Cost-Effectiveness Analysis of SBRT Versus IMRT: An Emerging Initial Radiation Treatment Option for Organ-Confined Prostate Cancer

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Objectives: The purpose of this study is to compare the cost-effectiveness of 2 external beam radiation therapy techniques for treatment of low- to intermediate-risk prostate cancer: stereotactic body radiation therapy (SBRT) and intensity-modulated radiation therapy (IMRT).

Materials and Methods: A Markov decision analysis model with probabilistic sensitivity analysis was designed with the various disease states of a 70-year-old patient with organ-confined prostate cancer to evaluate the cost-effectiveness of 2 external beam radiation treatment options.

Results: The Monte Carlo simulation revealed that the mean cost and quality-adjusted life-years (QALYs) for SBRT and IMRT were $22,152 and 7.9 years and $35,431 and 7.9 years, respectively. The sensitivity analysis revealed that if the SBRT cohort experienced a decrease in quality of life of 4% or a decrease in efficacy of 6%, then SBRT would no longer dominate IMRT in cost-effectiveness. In fact, with these relaxed assumptions for SBRT, the incremental cost-effectiveness ratio of IMRT met the societal willingness to pay threshold of $50,000 per QALY.

Conclusions: Compared with IMRT, SBRT for low- to intermediate-risk prostate cancer has great potential cost savings for our healthcare system payers and may improve access to radiation, increase patient convenience, and boost quality of life for patients. Our model suggests that the incremental cost-effectiveness ratio of IMRT compared with SBRT is highly sensitive to quality-of-life outcomes, which should be adequately and comparably measured in current and future prostate SBRT studies.

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The American Cancer Society estimates 241,740 patients newly diagnosed with prostate cancer, with 28,174 prostate cancer–related deaths, in 2012.[1] The National Institutes of Health estimate that the overall direct cost of cancer in the United States in 2010 was $102.8 billion, with prostate cancer being the fifth most costly cancer, accounting for more than $12 billion in annual cost in 2010 and $19 billion projected in 2020.[1,2] The rapidly increasing cost of prostate cancer treatment, driven by a combination of advanced surgical, radiation, and pharmaceutical treatment technologies, has catalyzed increased scrutiny regarding current treatment approaches for prostate cancer.[3-5] In fact, prostate cancer has been described as the litmus test for healthcare spending reform efforts.[6]

Hayes et al[7] recently examined a random-effects meta-analysis for patients with low-risk prostate cancer through a decision analysis, concluding active surveillance would be more effective than initial treatment options based on a quality-adjusted life expectancy end point. However, this study comparing initial treatment versus active surveillance did not include the emerging treatment option of stereotactic body radiation therapy (SBRT).

The traditional initial treatment options for low- and intermediate-risk prostate cancer have been prostatectomy, external beam radiation, or brachytherapy. Most recently, the external beam technique of 3-dimensional conformational radiation therapy was replaced by the more conformal technique of intensity-modulated radiation therapy (IMRT), which has allowed for dose escalation.[8] Similar to IMRT, SBRT is a form of highly conformal external beam radiotherapy, employing the use of advanced technologies including unique beam arrangements, stable patient immobilization, motion assessment and control, and daily image guidance. However, SBRT delivers a higher dose of radiation per fraction and at our institution includes additional patient immobilization (stereotactic body frame), motion control (rectal balloon), and motion assessment (intrafraction image guidance). This technique has been successfully applied in early-stage lung cancer and liver metastasis.[9-11] Prostate cancer may be uniquely appropriate for treatment with hypofractionation (large dose per fraction) because of a lower α-to-β ratio (approximately 1.5 to 3.0), which is similar to normal tissue

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late effects.[12-15] Stanford University treated patients at a dose of 36.25 Gy in 5 fractions, with no patient experiencing biochemical failure at 33-month follow-up.[16] Our institution recently published the toxicity rates of a phase I dose-escalation study of SBRT for prostate cancer, which compare favorably with acute toxicity reported in historical IMRT dose-escalation studies (**Table 1**).[17-32] In addition to several promising early outcome reports, Freeman et al[22] and King[26] recently published their 5-year biochemical progression-free survival (PFS) of 93%, with favorable rates of early and late toxicity compared with IMRT dose-escalation trials as well (Table 1).[22,23,26] Thus, on the basis of these results and the α-to-β ratio of prostate cancer, there seems to be a firm hypothesis that SBRT would be comparable to or better than IMRT from a biochemical control standpoint. However, by the same rationale, the late effects of normal tissue could potentially be worse and thus negatively affect the quality of life (QoL) of patients undergoing treatment with SBRT. To that end, this model aims to further describe the cost-effectiveness of SBRT while using a sensitivity analysis to establish the thresholds at which late effects as measured by utility may prove SBRT to be less cost-effective than IMRT.

