ways. First, we incorporated treatment planning codes specific to 3D-CRT to obtain a more homogenous comparison group.[14] Excluding patients treated with conventional radiotherapy removes bias since conventional therapy is associated with increased morbidity compared to 3D-CRT. Second, since IMRT is a newer technology, we included complications that occurred within the first year after treatment to assess both short- and long-term morbidity. Third, since the use of diagnosis codes to enumerate complications is typically less accurate than relying on procedure codes alone,[15] we limited our analysis to only those complications that required an intervention.

In addition to assessing complications, we examined the use of salvage therapy with ADT as a measure of cancer control. Due in part to prostate cancer's protracted clinical course, biochemical recurrence has generally been used as a proxy for cancer control,[6, 8] although such definitions of recurrence vary, and some feel lack precision.[23] In our study, the lower proportion of men receiving concurrent ADT with IMRT is congruent with the observation that more of these patients had lower-stage disease. Since salvage therapy is associated with nontrivial morbidity, the 20% reduction in its use among higher-risk patients treated with IMRT who did not receive concurrent ADT has important patient implications. Chronic ADT is commonly associated with numerous side effects, including hot flashes, severe fatigue, weight gain, and bone mineral loss.[24] This constellation of effects negatively impacts the health-related quality-of-life of men with prostate cancer,[25] may predispose them to metabolic conditions such as diabetes mellitus, and may exacerbate their risk of death due to cardiovascular disease.[26]

In contrast to the use of salvage therapy, complication risks were no different between IMRT and 3D-CRT. On the one hand, this finding is counterintuitive given the improved targeting capabilities of IMRT. On the other hand, given the likelihood that higher doses of radiation were delivered with IMRT, the similar complication risk may be seen as an advantage since cancer control appears superior in some patients.

Understanding the relative effectiveness of IMRT and 3D-CRT with respect to salvage therapy use and complications is important for clinical decision-making and patient care. Additionally, weighing the trade-offs between IMRT's modest benefit and its associated costs is of immediate interest to payers and policymakers, who regularly grapple with how to pay for new and expensive healthcare technologies. Many believe that the implementation

of new technology is to blame for the inexorable growth in healthcare spending.[27] Treating men in the United States with IMRT as opposed to 3D-CRT costs an additional \$11,000 per patient. In an era of constrained resources, understanding the comparative effectiveness of alternative radiation treatments for prostate cancer is imperative for getting the most value out of spending earmarked for cancer-related care. This is particularly important as newer and even more expensive prostate cancer treatment technologies, such as proton beam therapy, become more widely available.

While our findings provide insight into the comparative effectiveness of the two radiation approaches with respect to use of salvage and interventions for complications, at least two additional knowledge gaps must be addressed to establish overall value of IMRT compared with 3D-CRT. First, assessing differences in health-related quality-of-life, which is difficult to analyze using claims data,[28] would be important for identifying more subtle changes in toxicity after treatment. Given its enhanced targeting capabilities compared with 3D-CRT, it is highly plausible that IMRT may better preserve quality-of-life in those who never require an additional procedure. Ultimately, this question will not be answered until data from NCT 00326638 mature over the next 5 to 7 years. Second, differences in long-term mortality between the two approaches would likely sway opinions about effectiveness in favor of the superior approach, particularly if these differences are large. As a secondary outcome, we evaluated overall mortality, which was 2% lower among patients who received 3D-CRT. However, due to the prostate cancer's protracted natural history, assessing true differences in overall and prostate-specific mortality will not be practical for at least another decade.

In interpreting our findings, it is important to consider additional limitations. First, claims data are primarily designed to provide billing information and do not include specific codes for complications. Since reimbursement for physicians is driven by procedures rather than diagnoses,[29] complications derived from diagnosis codes may be underreported.[15, 28] For this reason, we measured only those complications that required an intervention. While this represents only a subset of the overall cohort having complications, we would expect the unmeasured subset to be non-differential with respect to radiation approach. Second, the generalizability of our findings is limited to Medicare beneficiaries undergoing radiation therapy for prostate cancer. Although approximately one-third of patients with prostate cancer are less than 65 years old,[30] those treated with external beam radiation therapy tend to be older than those undergoing alternative therapies (median age 69 years),[25] and thus our findings are generalizable to a population with the most interest in the comparative effectiveness of the two approaches.

