HEALTH CARE REFORM

Comparative Effectiveness of Intensity-Modulated Radiotherapy and Conventional Conformal Radiotherapy in the Treatment of Prostate Cancer After Radical Prostatectomy

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Importance: Comparative effectiveness research of prostate cancer therapies is needed because of the development and rapid clinical adoption of newer and costlier treatments without proven clinical benefit. Radiotherapy is indicated after prostatectomy in select patients who have adverse pathologic features and in those with recurrent disease.

Objectives: To examine the patterns of use of intensity-modulated radiotherapy (IMRT), a newer, more expensive technology that may reduce radiation dose to adjacent organs compared with the older conformal radiotherapy (CRT) in the postprostatectomy setting, and to compare disease control and morbidity outcomes of these treatments.

Design and Setting: Data from the Surveillance, Epidemiology, and End Results–Medicare–linked database were used to identify patients with a diagnosis of prostate cancer who had received radiotherapy within 3 years after prostatectomy.

Participants: Patients who received IMRT or CRT.

Main Outcomes and Measures: The outcomes of 457 IMRT and 557 CRT patients who received radiotherapy between 2002 and 2007 were compared using their claims through 2009. We used propensity score methods to balance baseline characteristics and estimate adjusted incidence rate ratios (RRs) and their 95% CIs for measured outcomes.

Results: Use of IMRT increased from zero in 2000 to 82.1% in 2009. Men who received IMRT vs CRT showed no significant difference in rates of long-term gastrointestinal morbidity (RR, 0.95; 95% CI, 0.66-1.37), urinary nonincontinent morbidity (0.93; 0.66-1.33), urinary incontinence (0.98; 0.71-1.35), or erectile dysfunction (0.85; 0.61-1.19). There was no significant difference in subsequent treatment for recurrent disease (RR, 1.31; 95% CI, 0.90-1.92).

Conclusions and Relevance: Postprostatectomy IMRT and CRT achieved similar morbidity and cancer control outcomes. The potential clinical benefit of IMRT in this setting is unclear. Given that IMRT is more expensive, its use for postprostatectomy radiotherapy may not be cost-effective compared with CRT, although formal analysis is needed.

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PROSTATE CANCER IS THE MOST common malignant neoplasm in American men, with more than 240 000 diagnoses and 30 000 deaths per year.[1] Recent advances in technology have brought forth costlier surgical and radiotherapy options, such as intensity-modulated radiotherapy (IMRT), which have been rapidly adopted for clinical use despite a lack of comparative effectiveness research. A recent study[2] showed that the use of new technologies in prostate cancer has increased health care costs by $350 million each year, with most of this cost associated with IMRT. Multiple major institutional bodies have called for comparative effectiveness research in prostate cancer,[3,4] with the Institute of Medicine[4] recently selecting the management of localized prostate cancer as one

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of its top priorities for comparative effectiveness research.

Radiotherapy has the potential to damage organs adjacent to the prostate, such

as the bladder and rectum, leading to long-term morbidity. Intensity-modulated radiotherapy is a newer technology in which the intensity of the radiation beam is varied at each treatment beam angle. This type of treatment requires more complicated radiotherapy planning and delivery, which have led to approximately 50% higher reimbursement rates than the older conformal radiotherapy (CRT).[2,5] Because IMRT planning studies have demonstrated that it can consistently reduce high radiation dose exposure to these nearby organs compared with CRT, the rapid adoption of IMRT in prostate cancer likely relates to its potential ability to reduce treatment-related morbidity. A recent study[6] demonstrated that, as primary treatment for prostate cancer, IMRT vs CRT was associated with lower gastrointestinal (GI) morbidity and improved cancer control, the latter likely the result of an ability of IMRT to safely allow higher radiation doses to be delivered to the prostate (dose-escalated radiotherapy). This was one of the first comparative effectiveness studies between IMRT and CRT in prostate cancer.

In addition to being used as primary prostate cancer treatment, radiotherapy also is used for select patients after prostatectomy, including those with adverse pathologic factors[7-9] and those with recurrent disease.[10] Up to half of patients may have an indication for radiotherapy after prostatectomy.[11] In this setting, because the prostate has been removed, the radiation dose is lower than that given for primary treatment.[8,9,12,13] Therefore, the potential benefit of IMRT vs CRT in terms of reducing treatment-related morbidity may be less pronounced. There is also no definitive evidence to support dose-escalated radiotherapy in the postprostatectomy setting, so the potential benefit of IMRT for cancer control is unclear. The comparative effectiveness of radiation techniques in the postprostatectomy setting is not well studied.

The goals of this institutional review board–exempt study were to examine the utilization patterns of postprostatectomy radiation techniques and to compare the morbidity and cancer control outcomes of IMRT vs CRT using the Surveillance, Epidemiology, and End Results (SEER)–Medicare–linked database. The population evaluated was a cohort of patients with recent prostate cancer.

METHODS

DATA SOURCE

The SEER-Medicare–linked data are commonly used in population-based studies of cancer treatment and outcomes.[14] Briefly, these data are composed of cancer-specific and demographic information from the SEER program of population-based cancer registries, which represent approximately 26% of the US population. These data are linked to administrative and health care claims data for Medicare, which insures Americans aged 65 years or older and documents the health care diagnoses, procedures, and dates of service for beneficiaries.