Cost-effectiveness analysis (CEA) using Markov modeling is a well-documented economic technique used to assess relative benefits of treatments, quality-adjusted life-years (QALYs), and costs of various treatment options for a given health condition. In 2009, in response to an ever-increasing percentage of our national gross domestic product spent on healthcare costs, $1.1 billion of the $787 billion stimulus package was allocated for comparative clinical effectiveness research. Thus, it is clear that CEA will increasingly be applied to economically evaluate alternative treatment options in our healthcare system.[33,34] To our knowledge, this is the first report that uses Markov CEA with Monte Carlo probabilistic sensitivity analysis to explore the cost-effectiveness of SBRT for patients with low- or intermediate-risk prostate cancer as compared with IMRT from the payer perspective.

MATERIALS AND METHODS

Decision Model

To evaluate a hypothetic clinical trial design, we developed a Markov decision tree using TreeAge Pro Healthcare 2011 (Tree-Age Software, Williamstown, Massachusetts) to capture the various disease states of a 70-year-old man with organ-confined prostate cancer (**Figure**). Similar to past and ongoing studies evaluating SBRT, the patient was assumed to have a Gleason score <7 and/or prostate-specific antigen ≤15, with limited organ-confined prostate cancer (≤pT2b). Given that the median age of diagnosis of prostate cancer in the United States is 68 years, and the average actuarial life expectancy of men is 78 years, the base case involved a 70-year-old man with low- or intermediate-risk disease treated with either IMRT or SBRT with a 10-year follow-up horizon.[1,35] The model captured the disease states a patient with prostate cancer could potentially experience after radiation: no evidence of disease, progression with response to hormonal therapy (hormone therapy), progression in a patient with hormone-refractory prostate cancer (chemotherapy), and death. Markov simulations allow hypothetic patient cohorts to transition between health states in defined increments of time.[33] In this model, the patient spends 1 year in a given disease state before the Monte Carlo simulation allows for a probabilistic transition to another state. Annual transition probabilities were calculated assuming rates using the formula: annual probability = 1 – exp(- annual rate/N), where the annual rate = [–lN(1 – P)/N], when P is the probability of biologic failure, and N is the number of years over which the rate is measured.[36]

Assumptions

Markov cost-effectiveness models require assumptions of the efficacy, utility, and cost of treatment options. The assumptions of the model and the probability distributions applied to these variables are noted in Table 1. These probabilities were extracted from an extensive literature review as well as a recent random-effects meta-analysis.[3,7]

Efficacy

The Phoenix definition (nadir +2) of biologic PFS (bPFS) was used, because this is the definition used in the recent SBRT 5-year study by King et al,[25] which reported 93% bPFS at 5 years. However, given the still-maturing body of research investigating SBRT for prostate cancer, we conservatively assumed equal efficacy of SBRT as compared with IMRT. This variable was heavily scrutinized under sensitivity analysis. The risk of a patient becoming unresponsive to hormonal therapy was based on previous reports.[27,37] A patient refractory to hormonal therapy was assumed to transition to the state of chemotherapy with a 1-year average life expectancy.[28,38] The model captured other-cause mortality through the application of actuarial life tables.[35] Although there are several newly available treatments for patients with castrate-resistant prostate cancer, including sipuleucel-T and abiraterone acetate, their use is not standardized, and none are curative, with an average extension of life expectancy of approximately 4 months.[39,40] We did not include them in our analysis, because they affect such a small fraction of patients; we did not feel they would have a significant impact on our model.

