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Long-term economic value of hypofractionated prostate radiation: Secondary analysis of a randomized trial

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Abstract

Purpose: Moderately hypofractionated intensity modulated radiation therapy (HIMRT) for prostate cancer shortens the treatment course while providing outcomes comparable with those of conventional intensity modulated radiation therapy (CIMRT). To determine the long-term economic value of HIMRT, including the costs of managing long-term radiation toxicities, a cost minimization analysis compared CIMRT with dose-escalated HIMRT using patient-level data from a randomized trial.

Methods and materials: Men with localized prostate cancer were randomized to CIMRT (75.6 Gy in 42 fractions over 8.4 weeks) or HIMRT (72 Gy in 30 fractions over 6 weeks). A decision tree modeled trial probabilities of maximum late bowel and urinary toxicities using patient-level data with a median follow-up of 6 years. Costs were estimated from the healthcare perspective using the 2014 national reimbursement rates for services received. Patient-level institutional costs, adjusted to 2014 dollars, verified reimbursements. A sensitivity analysis assessed model uncertainty.

Results: The cost for HIMRT and toxicity management was $22,957, saving $7,000 compared with

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CIMRT ($30,241). CIMRT was the common factor among the 5 most influential scenarios that contributed to total costs. Toxicity represented a small part (<10%) of the average total cost for patients with either grade 2-3 bowel toxicity or grade 2-3 urinary toxicity. However, toxicity management reached up to 26% of the total cost for patients with both high-grade bowel and urinary toxicities. There was no threshold at which CIMRT became the less costly regimen. Institutional costs confirmed the economic value of HIMRT ($6,000 in savings).

Conclusions: HIMRT is more cost-efficient than CIMRT for treating prostate cancer, even when taking into account the costs related to late radiation toxicities. HIMRT enhances the value of prostate radiation when compared with CIMRT.

Introduction

External beam radiation is an effective treatment option for localized prostate cancer, with improved prostate cancer control with higher radiation dose.[1-6] However, conventionally fractionated dose-escalated radiation therapy (CRT) requires often up to 9 weeks of therapy.[1-6] Moderately hypofractionated radiation therapy (HRT), which delivers higher daily doses of radiation, can shorten the treatment course with outcomes that are comparable to those of conventionally fractionated radiation therapy.[7-9] In recent randomized studies, evidence supports HRT as a new standard of care, with noninferior prostate control outcomes compared with CRT.[10,11]

Under the current fee-for-service payment model, the cost of radiation treatment is driven by the number treatments delivered.[12,13] Prostate HRT should be more resource-efficient and less costly than CRT. However, no study has determined the long-term economic value of prostate HRT, including management of long-term side effects of radiation that may occur months to years after completion of treatment. Analyses of randomized trials demonstrate an increased risk of late toxicity in subgroups of men treated with HRT.[8,10,11,14] Men with poor baseline urinary function[9] or a large prostate[8] may experience increased urinary toxicities. Men with a large prostate or men who receive high doses of radiation (≥65.4 Gy) to >20% of the rectum may experience more bowel toxicities.[8] The total cost of HRT, including the costs of late toxicity management, is not well known.

Herein, we report a cost minimization comparison of a dose-escalated moderately hypofractionated intensity modulated regimen (HIMRT; 72 Gy in 2.4 Gy fractions) and conventional intensity modulated radiation (CIMRT; 75.6 Gy in 1.8 Gy fractions) to determine whether long-term value of HIMRT persists after accounting for late radiation toxicity.

Methods and materials

Study design and data collection

For this analysis, we used data from a single, institutional review board–approved trial that enrolled men with organ-confined prostate cancer from January 2001 to January 2010. A total of 204 men were randomized to either CIMRT (75.6 Gy at 1.8 Gy per fraction over 42 treatments; 8.4 weeks) or HIMRT (72 Gy at 2.4 Gy per fraction over 30 treatments; 6 weeks). Eligible patients had biopsy-proven prostate adenocarcinoma; Zubrod score <2; clinical tumor stage T1b-T3b; prostate-specific antigen (PSA) levels <20 ng/mL; Gleason score <10; and no clinical, radiographic, or pathologic evidence of nodal or bone metastasis.[8] Radiation targeted the prostate and proximal seminal vesicles. Lymph nodes were not treated. Radiation details were previously reported.[8] Men were allowed to receive ≤4 months of androgen deprivation. PSA failure was defined using the Phoenix definition (PSA nadir plus 2 ng/mL).[15] Time to PSA failure was calculated from the start of radiation.