STUDY COHORTS

We identified a source population of 275 266 men with prostate cancer diagnosed between January 2000 and December 2007; their associated claims were obtained through December 31, 2009. From this cohort, we excluded men with additional cancer diagnoses, metastatic disease, or disease diagnosed at autopsy and those missing month of diagnosis, which left a sample of 251 787. The study sample was further restricted to men aged 66 years or older to allow at least 1 year of claims data before diagnosis for the assessment of baseline comorbidities, which may affect treatment selection and outcomes. To ensure complete capture of health services in claims for the duration of the study, we excluded men who were enrolled in a health maintenance organization or who were not enrolled in both Medicare Part A and Part B from the time of prostatectomy through an event or end of follow-up in claims (2009). This resulted in a cohort of 97 938 patients.

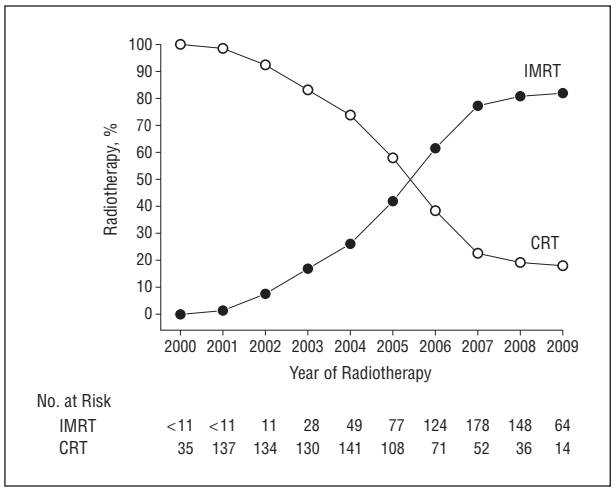

Figure 1. Use of postprostatectomy intensity-modulated radiotherapy (IMRT) vs conformal radiotherapy (CRT). All patients who received postprostatectomy radiotherapy from 2000 to 2009 were included.

Using Current Procedural Terminology/Healthcare Common Procedure Coding System procedure codes (eTable 1; http://www.jamainternalmed.com), we identified 1539 men who underwent radical prostatectomy and subsequent radiotherapy within 3 years of surgery, representing approximately 10% of prostatectomy patients during this period. The 3-year time window was selected to minimize identification of men undergoing palliative radiotherapy for metastatic disease. Because there was a large shift in the use of radiation techniques during the study period (**Figure 1**), we restricted our analysis to the 1014 men who received radiotherapy between 2002 and 2007 to maximize the overlap in baseline characteristics in the IMRT vs CRT cohorts and thus to allow the application of propensity score weighting. In this analytic sample, 457 men received IMRT and 557 received CRT. Patients who received both IMRT and CRT after surgery were excluded from the analysis.

OUTCOMES

Morbidity outcomes examined included conditions associated with radiotherapy for prostate cancer: GI morbidity, urinary incontinence, nonincontinence urinary morbidity, and sexual dysfunction.[15-18] Hip fracture was evaluated initially, but because of an insufficient number of events (n=11) was excluded from final analyses. Diagnoses and procedures (eTable 1) in each morbidity category were examined as separate outcomes. Because a goal of this study was to compare long-term morbidity associated with the 2 radiation techniques, we excluded person-time and diagnoses and procedures that occurred within 1 year of radiotherapy to prevent confounding from acute morbidity, most of which resolves and does not become long-term morbidity.[15]