Utility (QoL)

Patient-reported outcome (PRO) instruments used in various studies have included the Expanded Prostate Can-

Table 1. Toxicity, Outcomes, and Model Assumptions

	Toxicity					
	Acute (%)					
	IMRT			SBRT		
Cancer Type	Zietman et al[18]	Zelefsky et al[19]	Storey et al[20]	King et al[16]	Boike et al[17]	Jabbari et al[23]
GU						
RTOG grade						
<2	29	38	46	20	33	45
≥2	63	28	29	0	7	33
GI						
RTOG grade						
<2	26	22	42	13	54	5
≥2	64	4	42	7	0	0

	Outcomes	
	bPFS	
Study	Rate Range (%)	Survival (years)
Zietman et al[18]	91-98	5
Kuban et al[21]	88-94	8
Zelefsky et al[19]	86-92	3
King et al[25]	92.7	5

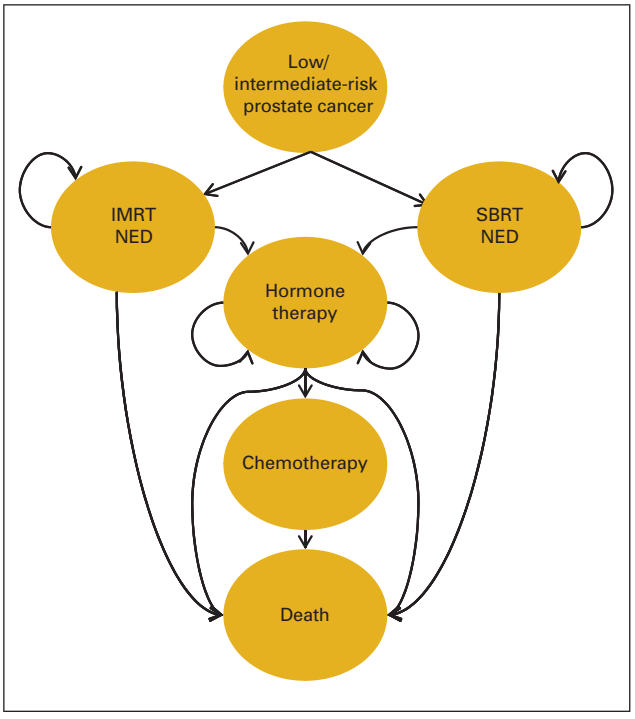
	Model Assumptions			
Variable	Baseline Value/Mean	SD	Range in Simulation	Distribution
Yearly transition rates				
IMRT	0.02	0.01	0.0036-0.04	β
SBRT	0.02	0.01	0.0036-0.04	β
Hormone therapy	0.13	0.0219	0.06-0.019	β
Chemotherapy	1	—	—	—
Utility values				
IMRT	0.9	0.05	0.8-1.0	β
SBRT	0.9	0.05	0.8-1.0	β
Hormone therapy	0.68	0.26	0.5-0.8	β
Chemotherapy	0.4	—	—	Uniform
Costs				
IMRT	$29,530	± 30%	$20,000-$40,000	Triangle
SBRT	$14,315	± 30%	$10,000-$20,000	Triangle
Hormone therapy	$7200	$4300	$2000-$15,000	Normal
Chemotherapy	$24,000	$15,000	$5000-$100,000	Normal

Costs are expressed in 2010 US dollars; detailed cost analysis provided in **Appendix A3**, online only.
ASTRO indicates American Society of Therapeutic Radiation Oncology; bPFS, biologic progression-free survival; GU, genitourinary; IMRT, intensity-modulated radiation therapy; PSA, prostate-specific antigen; RTOG, Radiation Therapy Oncology Group; SBRT, stereotactic body radiation therapy; SD, standard deviation; UTSW, University of Texas Southwestern.

cer Index Composite, American Urological Association scale, Sexual Health Inventory for Men, and EuroQoL EQ-5D, among many others. Unfortunately, comparing utility of patients treated with IMRT or SBRT is difficult because of the lack of uniformity of these instruments in these studies and the fact that of the PRO instruments mentioned here, only the Euro-QoL measures utility. Because of the similarity among reported treatment-related toxicity, the base patient case assumed equal utility for IMRT and SBRT. The treatment-related utility of 0.90, which is used in the model,

	Late (%)					
	IMRT			SBRT		
	Zietman et al[18]	Zelefsky et al[19]	Kuban et al[21]	King et al[16]	Freeman et al[22]	King et al[25]
	45	14	16	20	40	11
	29	11	10	13	29	5
	41	27	9	7	53	5
	29	25	2	7	15	3
PSA Failure Measurement						
PSA >4						
1996 ASTRO						
1996 ASTRO						
Phoenix						
Reference						
Zietman et al,[18] Zelefsky et al,[19] Kuban et al[21]						
Freeman et al,[22] Jabbari et al,[23] King et al[26]						
Shipley et al[27]						
Beekman et al[28]						
Konski et al,[24] Stewart et al[29]						
Konski et al,[24] Stewart et al[29]						
Bayoumi et al[30]						
Albertsen et al[31]						
Konski et al,[24] UTSW data						
UTSW data						
Red Book						
Piper et al[32]						