Physician-assessed toxicities were prospectively collected using the modified Radiation Oncology Therapy Group grading scale.[16] Maximum late radiation bowel and urinary toxicities were prospectively collected at least every 6 months for 2 years and then annually. Our analysis used patient-level toxicity data on 203 men with a median follow-up of 6 years. Because healthcare resources used to manage radiation side effects were not prospectively collected, we retrospectively reviewed medical and billing records to identify the procedures and medications used to evaluate and manage symptoms. Records were reviewed from the end of radiation to the date of the trial's toxicity analysis.[8]

Decision analytic model

At a median follow-up of 6 years, trial patients who were treated with HIMRT or CIMRT had similar biochemical progression-free survival; therefore, we performed a cost minimization analysis from the institutional healthcare perspective to determine the relative cost of these treatments, including late toxicity costs.[7] A decision tree model was constructed, with branches incorporating maximum grade gastrointestinal and genitourinary toxicities per patient (Fig 1). Trial results provided estimates of toxicity probabilities and PSA failure that were used in the base case analysis.

Base case probability inputs

Patient-level data were used for model inputs. There were no grade 4 or 5 toxicities. Owing to the rare incidence of

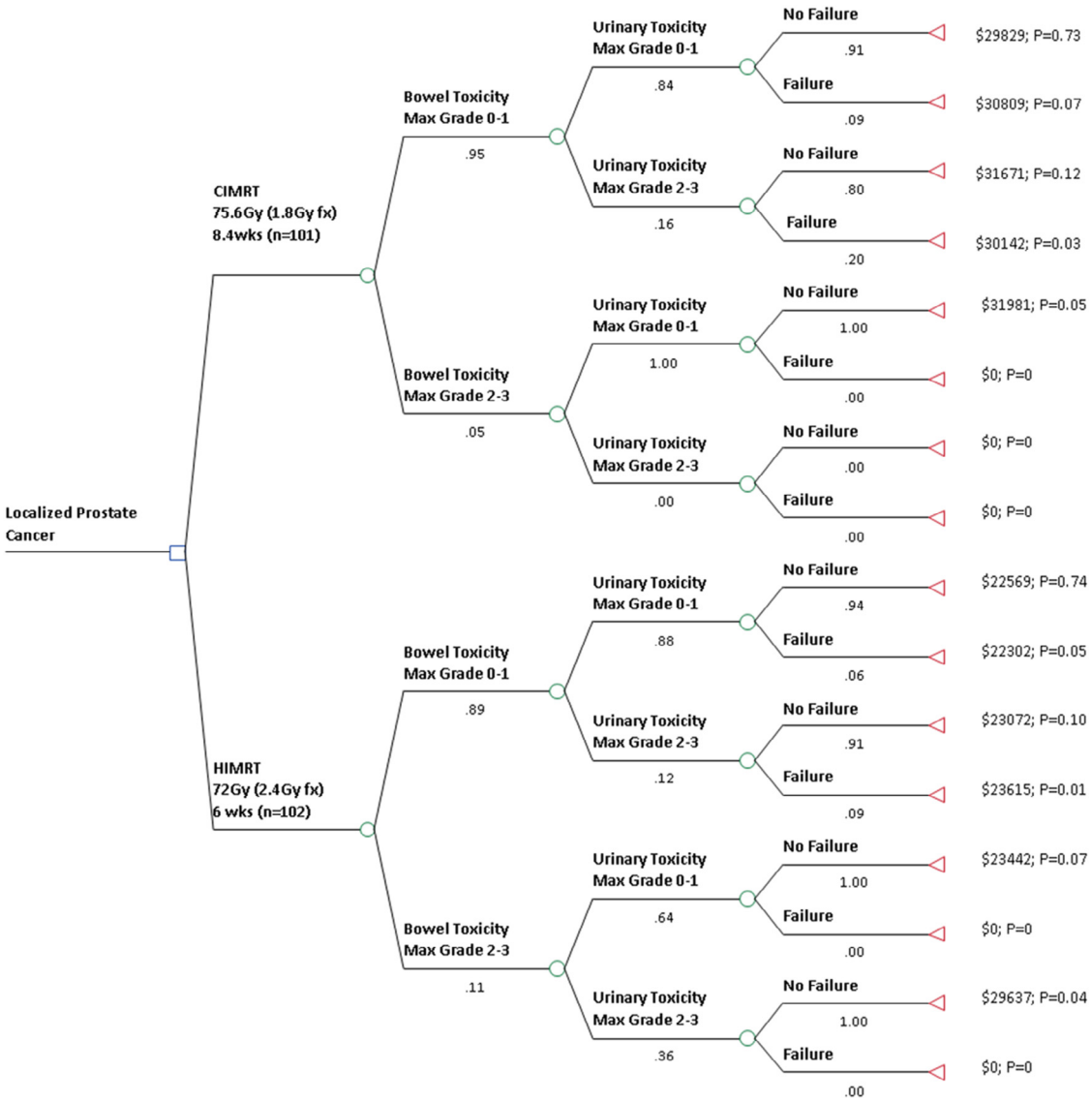

Figure 1 Decision tree comparing conventional intensity modulated radiation therapy (CIMRT) to dose-escalated moderately hypofractionated intensity modulated radiation therapy (HIMRT). Probabilities of maximum late bowel and urinary toxicities were obtained using patient-level data from a randomized trial with a median follow-up of 6 years.