Table 1. Baseline Characteristics

Characteristic	No. (%)			
	Before Propensity Weighting		After Propensity Weighting[a]	
	IMRT (n = 457)	CRT (n = 557)	IMRT (n = 443)	CRT (n = 590)
Year of radiotherapy				
2002	11 (2.4)	80 (14.4)	57 (12.9)	50 (8.5)
2003	28 (6.1)	112 (20.1)	52 (11.8)	76 (12.9)
2004	49 (10.7)	135 (24.2)	71 (16.1)	100 (16.9)
2005	77 (16.9)	108 (19.4)	69 (15.6)	96 (16.2)
2006	124 (27.1)	71 (12.8)	90 (20.4)	114 (19.3)
2007	168 (36.8)	51 (9.2)	103 (23.3)	155 (26.2)
Age at diagnosis, y				
66-69	287 (62.8)	337 (60.5)	275 (62.1)	377 (63.9)
70-74	143 (31.3)	176 (31.6)	144 (32.5)	179 (30.3)
≥75	27 (5.9)	44 (7.9)	24 (5.4)	34 (5.8)
Race				
White	410 (89.7)	494 (88.7)	393 (88.7)	529 (89.7)
Black	27 (5.9)	39 (7.0)	28 (6.3)	39 (6.6)
Other/unknown	20 (4.4)	24 (4.3)	22 (5.0)	22 (3.7)
SEER region				
Atlanta and rural Georgia	[b]	14 (2.5)	[b]	[b]
California	228 (49.9)	233 (41.8)	217 (49.0)	270 (45.6)
Connecticut	23 (5.0)	24 (4.3)	25 (5.6)	26 (4.4)
Detroit, Michigan	11 (2.4)	24 (4.3)	11 (2.5)	18 (3.0)
Hawaii	[b]	[b]	[b]	[b]
Iowa	13 (2.8)	45 (8.1)	15 (3.4)	31 (5.2)
Kentucky	26 (5.7)	34 (6.1)	31 (7.0)	34 (5.7)
Louisiana	47 (10.3)	53 (9.5)	48 (10.8)	59 (10.0)
New Jersey	57 (12.5)	32 (5.8)	38 (8.6)	64 (10.8)
New Mexico	15 (3.3)	[b]	11 (2.5)	18 (3.0)
Seattle, Washington	17 (3.7)	57 (10.2)	28 (6.3)	40 (6.8)
Utah	[b]	20 (3.6)	[b]	13 (2.2)
Tumor grade				
Well/moderately differentiated	[b]	185 (33.2)	[b]	[b]
Poorly differentiated	346 (75.7)	360 (64.6)	296 (66.8)	409 (69.3)
Unknown/not assessed	[b]	12 (2.2)	[b]	[b]
Clinical T category				
T1	217 (47.5)	219 (39.3)	191 (43.1)	257 (43.6)
T2	214 (46.8)	310 (55.7)	229 (51.7)	289 (49.1)
T3/T4	26 (5.7)	28 (5.0)	23 (5.2)	43 (7.3)
Baseline diabetes mellitus	114 (25.0)	119 (21.4)	102 (23.0)	146 (24.8)
Baseline anticoagulation, arrhythmia, or valvular disease	144 (31.5)	151 (27.1)	122 (27.5)	166 (28.1)
Baseline GI diagnosis/procedure	98 (21.4)	101 (18.1)	83 (18.7)	117 (19.8)
Baseline urinary nonincontinence diagnosis/procedure	110 (24.1)	134 (24.1)	100 (22.6)	129 (21.9)
Baseline urinary incontinence diagnosis/procedure	167 (36.5)	162 (29.1)	137 (30.9)	190 (32.3)
Baseline erectile dysfunction diagnosis/procedure	131 (28.7)	144 (25.9)	104 (23.5)	150 (25.4)
Marital status				
Married	374 (81.8)	454 (81.5)	369 (83.1)	480 (81.4)
Not married	65 (14.2)	86 (15.4)	60 (13.5)	86 (14.6)
Missing/unknown	18 (3.9)	17 (3.0)	15 (3.4)	24 (4.1)
Census income, %				
Low, 0-25	88 (19.3)	104 (18.7)	79 (17.9)	111 (18.8)
Low-medium, 26-50	112 (24.5)	142 (25.5)	116 (26.2)	158 (26.7)
Medium-high, 51-75	116 (25.4)	152 (27.3)	114 (25.8)	148 (25.0)
High, >75	141 (30.9)	159 (28.6)	133 (30.1)	174 (29.4)
Census educational level with at least high school education, %				
Low, <25	89 (19.5)	109 (19.6)	81 (18.3)	118 (20.0)
Low-medium, 26-50	108 (23.6)	157 (28.2)	114 (25.7)	155 (26.3)
Medium-high, 51-75	116 (25.4)	146 (26.2)	129 (29.1)	156 (26.5)
High, >75	144 (31.5)	145 (26.0)	119 (26.9)	160 (27.2)
Population density				
Metropolitan	405 (88.6)	466 (83.7)	395 (89.0)	510 (86.4)
Nonmetropolitan	52 (11.4)	91 (16.3)	49 (11.0)	80 (13.6)
RTOG affiliation	65 (14.2)	69 (12.4)	50 (11.3)	72 (12.2)
Concurrent androgen deprivation therapy	179 (39.2)	212 (38.1)	171 (38.6)	222 (37.6)
Type of prostatectomy				
Minimally invasive	95 (20.8)	42 (7.5)	61 (13.7)	98 (16.6)
Open	362 (79.2)	515 (92.5)	383 (86.3)	492 (83.4)

Abbreviations: CRT, conformal radiotherapy; GI, gastrointestinal; IMRT, intensity-modulated radiotherapy; RTOG, Radiation Therapy Oncology Group; SEER, Surveillance, Epidemiology, and End Results.

[a] The number of samples count in each cell was rounded to integers after implementing propensity weights; therefore, the sum of the numbers does not equal the total sample count because of rounding.

[b] Cells with fewer than 11 patients were suppressed from being presented in the Table in concordance with SEER-Medicare guidelines.