Third, as with all observational data, our inference may be biased by unmeasured differences between the two populations. For instance, in comparing IMRT with 3D-CRT, we are not directly measuring radiation dose, which is linked to both complications and cancer control. [21] Although radiation dose is not available in SEER-Medicare data, prior studies have made valuable inferences about cancer control and toxicity with IMRT and 3D-CRT in which radiation doses were either different between the two approaches[4, 6] or unobtainable.[9, 14] Thus, while dose may play a role in outcomes, our findings represent the average risk of both complications and use of salvage among patients treated with IMRT and 3D-CRT.

CONCLUSION

Among patients in the United States diagnosed with prostate cancer between 2001 and 2007 who were treated with external beam radiation, we observed a dramatic shift in approach from 3D-CRT to IMRT. Findings related to the comparative effectiveness of the two approaches showed a modest benefit with IMRT: the need for salvage therapy was less for a subset of men with higher-risk disease who did not receive concurrent ADT while the risk of a complication was no different between the two modalities. In this context, society must decide what price it is willing to pay for these benefits.

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Appendix

Appendix

Medicare codes used to define procedural-based complications after radiation treatment for prostate cancer

Complication Group	ICD-9-CM Procedure codes	CPT-4/HCPCS codes
Bowel		
Endoscopies (proctosigmoidoscopy, colonoscopy, anoscopy) with procedure (e.g., collection of specimen, dilation, control of bleeding, stent placement)	4823 4829	45300 45303 45317 45321 45327 45334 45335 45337 45340 45341 45345 45380 45381 45382 45386 45387 45391 46604 46614
Biopsies (rectal, cecal, anal)	4824 4525 492 4922 4923 4929 4835	45305 45331 45342 45380 45392 45395 45397 46606
Resections/major surgical interventions (rectal repair, colectomy, laparoscopic colectomy, proctectomy, colostomy)	4603 4610 4611 4613 4614 4862	44140 44141 44143 44144 44145 44146 44147 44150 44151 44152 44153 44155 44156 44160 44204 44205 44206 44207 44208 44210 44211 44212 45110 45111 45112 45113 45114 45116 45119 45123 45562 45563
Procedures for strictures (dilation rectal stricture/anal sphincter, anoplasty for stricture)	4891 4899 9622 9623	45150 45905 45910 46700
Argon laser destruction and electrocautery	4831 4832 4833	
Other surgical interventions (proctoplasty for stenosis, closure of fistula, fistula repair, anal sphincter repair)	484 4841 4842 4843 4849 485 4850 4851 4852 4859 486 4861 4863 4864 4865 4869 487 4871 4872 4873 4874 4875 4876 4879 489 4893 491 4911 4912 496 497 4971 4972 4973 4974 4975 4976 4979 5783	45000 45005 45020 45500 45805 45820 45825 46270 46275 46280 46285 46706
Urinary		

Complication Group	ICD-9-CM Procedure codes	CPT-4/HCPCS codes
Stricture, obstruction, retention	572 5721 5722 5794 5994	
Clot evacuation, figuration	570 5793	51700 52001 52214
Dilation, urethrotomy, urethroplasty, sphincterotomy	5717 5718 5719 5785 5789 5791 5792 5795 580 581 5831 5839 5844 5846 5847 5849 585 586 5899 6095	51010 51040 51102 52275 52276 52277 52281 52510 53000 53010 53400 53405 53410 53415 53420 53425 53431 53600 53601 53605 53620 53621
Transurethral prostate resection/destruction	602 6021 6029 6096 6097	52450 52500 52601 52612 52614 52620 52630 52647 52648 53850 53852 53853
Urethral stent		52282
Injection for stricture		52283
Urethra, sphincter injection	5972	51715 L8603 L8606
Artificial sphincter	5893	53444 53445 53447 53448 53449 C1815
Incontinence repair (sling, urethroplasty)	593 594 595 596 597 5971 5979	11950 11951 11952 11954 51840 51841 51990 51992 53440 53442 53443 57288 C2631
fistula repair	5784 5843	44660 44661 45800 53520
Sexual		
Penile prosthesis	6494 6495 6496 6497	54400 54401 54402 54405 54407 54408 54409 54410 54411 54416 54417 C1007 C1813 C2622 C3500 C8514 C8516 C8534 L7900
Intracavernosal injection		54231 54235 J0270 J0275 J2440 J2760