grade 3 toxicity (2 HIMRT and 2 CIMRT), maximum grade toxicity was categorized as grade 0-1 or grade 2-3. No men who were treated with CIMRT developed both grade 2-3 gastrointestinal and grade 2-3 urinary toxicity. Because there were no patient-level data for this scenario, the probability of PSA failure for all men who were treated with CIMRT was applied.

Base case cost inputs

2014 U.S. payment rates

We used the 2014 national professional, technical, procedural, and drug reimbursement rates to inform cost estimates in our base case analysis (Supplementary Tables 2 and 3). We used the 2014 national payment rates for hospital-based outpatient care to estimate the cost of radiation and late toxicities.[12,13,17,18] Professional reimbursement data were obtained from the Centers for Medicare and Medicaid Services (CMS) Physician Fee Schedule.[13] All technical fees were obtained from the ambulatory payment classification in accordance with the CMS Outpatient Prospective Payment System Addendum B.[12] Payments for procedural medical supplies that were not bundled with technical reimbursements were determined using other CMS fee schedules.[17] Supplementary Tables 2 and 3 list the current procedural and technology codes and procedural times used to determine the reimbursement rates.

Total radiation payment was calculated from the date of the radiation planning scan to the last treatment and included all associated radiation procedures including image

guidance. Radiation follow-up visit reimbursements were excluded because the 2 arms had similar follow-ups.

For men with side effects that required intervention, we assumed specialty clinic visit reimbursements as new patients at the initial appointment and subsequently as established patients. Clinic visit reimbursements were determined using a level 3 visit. Reimbursement for subsequent interventions included an established clinic visit in the cost estimation. Emergency room reimbursements were determined using a level 4 visit.

The drug cost for treating toxicity was estimated using the average wholesale price per unit, multiplied by dosage and duration of use.[19] Drug dosage was determined from the maximum allowed medication dosage per modified Radiation Oncology Therapy Group grade toxicity observed, the dosage found in the retrospective medical chart review, or, if the first 2 options were not available, the typical drug dosage for the recorded toxicity duration.[20] For men with baseline urinary or bowel symptoms that required medications unrelated to toxicity, drug use was determined by multiplying the routine dosing schemes by the duration of follow-up until the date of the toxicity analysis.

Cost estimate verification using patient-level institutional costs

Single-institution costs for radiation treatment and toxicity management were used to inform alternative case analyses. To verify the costs estimated from national payment rates, we obtained single-institution costs from the date of the radiation planning scan to the trial's toxicity analysis date. Institutional costs excluded the drug costs and were inflated to January 2014 U.S. dollars using the producer price index.[21] No future discounting of institutional cost was applied because a cost analysis was performed at the specified date of the trial's toxicity analysis. We identified 14 men with cancers unrelated to radiation who received another cancer treatment during the postradiation follow-up. Because institutional costs also included treatment costs for these other cancers, we performed cost verification using institutional data for all patients (n = 203) and for the cohort of patients excluding those with other cancers (n = 189).

For simplicity, cost estimates using the 2014 national reimbursement rates will be referred to as costs. Patient-level institutional costs will be referred to as institutional costs.

Data analysis

We created a decision tree and performed the analysis using TreeAge Pro 2014 (TreeAge Software, Williamstown, MA). The mean costs, also known as the expected value, for CIMRT and HIMRT were determined by adjusting the mean cost of patients who were categorized into each terminal branch of the model with the probabilities in the terminal branch and in each preceding branch. Descriptive analysis was performed using STATA version 12 (StataCorp, College Station, TX).

Sensitivity analysis

To evaluate probability and cost uncertainties in the decision model, we used sensitivity analyses to identify the most influential parameters in determining the more costly strategy. We used tornado analyses to rank the most influential parameters.[22] In the first-order sensitivity analyses, we varied the range of input probabilities from 0 to 1 and cost from minimum to maximum mean values to determine univariate effects on costs. We used Monte Carlo second-order probabilistic sensitivity analyses to estimate costs using 10,000 micro-simulations with beta distributions for each probability and gamma distributions for each cost variable (Supplementary Methods).[22] Sensitivity analyses in this study only evaluated changes in the model parameters in Figure 1. If analyses demonstrated that the average total cost associated with HIMRT was less than that of CIMRT, threshold sensitivity analyses were used to identify the threshold values below which the CIMRT total cost would be less than HIMRT.