Table 2. Unadjusted and Propensity Model–Adjusted Outcomes for IMRT vs CRT

Outcome per 100 Person-years	Unadjusted				Propensity Model–Adjusted			
	IMRT Events	CRT Events	IMRT vs CRT, RR (95% CI)	*P* Value	IMRT Events	CRT Events	IMRT vs CRT, RR (95% CI)	*P* Value
Gastrointestinal								
Procedure	16.3	16.7	0.98 (0.79-1.20)	.83	15.6	17.4	0.90 (0.67-1.20)	.46
Diagnosis	9.2	9.7	0.95 (0.74-1.23)	.71	9.4	9.9	0.95 (0.66-1.37)	.78
Urinary nonincontinence								
Procedure	4.2	4.1	1.02 (0.71-1.46)	.91	4.0	4.5	0.89 (0.55-1.44)	.63
Diagnosis	10.9	9.7	1.12 (0.88-1.44)	.37	9.9	10.6	0.93 (0.66-1.33)	.70
Urinary incontinence								
Procedure	11.9	8.7	1.37 (1.07-1.76)	.01	11.0	9.4	1.18 (0.84-1.67)	.35
Diagnosis	16.6	10.9	1.52 (1.20-1.91)	<.01	11.8	12.0	0.98 (0.71-1.35)	.91
Erectile dysfunction								
Procedure	2.1	2.4	0.87 (0.54-1.41)	.58	1.8	2.9	0.63 (0.33-1.22)	.17
Diagnosis	15.0	11.7	1.28 (1.01-1.62)	.04	11.7	13.8	0.85 (0.61-1.19)	.33
Subsequent cancer therapy	8.4	7.1	1.19 (0.91-1.55)	.20	9.5	7.2	1.31 (0.90-1.92)	.16

Abbreviations: CRT, conformal radiotherapy; IMRT, intensity-modulated radiotherapy; RR, rate ratio.

Consistent with prior studies,[6,19-21] we identified men requiring further cancer treatment after radiotherapy as an indicator of disease recurrence. We defined subsequent treatment as that which occurred 9 months or more after the initiation of radiotherapy, also consistent with prior work.[6] Furthermore, for patients who received concurrent androgen deprivation therapy, additional treatment was defined as cessation of all treatment for 9 months or more followed by reinitiation of androgen deprivation therapy or another salvage treatment. Survival was not examined because death due to prostate cancer is minimal within 5 years of treatment and is not expected to be significantly different by radiation technique within this time frame.[1]

CONTROL VARIABLES

Patient-level demographic variables, such as race, age at diagnosis, and marital status; census tract measures of income and education; SEER region; and population density (urban vs rural) were provided by SEER data. Medicare claims data provided information on the treatments received, date of treatment, baseline comorbid conditions, and institutional affiliation with the Radiation Therapy Oncology Group, a radiation-specific clinical trials cooperative group that requires special quality-control measures and credentialing. Surgical technique (minimally invasive radical prostatectomy vs open radical prostatectomy) and the use of androgen deprivation therapy concurrently with radiation were included as covariates because of their potential effects on long-term morbidity and disease control.[22] Baseline diabetes mellitus and conditions associated with the use of therapeutic anticoagulation (eg, atrial fibrillation and valvular disease) can increase morbidity risk from radiotherapy[23-25] and were also included.

STATISTICAL ANALYSIS

We used propensity score weighting to adjust for potentially important baseline characteristics. Specifically, we first used logistic regression to estimate the probability of receiving IMRT vs CRT using all covariates listed in **Table 1**.[26] No variable selection was performed for the propensity score model given the large number of patients. Distribution of propensity scores was evaluated by treatment group to examine for sufficient overlap among the groups to ensure comparability. We trimmed the sample by removing 89 patients with nonoverlapped propensity score distribution (IMRT, 10; CRT, 79). A propensity score weight was calculated as the inverse of the propensity for the radiotherapy received. The weight then was multiplied by the marginal prevalence of treatment actually received to reflect the original sample size for each treatment group. This creates pseudocohorts by weighting each patient by the inverse of the estimated probability of receiving the treatment actually received.[27-32] We then ran Poisson regression models in these pseudocohorts that included only the treatment variable as the independent variable for each outcome. Because each patient was monitored for varying lengths of time, we also included the length of time to the first morbidity event as the offset variable in the model. This allowed us to calculate incidence rate ratios and their 95% CIs.

For each morbidity and disease control outcome, we calculated the number of events per 100 person-years of follow-up to be consistent with published studies.[6,19] Follow-up time was determined from the start of follow-up (12 months after the start of radiotherapy for morbidity and 9 months for subsequent cancer therapies) until an event or censoring due to death or at the end of the study (December 31, 2009). Median follow-up was 45.6 months for CRT patients and 27.5 months for IMRT patients. As a sensitivity analysis, we also applied Cox proportional hazards regression models using both the inverse of the estimated probability of receiving the treatment and the conventional outcome model. Furthermore, because incidence rates may not be constant over time, we performed sensitivity analyses restricting the follow-up time to 24 months. Statistical significance was set at $P = .05$, and all tests were 2-tailed. Analyses were performed using commercial software (SAS, version 9.2; SAS Institute, Inc).

RESULTS

Among the patients who received postprostatectomy radiotherapy, use of IMRT vs CRT increased from zero in 2000 to 82.1% in 2009 (Figure 1). There were geographic variations in the use of IMRT, as well as increased IMRT use in metropolitan vs nonmetropolitan areas (Table 1). After propensity score weighting, baseline characteristics among CRT and IMRT patients were balanced.