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Figure 1.

Percentage of men treated with IMRT and 3D-CRT for prostate cancer between 2001 and 2007

3D-CRT = 3-dimensional conformal therapy; IMRT = intensity-modulated radiotherapy
Among Medicare beneficiaries diagnosed with prostate cancer from 2001 through 2007, there is an 84% increase in the proportion of patients treated with IMRT as compared to 3D-CRT.

Figure 2.

Five-year adjusted percentage of having a complication requiring a procedure and use of salvage ADT among low-risk patients

ADT = androgen deprivation therapy; 3D-CRT = 3-dimensional conformal therapy IMRT = intensity-modulated radiotherapy

For men with low-risk disease, the likelihood of having a complication requiring an intervention or needing salvage therapy was similar between the two approaches (all $p > 0.05$). Percentages are adjusted for age, comorbidity, socioeconomic status, race/ethnicity, tumor grade and stage, and year of treatment.

Figure 3.

Five-year adjusted percentage of having a complication requiring a procedure and use of salvage ADT among higher-risk patients

ADT = androgen deprivation therapy; 3D-CRT = 3-dimensional conformal therapy; IMRT = intensity-modulated radiotherapy

The risks of a bowel, urinary, or sexual complication requiring an intervention were similar for IMRT and 3D-CRT. However, among higher-risk patients who did not receive concurrent ADT, those treated with IMRT were less likely to undergo salvage therapy with ADT compared to those treated with 3D-CRT (16% vs. 20%, $p=0.02$). Percentages are adjusted for age, comorbidity, socioeconomic status, race/ethnicity, tumor grade and stage, and year of treatment.

Table 1

Demographics and clinical characteristics of the study population according to radiation approach

Characteristics	3D-CRT (n=6,976)	IMRT (n=11,039)	P Value
Age, years (%)			
65–69	1347 (19)	2237 (20)	p=0.38
70–74	2506 (36)	3848 (35)	
75–79	2190 (32)	3407 (31)	
80–84	777 (11)	1313 (12)	
85+	156 (2)	234 (2)	
Race/ethnicity (%)			
White	5913 (85)	9253 (84)	p<0.01
Black	685 (10)	942 (8)	
Hispanic	138 (2)	198 (2)	
Asian	131 (2)	320 (3)	
Other/unknown	109 (1)	326 (3)	
Socioeconomic status (%)			
Low	4040 (58)	6280 (57)	p=0.02
Medium	1620 (23)	2499 (23)	
High	1316 (19)	2260 (20)	
Comorbidity (%)			
0	4358 (63)	6999 (64)	p=0.97
1	1756 (25)	2570 (23)	
2	554 (8)	895 (8)	
3+	308 (4)	575 (5)	
Tumor grade (%)			
Well/moderately differentiated	4227 (60)	5143 (46)	p<0.01
Poorly/undifferentiated	2630 (38)	5810 (53)	
Unknown	119 (2)	86 (<1)	
AJCC Clinical stage (%)			
T1	2723 (39)	5745 (52)	p=0.01
T2	3864 (56)	4888 (44)	
T3	301 (4)	360 (3)	
T4	88 (1)	46 (<1)	
Concurrent ADT (%)			
	3777 (54)	4323 (39)	p<0.01

Abbreviations: ADT, androgen deprivation therapy; AJCC, American Joint Committee on Cancer (6th edition); 3D-CRT, 3-dimensional conformal therapy; IMRT, intensity-modulated radiotherapy