Figure. Various Disease States of a 70-Year-Old Man With Organ-Confined Prostate Cancer



IMRT indicates intensity-modulated radiation therapy; NED, no evidence of disease; SBRT, stereotactic body radiation therapy.

is consistent with several previous reports of utility scores for patients with prostate cancer treated with radiation.[29,41] The utility of hormonal therapy was 0.68, as reported by Bayoumi et al[30] and similar to that reported by Stewart et al.[29] The utility of chemotherapy was estimated to be 0.4, which was based on reported QoL among patients with metastatic prostate cancer.[30,31]

Economics

The calculated costs reported by the model herein are the mean costs of the entire cohort analyzed in the model. For simplicity, mean costs will be referred to as costs. Costs were based on the 2010 ambulatory payment classification to estimate the technical component of treatment. The expected reimbursement from physician cost was calculated based on resource-based relative value units multiplied by the 2010 conversion factor, which estimates Medicare allowable costs. Thus, given these assumptions, the analysis took the perspective of the payer (Medicare). The annual cost of hormonal therapy with a luteinizing hormone–releasing hormone agonist was calculated based on the average wholesale price from the Drug Red Book. The cost of the last year of life, which also included the cost of chemotherapy in this model, was adapted from the literature and estimated to be $24,000.[32] Costs and utilities were discounted at a rate of 3% per year as recommended by the Panel on Cost-Effectiveness in Health and Decision Making.[42]

Sensitivity Analysis

Sensitivity analysis is used in cost-effective models to investigate the effect of adjusting base case assumptions such as costs, efficacy outcomes (ie, bPFS), utility measures (ie, QoL), and willingness-to-pay (WTP) thresholds. One- and 2-way sensitivity analyses were performed to investigate the impact on the model when adjusting the base case assumptions. Monte Carlo simulation with second-order probabilistic sensitivity analysis was performed to address the uncertainty inherent in the model assumptions. For radiation cost estimates, a triangular distribution was assumed using the average cost as the likeliest value with a ± 30% increment to define the range.[43] All other costs were modeled using reported mean values, with standard deviations (SDs) to define normal distribution. A total of 5000 patients were used in the Monte Carlo simulation for probabilistic sensitivity analysis. This simulation was performed based on the ranges of values and distributions as noted in the model assumptions listed in Table 1. Treatment options that are both equally or more effective (higher QALYs) and less costly are described as dominating alternative treatment strategies. If, however, a treatment option is more effective but also more costly, then the medical benefit is reported as the incremental cost-effectiveness ratio (ICER).

RESULTS

Under the assumptions of the base case analysis, patients treated with SBRT had a mean QALY of 7.9 (SD, 0.47) and mean cost of $22,152, as compared with a mean QALY of 7.9 (SD, 0.47) and mean cost of $35,431 for a patient treated with IMRT. As expected, given the model assumptions of equal efficacy and utility, the model predicted equal effectiveness. The results from the probabilistic sensitivity analysis and acceptability curve revealed that SBRT dominated IMRT as a treatment strategy, and an ICER of <$50,000 per QALY was obtained in 66% of the model iterations.

Despite the initial 5-year bPFS of 93% as reported by King et al[25] for SBRT, we acknowledge the data for SBRT efficacy are still maturing. The factors that affect cost-effectiveness are cost, utility (QoL), and efficacy (bPFS). One-way sensitivity analyses for bPFS and utility show that small changes in these variables can have a significant impact on the incremental cost-effectiveness ratio. We then proceeded with a 2-way sensitivity analysis, relaxing the assumptions regarding the efficacy (bPFS) and utility of SBRT, as summarized in **Table 2**. At interval decreases in efficacy of 2%, the 2-way sensitivity analysis revealed that at a near-6% decrease in the bPFS for SBRT, the IMRT ICER is $52,918, which approaches the widely accepted WTP value of $50,000 (Table 2). Similarly, if SBRT results in lower QoL than IMRT by 4.0%, then the ICER of IMRT reaches $49,979. Thus, Table 2 allows comparison of ICER assuming varying differences in bPFS and QOL between SBRT and IMRT.