Unadjusted and propensity model–adjusted outcomes for IMRT vs CRT are reported in **Table 2**. In the

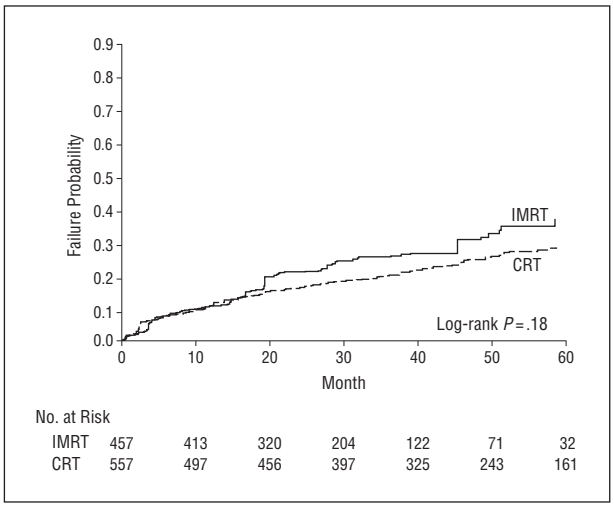

Figure 2. Adjusted rates of subsequent cancer treatment for patients who received intensity-modulated radiotherapy (IMRT) vs conformal radiotherapy (CRT). Time 0 was the start of follow-up as defined in the Methods section, which was 9 months after the start of radiotherapy.

adjusted analysis, there were no significant differences between the 2 groups in GI or urinary diagnoses or procedures, as well as in erectile dysfunction. There also was no significant difference in receipt of subsequent cancer therapies (Table 2 and **Figure 2**) that may suggest a recurrence of prostate cancer. Sensitivity analyses using Cox proportional hazards regression models produced very similar results for the effect estimates in magnitude and precision (eTable 2). The results of sensitivity analyses performed at 24 months of follow-up were consistent with the main analyses (data not shown).

DISCUSSION

In prostate cancer, there has been recent development of newer and promising surgical and radiation treatments. There also has been a trend of increased adoption of these newer treatments without (or before) proven benefit relative to older treatments.[6,19] These trends and their associated costs to the health care system[33] highlight the importance of comparative effectiveness research. The Institute of Medicine included the management of localized prostate cancer as a first-quartile priority topic in its top 100 topics for comparative effectiveness research.[4]

To our knowledge, this population-based study is the first to demonstrate the rapid adoption of IMRT for postprostatectomy radiotherapy despite a relative lack of comparative effectiveness data demonstrating benefit in patient outcomes compared with the older CRT. From 2000 to 2009, IMRT use increased from zero to 82.1%. This rate of increase closely resembles that reported[6] for primary radiotherapy for prostate cancer; however, it appears that there is not yet complete adoption of IMRT for postprostatectomy treatment. The reason for this rapid increase may be related to expectations by physicians and patients of a reduction in treatment morbidity from IMRT or in part because of higher reimbursement for the use of IMRT.[5] Both the United Kingdom and Canada have experienced increased use of advanced radiation technology such as IMRT, but not to the level of the United States.[34,35]

Our study shows that these expectations may not be based in clinical reality. In contrast to prior findings[6] of IMRT being associated with reduced GI morbidity and improved cancer control compared with CRT in the primary treatment setting, we found no significant difference in the present study in any outcome between the 2 techniques for postprostatectomy radiotherapy. One potential explanation for this null finding is the lower postprostatectomy radiation dose and therefore less potential need for using a more advanced technique to meet dose requirements to limit exposure of adjacent organs. This is supported by the low rates of morbidity as reported in prospective clinical trials[7,9] of postprostatectomy radiotherapy using CRT: less than 5% long-term GI and urinary adverse effects. It is unclear if and, if so, by how much IMRT is able to lower these rates. Another possible explanation is that the effect of prostatectomy may be the dominant factor causing morbidities such as urinary incontinence and erectile dysfunction[36,37]; thus, morbidities from postsurgical radiotherapy become less pronounced. Studies[36,37] that examined physician- and patient-reported outcomes in prostate cancer suggest that this may be the case. However, surgical morbidity may be higher in the overall Medicare population than that in high-volume academic centers, masking a potential difference between IMRT and CRT. Finally, because there is no clear role for dose escalation for postprostatectomy radiotherapy, the lack of difference in receipt of subsequent cancer therapies in patients receiving IMRT vs CRT is consistent with a priori clinical expectations.

This study adds information to recent comparative effectiveness studies examining patient outcomes with newer vs older prostate cancer treatments, which have shown mixed results,[6,19] and is broadly illustrative of a difficulty in health care in which new technologies are rapidly adopted before evidence of clinical superiority.[38] A study[19] comparing minimally invasive prostatectomy vs the older open prostatectomy technique demonstrated that, although minimally invasive surgery was associated with lower rates of short-term postoperative complications, it also was associated with higher rates of genitourinary morbidity, incontinence, and erectile dysfunction. However, a study[6] comparing IMRT with CRT for primary prostate cancer treatment found that IMRT was associated with lower rates of long-term GI morbidity and need for subsequent cancer treatments.