Results

The 2 arms had similar clinical characteristics (Table 1). A total of 101 men received CIMRT, and 102 men received HIMRT. The median age was 68 years, and the majority of men had T1 tumors (72%), PSA levels <10 ng/mL (89%), and a Gleason score of 7 (65%). During a median follow-up of 6 years, few men developed grade 2-3 bowel (5% CIMRT and 11% HIMRT) or grade 2-3 urinary (15% CIMRT and 15% HIMRT) toxicity. Supplementary Tables 1 to 3 demonstrate the base case probabilities per branch and the cost components (radiation, toxicity interventions, and drugs) used in the cost-minimization analysis. Figure 1 demonstrates the branch probabilities and average total cost of each terminal scenario, accounting for toxicity costs. Table 2 demonstrates reimbursements associated with radiation and management of radiation toxicity.

Base case cost-minimization analysis

From a healthcare perspective, the 2014 cost of CIMRT and the management of corresponding late radiation toxicities was $30,241, whereas the cost of HIMRT and the management of corresponding late radiation toxicities was $22,957. Therefore, hypofractionated radiation was the least costly strategy, with a cost savings of $7,284 (Table 3).

Table 1 Clinical characteristics of men with organ-confined prostate cancer in a randomized trial comparing CIMRT (8.4 weeks of treatment) to HIMRT (6 weeks of treatment)

Characteristic	CIMRT (75.6 Gy in 1.8 Gy fxns) 8.4 weeks n = 101	HIMRT(72 Gy in 2.4 Gy fxns) 6 weeks n = 102	*P*-value
Median age (range), y	67 (48-84)	69 (41-83)	.15
Tumor stage			.29
T1	76 (75%)	70 (69%)	
T2	25 (25%)	32 (31%)	
PSA			.35
<10	88 (87%)	93 (91%)	
10-20	13 (13%)	9 (9%)	
Gleason score			.81
6	37 (37%)	33 (32%)	
7	63 (62%)	68 (67%)	
8	1 (1%)	1 (1%)	
Risk group			.98
Low	29 (29%)	28 (27%)	
Intermediate	71 (70%)	73 (72%)	
High	1 (1%)	1 (1%)	
Androgen deprivation therapy			.77
Yes (<4 mo)	23 (23%)	25 (25%)	
No	78 (77%)	77 (75%)	
Median follow-up (range), y	5.6 (0.8-11.4)	6.3 (0.9-11.2)	.67
Late genitourinary toxicity, grade			
0	71 (70%)	77 (75%)	
1	15 (15%)	10 (10%)	
2	14 (14%)	15 (15%)	
3	1 (1%)	0 (0%)	.52
Late gastrointestinal toxicity, grade			
0	79 (78%)	64 (63%)	
1	17 (17%)	27 (26%)	
2	4 (4%)	9 (9%)	
3	1 (1%)	2 (2%)	.11
5-Year PSA failure[a]	6%	5.5%	.30

CIMRT, conventional intensity modulated radiation therapy; fxns, fractions; HIMRT, dose-escalated moderately hypofractionated intensity modulated radiation therapy; PSA, prostate-specific antigen.

[a] 5-year PSA failure is reported for 204 men. One patient in the HIMRT arm was censored almost immediately after treatment due to death.

Sensitivity analysis

Tornado analysis ranked the influence of parameters on the cost of treatment (Fig 2; Table 3). The most influential parameter was the cost of treatment and toxicity management in men who were treated with CIMRT who had grade 0-1 bowel and grade 0-1 urinary toxicities and no PSA failure. On univariate analysis, the mean cost of the CIMRT regimen proportionally increased with the increased cost of this parameter. In this scenario, HIMRT had a minimum possible cost savings of approximately $7,000 and a maximum cost savings of approximately $12,300 over CIMRT (Table 3).

The second most influential parameter was the probability of CIMRT patients developing grade 0-1 bowel toxicity. As the probability of this scenario increased from 0 to 1, the mean cost of CIMRT decreased, and HIMRT cost savings decreased from $9,000 to $7,200. The third most influential parameter was the cost of CIMRT patients who developed grade 0-1 bowel toxicity, grade 2-3 urinary toxicity, and no PSA failure (Table 3). Sensitivity analyses demonstrated that the top 5 parameters could influence HIMRT savings from approximately $6,000 to $12,000 when compared with CIMRT.