DISCUSSION

We have shown under a wide range of assumptions varying efficacy, utility, and cost that SBRT for patients with low- or intermediate-risk prostate cancer would potentially be an attractive alternative to IMRT from the cost-effectiveness perspective of the payer. One- and 2-way sensitivity analyses showed that the model was most sensitive to QoL outcomes or PROs. As such, evaluating QoL is critical to assessing the cost-effectiveness of SBRT. PFS is also important but has a lesser impact on cost-effectiveness. The reason for this discrepancy is the fact that QoL outcomes affect all patients who receive treatment, yet differences in recurrence rates still affect only a small fraction. For example, a 5% decrease in QoL for 1 treatment results in an absolute decrease in QoL of 5%. On the other hand, a 50% increase in recurrence only affects an additional 1% of patients from 2% to 3%.

Although this decision analysis took the perspective of the payer, from a societal standpoint, the costs associated with treating prostate cancer are significant, with more than $12 billion per year being spent to treat patients with prostate cancer.[1] More than 100,000 patients per year are diagnosed with organ-confined prostate cancer, and 35% to 46% elect to undergo radiation therapy. At a savings of $13,000 per patient, if 50% of these patients were eligible for SBRT and treated with SBRT instead of IMRT, then a conservative societal-level savings would approach $250 million per year.[1] In addition, from the patient perspective, the indirect cost savings of this hypofractionated treatment option, such as time lost from work and the treatment-related costs of transportation and housing, are substantial. Thus, the use of SBRT as an initial treatment option could potentially have a profound economic impact from both societal and individual patient perspectives as well.

This model builds on several studies that have evaluated the cost-effectiveness of radiation treatment options for patients with low- and intermediate-risk prostate cancer. These analyses have all been based on the decision analysis first modeled by Fleming et al.[44] In a prior analysis, 3-dimensional conformational radiation therapy was compared with IMRT, with the conclusion that IMRT is a cost-effective treatment option given a societal WTP threshold of $50,000 per QALY, especially given the ability for improved dose escalation and sparing of normal structures.[24] In a recently published robust analysis of initial treatment options for low-risk prostate cancer, Hayes et al[7] examined several initial treatment options for low-risk prostate cancer including brachytherapy, IMRT,

Table 2. Two-Way Sensitivity Analysis: IMRT Cost-Effectiveness (ICER) Varying QoL and Efficacy for SBRT

		Efficacy at 5 Years (bPFS)					
QoL (%)	Change (%)	–6%	–4%	–2%	Base	2%	4%
		0.84	0.86	0.88	0.90	0.92	0.94
0.765	–5.0	8232	8987	10,254	11,678	13,286	15,115
0.864	–4.0	20,238	27,919	36,841	49,979	76,013	134,220
0.873	–3.0	23,238	30,380	40,921	58,390	92,879	192,587
0.891	–1.0	40,110	50,361	81,585	175,170	[a]	[a]
0.9	Base	52,918	75,037	162,151	[a]	[a]	[a]
0.909	1.0	77,742	164,700	[a]	[a]	[a]	[a]
0.927	3.0	222,674	[a]	[a]	[a]	[a]	[a]
0.945	5.0	[a]	[a]	[a]	[a]	[a]	[a]

ICER per QALYs gained for IMRT when relaxing the assumptions for SBRT efficacy and utility. All ICERs are expressed in $/QALYs.
bPFS indicates biologic progression-free survival; ICER, incremental cost-effectiveness ratio; IMRT, intensity-modulated radiation therapy; QoL, quality of life; SBRT, stereotactic body radiation therapy.
[a]Dominated.

and prostatectomy as compared with active surveillance. This comparative effectiveness analysis concluded that active surveillance would be more effective than initial treatment based on a quality-adjusted life expectancy end point. Despite its emergence as a well-tolerated, noninvasive, efficacious treatment option, SBRT was not included in the model reported by Hayes et al. Given the impressive recent 5-year bPFS data reported by Freeman et al[22] and King et al,[26] with an accumulation of early toxicity data from several phase I and II SBRT trials showing highly comparable toxicity data, it is clear that SBRT warrants consideration as a cost-effective initial treatment option for patients with organ-confined prostate cancer.