Radiotherapy for prostate cancer can cause damage to organs adjacent to the prostate, thus causing long-term morbidity. The ability of IMRT to reduce radiation doses to the organs (eg, bladder and rectum) compared with CRT likely explains the reduced long-term morbidity found in the prior study.[6] Furthermore, for primary radiotherapy in prostate cancer, 3 randomized trials[13,39,40] have consistently demonstrated that higher radiation doses (78-79 Gy) resulted in improved cancer control compared with lower doses (68-70 Gy). Thus, the ability of IMRT to safely deliver dose-escalated radiotherapy is a plausible mechanism for its association with improved cancer control compared with CRT.

Although IMRT for the primary treatment of prostate cancer has a strong theoretical basis, the rationale for its use in the postprostatectomy setting is less compelling because a lower dose is used.[41-43] With a lower dose, the need to use a more sophisticated technique to maintain doses to nearby organs below guideline levels may be less pronounced. Indeed, dosimetric studies[41-43] have demonstrated conflicting results on the usefulness of postprostatectomy IMRT compared with CRT.

The optimal postprostatectomy radiation technique is unknown. To our knowledge, prior to this investigation, only one other large study[44,45] has directly compared patient outcomes of postprostatectomy IMRT with those of CRT. In a retrospective single-institutional series of 285 patients, Goenka et al[45] reported no significant difference in urinary incontinence, other urinary morbidity, or sexual dysfunction among patients who received these 2 radiation techniques; these findings are consistent with ours. In addition, no significant difference in disease recurrence was described. However, Goenka et al found a lower rate of GI morbidity in patients receiving IMRT (5-year rate, 1.9% vs 10.2% for CRT). Their study included patients who received CRT as early as 1988, which may not reflect the outcomes of more modern treatment, with patients having the benefit of computed tomography–based radiation planning. This is exemplified by the rate of GI morbidity associated with CRT (10.2%), which is significantly higher than that reported by other studies. In randomized trials[7,46] of postprostatectomy observation compared with immediate radiotherapy using CRT, long-term GI morbidity in radiation-treated patients was 3.3% or less. Therefore, in the more recent setting, whether IMRT vs CRT reduces bowel morbidity requires further study.

The strengths of our study include the use of a population-based cohort that reflects treatment outcomes in the community setting. To the best of our knowledge, this is the first study to demonstrate the rapid uptake of postprostatectomy IMRT and the largest study to compare patient outcomes from IMRT with those from CRT. Furthermore, we adjusted for baseline morbidity and included covariates that could influence treatment outcomes, such as anticoagulation, Radiation Therapy Oncology Group affiliation, and prostatectomy technique, in an attempt to minimize confounding by these variables.

However, there are limitations to the use of SEER-Medicare data for the assessment of clinical outcomes. Because claims files are not designed to provide detailed clinical information, outcomes examined may be subject to misclassification, and certain outcomes (eg, erectile dysfunction) may be underreported.[47] We believe that claims should have an equally high specificity in the 2 patient cohorts included in this analysis to allow comparison of relative rates of morbidity; however, it is possible that patients receiving a novel technique may have falsely elevated outcome expectations and thus be more likely to report morbidity after treatment. Furthermore, treatment choice may lead to confounding. Although we attempted to control for a comprehensive list of observed covariates, residual confounding from unmeasured covariates is possible. However, despite the limitations of SEER-Medicare, this data set represents an important resource with an established method for comparative effectiveness research. Results from this study represent outcomes of recent patients who received treatments widely available in the community. Whether patient outcomes are better in high-volume centers requires further study. The population-based examination of patient outcomes broadens the generalizability of results over institutional series, but the study is limited by the need to exclude patients with discontinuous Medicare coverage.

In summary, IMRT use has increased markedly for the treatment of prostate cancer in patients who require radiotherapy following prostatectomy. We found no significant difference in the rates of morbidity in patients who received IMRT vs CRT or in the rate of receiving subsequent additional cancer therapies. Our results provide new and important information to patients, physicians, and other decision makers on the currently available evidence regarding the outcomes of different postprostatectomy radiation techniques. The potential clinical benefit of IMRT compared with CRT in this setting is unclear.