HIMRT remained less costly according to Monte Carlo analysis, which analyzed full model uncertainty using all parameters (Table 3). There was no threshold value at which CIMRT cost less than HIMRT within the range of possible mean costs for CIMRT patients who had grade 0-1 bowel and grade 0-1 urinary toxicities.

Alternative case scenario

To verify reimbursement for radiation and toxicity management, institutional costs (adjusted to 2014) for all men

Table 2 Reimbursements associated with radiation and management of radiation toxicity

Treatment	2014 value	Reference
Radiation		
Conventional	29,367.16	CMS
Hypofractionated	21,904.68	CMS
Procedures		
Colonoscopy, diagnostic	976.26	CMS
Colonoscopy, with control of bleeding	1090.9	CMS
Flexible sigmoidoscopy, diagnostic	543.52	CMS
Flexible sigmoidoscopy, for control of bleed	963.96	CMS
Anesthesia for lower endoscopy	248.05	CMS
Catheterization urinary	136.88	CMS
Catheterization, with dilatation	192.77	CMS
Catheterization, with indwelling Foley catheter[a]	667.89	CMS, AWP
Catheterization, with bladder irrigation	341.59	CMS
Cystourethroscopy	761.32	CMS
Cystourethroscopy, with irrigation and clot removal	1319.93	CMS
Cystourethroscopy, requiring general anesthesia	941.34	CMS
Fluoro-urodynamic study	1903.95	CMS
Transurethral resection of the prostate	4885.21	CMS
Direct visual internal urethrotomy and mitomycin-C injection	5277.71	CMS
Imaging and work-up		
CT pelvis, with contrast	367.94	CMS
CT abdomen, with/without contrast	422.98	CMS
Intravenous pyelogram	307.76	CMS
Post void residual ultrasound	72.43	CMS
Renal ultrasound	172.18	CMS
Transabdominal ultrasound		CMS
Urine analysis and culture	27.08	CMS
Urine cytology	42.77	CMS
Clinic visits		
Outpatient new visit, level 3	169.55	CMS
Outpatient established visit, level 3	144.11	CMS
Emergency room visit, level 4	415.15	CMS
Medications, dose		
Hydrocortisone acetate (Anusol HC, Proctocort), 25 mg	5.92	AWP
Pramoxine hydrochloride foam (Proctofoam HC), 15 g	3.50	AWP
Psyllium (Metamucil), 3.4 g	0.01	AWP
Docusate sodium (Colace), 100 mg	0.01	AWP
Magnesium hydroxide (Milk of Magnesia), 30 mL	0.00	AWP
Loperamide, 2 mg	0.15	AWP
Diphenoxylate-atropine (Lomotil), 0.025-2.5 mg	1.85	AWP
Tamsulosin (Flomax), 0.4 mg	0.20	AWP
Alfuzosin (Uroxatral), 10 mg	0.47	AWP
Terazosin, 10 mg	1.60	AWP
Terazosin, 2 mg	1.45	AWP
Oxybutynin (Ditropan[b]), 10 mg	6.32	AWP
Tolterodine tartrate (Detrol), 1 mg	3.31	AWP
Tolterodine tartrate (Detrol LA[b]), 4 mg	9.83	AWP
Solifenacin (VESIcare[b]), 5 mg	8.85	AWP
Dutasteride (Avodart[b]), 0.5 mg	4.07	AWP
Finasteride (Proscar), 5 mg	3.11	AWP
Ciprofloxacin hydrochloride, 500 mg	0.21	AWP
Levofloxacin (Levaquin), 500 mg	15.60	AWP
Doxycycline, 100 mg	1.94	AWP
Trimethoprim/sulfamethoxazole (Bactrim DS[b]), 800-160 mg	3.12	AWP
Ibuprofen, 200 mg	3.12	AWP
Calcium glycerophosphate (Prelief[b]), 1 tablet	0.02	AWP

AWP, average wholesale price; CMS, Centers for Medicare and Medicaid Services; CT, computed tomography; HC, hydrocortisone acetate and pramoxine hydrochloride.

[a] Reimbursement for 1 month of levofloxacin was included in procedural costs on the basis of actual patient scenario.

[b] When pricing of the generic form of this medication was unavailable, the unit average wholesale price of the nongeneric medication was provided.