There are several potential limitations to our model. First, the data on bPFS and long-term toxicity from SBRT for prostate cancer are still maturing; however, recent reports are promising, as shown in Table 1. The results of this study highlight the importance of utility outcomes or PROs, because late effects and toxicities to nearby normal tissues such as the rectum, bladder, and urethra could potentially affect patient-reported QoL as well as increase treatment-related costs in the model. Should late effects for SBRT prove to be higher, the actual impact of these toxicities as measured by PROs would be valuable in determining the cost-effectiveness of SBRT as compared with IMRT. Thus, a major limitation to the study is the lack of long-term utility data available on SBRT for prostate cancer. It is encouraging that a currently enrolling Radiation Therapy Oncology Group study is comparing a 5-fraction SBRT treatment course with a 12-fraction IMRT treatment course, with the primary end point of patient-reported QoL at 1 year. Additionally, Markov decision analyses implicitly require assumptions regarding cost, efficacy, and utility outcomes. Thus, these assumptions raise concerns regarding the accuracy of costs and transition rates given the variability of different practice patterns, local costs, and differences in reported prostate cancer outcomes in clinical trials. To account for these variances, Markov decision models typically employ Monte Carlo simulation, which uses a range of values with characteristic distributions for imputed variables to simulate a large cohort of patients. However, by assuming equal efficacy based on several published reports of 5-year bPFS for IMRT in dose-escalation trials, the model actually conservatively underestimated bPFS compared with the recent SBRT bPFS 5-year report by King et al.[25]

In conclusion, the recent 5-year bPFS data on SBRT for organ-confined prostate cancer are promising, and as such, the cost-effectiveness of SBRT has great potential in improving the treatment of organ-confined prostate cancer from the payer perspective in addition to patient and societal perspectives. Our study using the Markov decision tree with Monte Carlo simulation found that SBRT is more cost-effective than IMRT, assuming similar outcome measures. SBRT loses its cost-effectiveness with small decreases in QoL or effectiveness. Future studies evaluating SBRT need to focus on both acute and long-term QoL outcomes as well as efficacy.

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Appendix. Unit Charge per Cost Capture

Description	CPT Code	Professional	Technologic	Global	IMRT	SBRT
Consult level 4	99204	$156.79	$0.00	$156.79	1	1
Simulation						
Complex simulation	77290	$81.12	$421.92	$503.04	1	1
Complex treatment device	77334	$64.38	$90.47	$154.85	0	0
Simple simulation	77280	$36.46	$146.94	$183.40	0	5
Treatment planning						
Complex treatment planning	77263	$167.78	$0.00	$167.78	1	1
Chemotherapy planning	77014	$0.00	$141.77	$141.77	1	1
Special treatment procedure	77470	$106.09	$369.09	$475.18	1	1
Physics plan						
Basic dose calculation	77300	$32.37	$38.06	$70.43	8	10
Radiotherapy dose plan for IMRT	77301	$417.69	$1797.04	$2214.73	1	0
Complex treatment device	77334	$64.38	$90.47	$154.85	1	10
MLC treatment device for IMRT	77338	$234.11	$257.38	$491.49	1	0
Weekly physics	77336	$0.00	$54.67	$54.67	8	1
Three-dimensional planning	77295	$238.66	$883.04	$1121.70	0	1
Special physics consult	77370	$0.00	$113.8	$113.80	0	1
Linac robotic plan	G0338	$0.00	$1150.00	$1150.00	0	0
Treatment/management						
Five treatments	77427	$200.92	$0.00	$200.92	8	0
One SBRT	77435	$704.24	$0.00	$704.24	0	1
Treatment delivery, IMRT	77418	$0.00	$511.24	$511.24	44	0
Stereo body robotic treatment						
1	G0339	$0.00	$3761.2	$3761.24	0	0
2-5	G0340	$0.00	$2551.3	$2551.34	0	0
Stereo body nonrobotic treatment	77373	$0.00	$1526.1	$1526.05	0	5
Port films	77417	$0.00	$15.17	$15.17	8	0
Total					$29,529.71	$14,314.87

2010 Medicare allowable SBRT codes are for descriptive purposes, because many local Medicare coverage descriptions do not cover prostate cancer; G codes are for descriptive purposes.
CPT indicates current procedural terminology; IMRT, intensity-modulated radiation therapy; MLC, multileaf collimator; SBRT, stereotactic body radiation therapy.