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REFERENCES

1. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin*. 2011;61(4):212-236.
2. Nguyen PL, Gu X, Lipsitz SR, et al. Cost implications of the rapid adoption of newer technologies for treating prostate cancer. *J Clin Oncol*. 2011;29(12):1517-1524.
3. Institute for Clinical and Economic Review. *Management Options for Low-Risk Prostate Cancer: A Report on Comparative Effectiveness and Value*. Boston, MA: Institute for Clinical and Economic Review; 2009.
4. Ratner R, Eden J, Wolman D, Greenfield S, Sox H, eds. *Initial National Priorities for Comparative Effectiveness Research*. Washington, DC: Institute of Medicine; 2009:107.
5. Carreyrou J, Tamman M. A device to kill cancer, lift revenue. *Wall Street Journal*. December 7, 2010. http://online.wsj.com/article/SB10001424052748703904804575631222900534954.html. Accessed January 19, 2013.
6. 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*. 2012;307(15):1611-1620.
7. Wiegel T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol*. 2009;27(18):2924-2930.
8. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol*. 2009;181(3):956-962.
9. Bolla M, van Poppel H, Collette L, et al; European Organization for Research and Treatment of Cancer. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). *Lancet*. 2005;366(9485):572-578.
10. Stephenson AJ, Shariat SF, Zelefsky MJ, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *JAMA*. 2004;291(11):1325-1332.
11. Swindle P, Eastham JA, Ohori M, et al. Do margins matter? the prognostic significance of positive surgical margins in radical prostatectomy specimens. *J Urol*. 2005;174(3):903-907.
12. 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*. 2008;70(1):67-74.
13. Dearnaley DP, Sydes MR, Graham JD, et al; RT01 Collaborators. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol*. 2007;8(6):475-487.
14. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. *Med Care*. 2002;40(8)(suppl):IV-3-IV-18.
15. Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2008;70(4):1124-1129.
16. 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*. 2011;81(4):e325-e334. doi:10.1016/j.ijrobp.2011.02.006.
17. Al-Mamgani A, Heemsbergen WD, Peeters ST, Lebesque JV. Role of intensity-modulated radiotherapy in reducing toxicity in dose escalation for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2009;73(3):685-691.
18. Lips I, Dehnad H, Kruger AB, et al. Health-related quality of life in patients with locally advanced prostate cancer after 76 Gy intensity-modulated radiotherapy vs. 70 Gy conformal radiotherapy in a prospective and longitudinal study. *Int J Radiat Oncol Biol Phys*. 2007;69(3):656-661.
19. Hu JC, Gu X, Lipsitz SR, et al. Comparative effectiveness of minimally invasive vs open radical prostatectomy. *JAMA*. 2009;302(14):1557-1564.
20. Lu-Yao GL, Potosky AL, Albertsen PC, Wasson JH, Barry MJ, Wennberg JE. Follow-up prostate cancer treatments after radical prostatectomy: a population-based study. *J Natl Cancer Inst*. 1996;88(3-4):166-173.
21. Lowrance WT, Elkin EB, Jacks LM, et al. Comparative effectiveness of prostate cancer surgical treatments: a population based analysis of postoperative outcomes. *J Urol*. 2010;183(4):1366-1372.
22. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med*. 2005;352(2):154-164.
23. Choe KS, Jani AB, Liauw SL. External beam radiotherapy for prostate cancer patients on anticoagulation therapy: how significant is the bleeding toxicity? *Int J Radiat Oncol Biol Phys*. 2010;76(3):755-760.
24. Valdagni R, Rancati T, Fiorino C, et al. Development of a set of nomograms to predict acute lower gastrointestinal toxicity for prostate cancer 3D-CRT. *Int J Radiat Oncol Biol Phys*. 2008;71(4):1065-1073.
25. Giordano SH, Lee A, Kuo YF, Freeman J, Goodwin JS. Late gastrointestinal toxicity after radiation for prostate cancer. *Cancer*. 2006;107(2):423-432.
26. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Stürmer T. Variable selection for propensity score models. *Am J Epidemiol*. 2006;163(12):1149-1156.
27. Shah BR, Laupacis A, Hux JE, Austin PC. Propensity score methods gave similar results to traditional regression modeling in observational studies: a systematic review. *J Clin Epidemiol*. 2005;58(6):550-559.
28. Glynn RJ, Schneeweiss S, Stürmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. *Basic Clin Pharmacol Toxicol*. 2006;98(3):253-259.
29. Stürmer T, Joshi M, Glynn RJ, Avorn J, Rothman KJ, Schneeweiss S. A review of the application of propensity score methods yielded increasing use, advantages in specific settings, but not substantially different estimates compared with conventional multivariable methods. *J Clin Epidemiol*. 2006;59(5):437-447.
30. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17(19):2265-2281.
31. Rosenbaum P, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70(1):41-55.
32. Cepeda MS, Boston R, Farrar JT, Strom BL. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. *Am J Epidemiol*. 2003;158(3):280-287.
33. Williams SB, Gu X, Lipsitz SR, et al. Utilization and expense of adjuvant cancer therapies following radical prostatectomy. *Cancer*. 2011;117(21):4846-4854.
34. AlDuhaiby EZ, Breen S, Bissonnette JP, et al. A national survey of the availability of intensity-modulated radiation therapy and stereotactic radiosurgery in Canada. *Radiat Oncol*. 2012;7:18. doi:10.1186/1748-717X-7-18.
35. Mayles WP; Radiotherapy Development Board. Survey of the availability and use of advanced radiotherapy technology in the UK. *Clin Oncol (R Coll Radiol)*. 2010;22(8):636-642.
36. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med*. 2008;358(12):1250-1261.
37. Chen RC, Clark JA, Talcott JA. Individualizing quality-of-life outcomes reporting: how localized prostate cancer treatments affect patients with different levels of baseline urinary, bowel, and sexual function. *J Clin Oncol*. 2009;27(24):3916-3922.
38. Leff B, Finucane TE. Gizmo idolatry. *JAMA*. 2008;299(15):1830-1832.
39. Zietman AL, Bae K, Slater JD, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarci-