Table 3 Cost estimates in base and alternative case scenarios using 2014 national reimbursements, verified with institutional cost[a]

Parameter	Estimated cost per patient (2014 $US)		CIMRT-HIMRT cost difference (range[b])	Relative cost of HIMRT
	CIMRT	HIMRT		
2014 National Reimbursement (Base Case)	30,241	22,957	7284	.76
Parameter 1[c]	29,905-35,244	22,957	6948-12,287	.77-.65
Parameter 2[d]	31,981-30,149	22,957	9024-7192	.72-.76
Parameter 3[e]	29,974-31,646	22,957	7017-8689	.77-.73
Parameter 4[f]	28,642-30,241	22,957	5685-7284	.80-.76
Parameter 5[g]	28,642-30,241	22,957	5685-7284	.80-.76
Model, beta distribution	30,232	23,001	7231	.76
Model, gamma distribution	30,251	22,979	7272	.76
Model, gamma and beta distribution	30,233	22,965	7268	.76
Institutional cost,[a] n = 203			15,856	.61
Institutional cost,[a] excluding men with treatment of other cancers, n = 189			5840	.80
Model using institutional cost,[a] gamma and beta distribution			5826	.80

CIMRT, conventional intensity modulated radiation therapy; HIMRT, dose-escalated moderately hypofractionated intensity modulated radiation therapy; PSA, prostate-specific antigen.

[a] Range of difference determined by increasing the cost (minimum to maximum) or probability parameter (0 to 1) of patients in a sensitivity analysis.

[b] Institutional costs were adjusted to year 2014 and do not include the cost of drugs used.

[c] The cost of treatment and toxicity management in men who were treated with CIMRT and had grade 0-1 bowel toxicity, grade 0-1 urinary toxicity, and no PSA failure.

[d] The probability of men who were treated with CIMRT and had grade 0-1 bowel toxicity.

[e] The cost of treatment and toxicity management in men who were treated with CIMRT and had grade 0-1 bowel toxicity, higher grade 2-3 urinary toxicity, and no PSA failure.

[f] The probability of men who were treated with CIMRT and had higher grade 2-3 bowel toxicity, grade 0-1 urinary toxicity, and no PSA failure.

[g] The probability of men who were treated with CIMRT and had higher grade 2-3 bowel toxicity and grade 0-1 urinary toxicity.

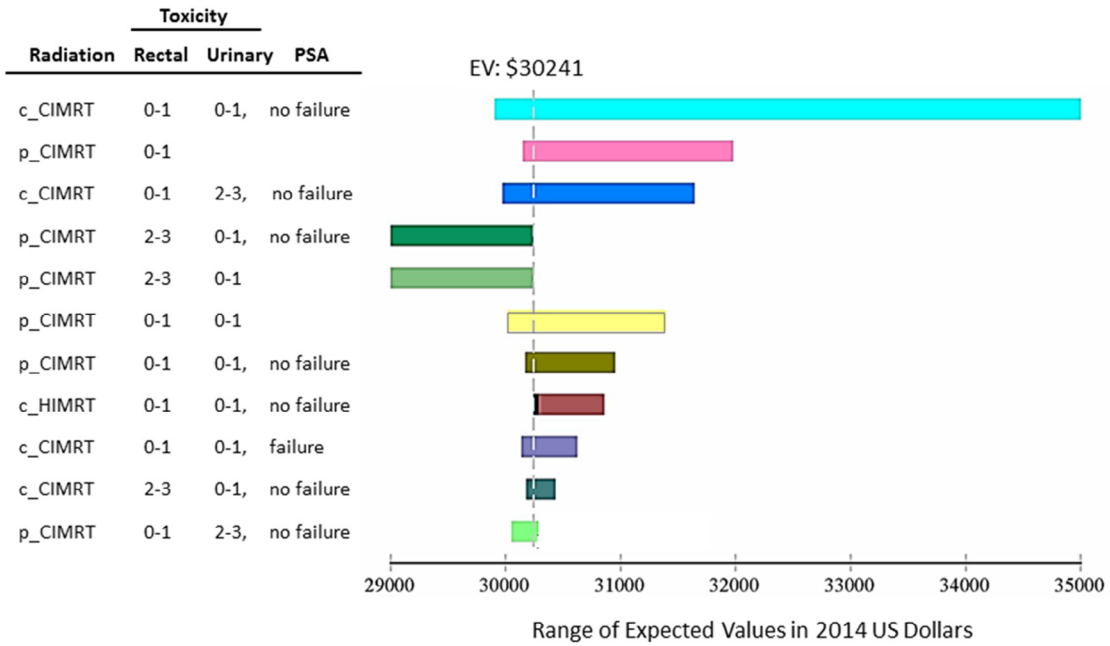

Figure 2 Tornado analysis ranking in order of influence the univariate effects of probabilities (p_) and cost (c_) variations on expected value (mean cost). c_, cost of parameter; p_, probability of parameter; CIMRT, conventional intensity modulated radiation therapy; HIMRT, dose-escalated hypofractionated intensity modulated radiation therapy; 0-1, maximum grade 0 or grade 1 toxicity; 2-3, maximum grade 2 or grade 3 toxicity; EV, expected value in 2014 U.S. dollars.

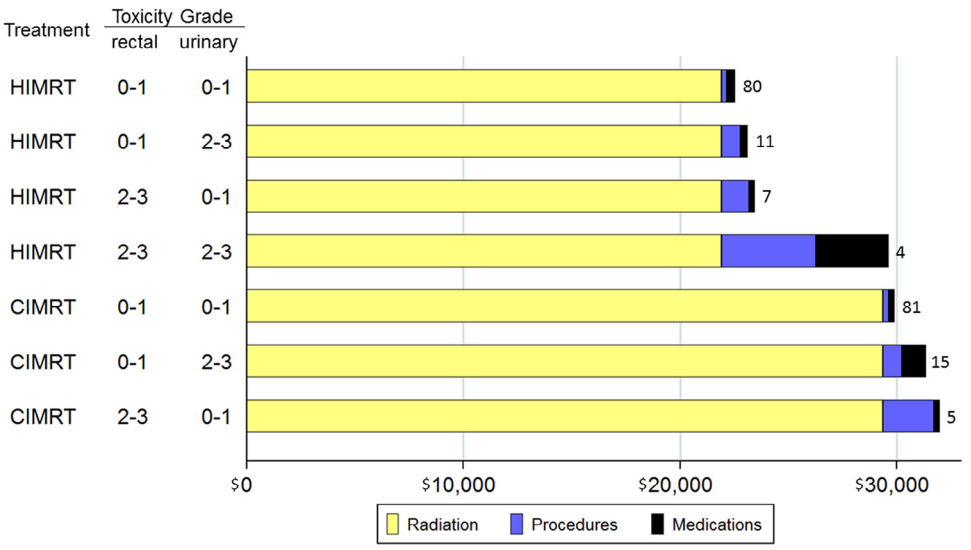

Figure 3 Components of total cost for patients with organ-confined prostate cancer treated with dose-escalated moderately hypofractionated intensity modulated radiation therapy (HIMRT) or conventional intensity modulated radiation therapy (CIMRT). No men who were treated with CIMRT developed both grade 2-3 bowel and grade 2-3 urinary toxicities. Thus, cost components in 2014 U.S. dollars for this subgroup are not displayed. The number of patients in each subgroup is displayed at the far end of the bar graph.

were applied to the decision model. Institutional cost included all nonpharmacologic healthcare resources used from the time of radiation planning to the end of the late toxicity analysis. HIMRT was more cost efficient than CIMRT by approximately $15,900 (Table 3). Fourteen men (7 CIMRT and 7 HIMRT) had other cancers that were treated in the postradiation period. Therefore, these men had the cost of other cancer treatments included in the patient-level institutional costs. After excluding these 14 men, HIMRT remained the least costly strategy by approximately $5,800, which was comparable to the difference in mean cost using reimbursement data (approximately $7,300) (Table 3).

Radiation and late toxicity management cost components

To better understand how the distribution of cost components affected average total cost, we plotted the average reimbursements for radiation, toxicity procedures, and medications against the radiation regimen and the severity of bowel and urinary toxicities (Fig 3). The cost of toxicity management was minor compared with that of radiation. For patients with either grade 2-3 bowel or urinary toxicity, the average cost of toxicity management was less than 10% of the total cost (average cost, 5%-8%; Range, 0%-44%). Four of the 203 patients (all HIMRT) developed both grade 2-3 urinary and grade 2-3 bowel toxicities, and their average toxicity management cost was 26% (Range, 1%-63%) of the total cost. The average cost of treatment and toxicity management for HIMRT patients who had both grade 2-3 bowel and grade 2-3 urinary toxicities was still lower than the average cost for CIMRT patients with low grade 0-1 bowel and urinary side effects (Fig 3). For patients who were treated with CIMRT and who had low grade 0-1 bowel and urinary side effects, the average cost of toxicity management was 2% to 3% (Range, 0%-51%) of the average total costs. Long-term medication use for symptom management, especially urinary symptoms potentially unrelated to radiation, can substantially affect cost components distribution, with mediations cost comprising up to 51% of the average total cost (Supplementary Table 4).

Discussion

From a healthcare perspective, our cost analysis demonstrated that HIMRT, including costs of radiation and late toxicity evaluation and management, was more cost efficient than CIMRT at a median follow-up of 6 years. Radiation was the dominant component of total cost. Long-term use of medications also highly affected cost.