noma of the prostate: long-term results from Proton Radiation Oncology Group/American College of Radiology 95-09. *J Clin Oncol*. 2010;28(7):1106-1111.
40. Pollack A, Zagars GK, Starkschall G, et al. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys*. 2002;53(5):1097-1105.
41. Koontz BF, Das S, Temple K, et al. Dosimetric and radiobiologic comparison of 3D conformal versus intensity modulated planning techniques for prostate bed radiotherapy. *Med Dosim*. 2009;34(3):256-260.
42. Digesu C, Cilla S, De Gaetano A, et al. Postoperative intensity modulated radiation therapy in high risk prostate cancer: a dosimetric comparison. *Med Dosim*. 2011;36(3):231-239.
43. Pinkawa M, Siluschek J, Gagel B, et al. Postoperative radiotherapy for prostate cancer: evaluation of target motion and treatment techniques (intensity-modulated versus conformal radiotherapy). *Strahlenther Onkol*. 2007;183(1):23-29.
44. Goenka A, Magsanoc JM, Pei X, et al. Improved toxicity profile following high-dose postprostatectomy salvage radiation therapy with intensity-modulated radiation therapy. *Eur Urol*. 2011;60(6):1142-1148.
45. Goenka A, Magsanoc JM, Pei X, et al. Long-term outcomes after high-dose postprostatectomy salvage radiation treatment. *Int J Radiat Oncol Biol Phys*. 2012;84(1):112-118.
46. Thompson IM Jr, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. *JAMA*. 2006;296(19):2329-2335.
47. Potosky AL, Warren JL, Riedel ER, Klabunde CN, Earle CC, Begg CB. Measuring complications of cancer treatment using the SEER-Medicare data. *Med Care*. 2002;40(8)(suppl):IV-62-IV-68.

INVITED COMMENTARY

Expanding Utilization of Intensity-Modulated Radiotherapy for Prostate Cancer

Soaring Costs, Dubious Benefits

Prostate cancer in the United States is characterized by a unique epidemiology: a prevalence unrivaled by any other visceral malignant neoplasm among men and a prolonged natural history often measurable in decades rather than years. Early detection and aggressive management of higher-risk prostate cancer explain a substantial proportion of the more than 40% drop in prostate cancer mortality rates observed since the 1990s.[1] The price of this remarkable success, however, has been high rates of avoidable overtreatment of both newly diagnosed and recurrent prostate cancer, with excessive attendant morbidity and cost. Reflecting both screening of asymptomatic men and increasingly intensive surveillance (eg, with ultrasensitive prostate-specific antigen [PSA] tests, more extensive biopsies, and growing use of advanced imaging) of those treated, men are receiving both primary and salvage treatments at younger ages and earlier in the natural history of the disease. Reducing the potential morbidity of these treatments remains one of the central goals of prostate cancer clinical research.

The recent evolution of management options for localized prostate cancer largely reflects the advent of 2 technologies: robot-assisted laparoscopic surgery and intensity-modulated radiotherapy (IMRT). The promulgation of these 2 treatment platforms for prostate cancer has been in many respects parallel: both have been marketed aggressively and widely adopted based on relatively limited and sometimes contradictory data. The growth of IMRT has been particularly explosive: IMRT accounted for 0.15% of external-beam radiotherapy treatments in 2000 and 95.9% in 2008.[2] In general, IMRT is associated with lower toxicity than conventional 3D conformal radiotherapy (CRT), although the benefits are fairly modest, and at least one analysis[2] found greater sexual dysfunction after IMRT than after CRT.

External-beam radiation also may be combined with brachytherapy, and following radical prostatectomy—whether open or robot-assisted—it may be administered to men with high-risk pathology and/or persistent or recurrent PSA as adjuvant or salvage therapy. Recent trials generally support a greater role for postoperative radiotherapy, and utilization of this combination of surgery with radiotherapy may be expected to increase, particularly for men with higher-risk disease.[3] Although at least some evidence exists to support the use of IMRT over CRT for primary monotherapy of prostate cancer, data for its use in these other contexts are essentially absent. For combination brachytherapy with external radiation, IMRT utilization nearly quadrupled in 3 years—from 8.5% in 2002 to 31.1% in 2005, with no published studies suggesting a benefit in this setting.

Goldin et al[4] used Medicare data to examine trends and outcomes for radiation given as adjuvant or salvage therapy after prostatectomy. The authors found that here, as in other settings, IMRT has rapidly overtaken CRT as the dominant radiation modality, rising from zero cases in 2000 to 82.1% of cases in 2009. Once again, there were no observed benefits—in terms of either cancer control or any quality-of-life domain—observed for IMRT vs CRT.

Important caveats to this analysis should be noted. Aside from the fact that Medicare only enrolls men older than 65 years, the Centers for Medicare & Medicaid Services data files only include men in Medicare fee-for-service. Indeed, more than 61% of the potential sample was excluded either for the availability of less than 1 year of preradiotherapy claims data and/or for discontinuous fee-for-service enrollment. How representative the remaining men are of the broader population of men with prostate cancer is unclear because there are likely important differences between those enrolling in managed care plans and those choosing to remain in fee-for-service. As more Medicare participants en-