Generally, toxicity costs accounted for <10% of the total therapy cost. This increased to 26% of the total cost in men with both high-grade bowel and urinary toxicities. The development of such dual toxicities was uncommon (4 of 102 HIMRT patients). Men treated with HIMRT had a nonsignificant numeric increase in bowel toxicity compared with men treated with CIMRT (11% vs 5%) but not in urinary toxicity. Considering that HIMRT delivers an increased biologic equivalent dose of 85 Gy at 1.8 Gy per fraction (assuming an alpha-beta of 1.5), such toxicities were relatively rare and remained a fraction of the total cost. Furthermore, there was no cutoff toxicity probability that

would make HIMRT more expensive than CIMRT in our sensitivity analyses.

Long-term symptom-management medication use can substantially increase the total cost of prostate cancer care. In men who were treated with CIMRT or HIMRT and who had grade 0-1 urinary and bowel symptoms, daily medication use comprised 25% to 51% of the average total costs. The majority of these medications were used to manage urinary symptoms. Notably, this subset of patients included men with baseline urinary or bowel symptoms that were unrelated to late radiation toxicities. Interestingly, although cystoscopies for urinary toxicities were less common than gastrointestinal endoscopies for bowel toxicities in this trial, urinary procedures cost more. Thus, maintaining low urinary toxicity rates also may be important in reducing healthcare expenditures.

Our study suggests that reducing the total radiation treatments and minimizing late radiation toxicities, particularly urinary toxicities, could reduce the healthcare resources that are used in prostate radiation. This is important when U.S. healthcare policy changes are directed at increasing the value of cancer treatments by reducing healthcare expenditures.

Several points deserve further consideration. Our dataset was limited to a single institution during a limited time period. Economic analyses typically use evidence from systematic literature reviews and reflect a lifetime interval to include all outcome and cost effects between interventions.[23] However, trials evaluating long-term prostate cancer outcomes and toxicities with similar hypofractionation regimens (70 Gy at 2.5 Gy per day over 5.6 weeks; 70.2 Gy at 2.7 Gy per day over 5.2 weeks) have only recently been published, with median follow-up ranging from 3.5 to 6 years. Of these studies, our trial has the longest follow-up.[8-10,24] Our analysis uniquely used patient-level instead of aggregate trial data. The majority of high-grade toxicity events was likely captured in this analysis at median follow-up of 6 years with the cumulative incidence of grade 2-3 bowel toxicities plateauing after 2 years and grade 2-3 urinary toxicities plateauing after 4 years.[8] Finally, our results are applicable to the moderately hypofractionated treatment regimen evaluated in this randomized trial. They may not apply to more aggressive hypofractionation regimens that deliver even larger doses of radiation over a shorter duration.[11,14]

Ideally, this study would have evaluated the costs associated with more generic outcomes, including health-related quality-of-life data, to produce quality-adjusted outcome data from the patient's perspective. However, patient preferences with regard to treatment duration, prostate cancer control, and toxicity to determine health-related quality-of-life data were not included in this trial, which was designed in the late 1990s before the emphasis on understanding patient utilities. An analysis from the patient's perspective would also provide data on the costs of hypofractionated versus conventionally fractionated radiation that directly affecting the patient and would be the next step in evaluating the long-term economic value of hypofractionated prostate radiation.

Additionally, this cost minimization analysis was based on cancer control outcome, which was the primary trial endpoint, rather than on overall survival. However, this trial demonstrated similar early cancer control and survival outcomes between men who were treated with HIMRT and those treated with CIMRT, but this will need to be confirmed with additional follow-up.[7] Given the longer natural history of prostate cancer, longer-term total costs associated with HIMRT versus CIMRT in this trial will be available with additional follow-up. One study estimated an 820 Euro cost savings benefit, without a quality-adjusted life year benefit, when comparing HIMRT with CIMRT using data from limited published studies in a Markov model.[25] Our study is unique in that it captures true patient-level healthcare resources utilized in the management of late toxicity rather than an estimation of the resources utilized.

Despite these limitations, our study clearly demonstrates the cost-minimizing value of HIMRT in treating prostate cancer when compared with CIMRT. Furthermore, the robustness of these cost estimates, which used national payment rates, was confirmed with actual patient-level institutional costs. Our analysis shows that HIMRT was more cost efficient than CIMRT when considering similar prostate cancer outcomes. Provided that longer-term cancer outcomes are similar and that low toxicity rates hold as data accrue, HIMRT may be the preferred regimen for men who elect for definitive external beam radiation for localized prostate cancer in both the current fee-for-service health payment system as well as possible future bundled payment systems.

Conclusions

Cost analysis results indicate that moderately hypofractionated prostate radiation was more cost efficient than conventional radiation, even after accounting for costs of evaluating and managing late radiation toxicity. Moderate hypofractionation enhances the value of prostate radiation therapy when compared with conventionally fractionated prostate radiation.

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Supplementary data

Supplementary material related to this article can be found online at doi:10.1016/j.adro.2017.07.006.

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