Review Article

Cost effectiveness of prostate cancer radiotherapy

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Abstract: The use of radiotherapy in the treatment of prostate cancer has evolved from treatments utilizing large fields with hand placed blocks to radiotherapy treatments given with a linear accelerator moving around the patient on a robotic arm. These technologic developments have allowed radiation dose escalations resulting in improvements in disease and patient reported outcomes with longer biochemical disease-free survival (DFS) as well as improved quality of life. Increased costs have accompanied these technologic improvements with some private payers questioning the increased cost of the newer treatments and in some instances refusing to pay for some treatment modalities such as intensity-modulated radiotherapy (IMRT) or proton beam therapy (PBT). Cost-effectiveness analysis have been used in an attempt to illustrate these new treatments were cost-effective when compared to the older treatments. Cost-effectiveness analyses will need to be adapted in the current health care environment to provide an assessment of value as many payers, including medicare, move to a value-based reimbursement system.

Keywords: Prostate cancer; radiotherapy; cost-effective

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Introduction

Radiotherapy, either alone or combined with hormone therapy, is an effective treatment for patients with all stages of prostate cancer. Higher doses of radiotherapy, resulting in greater biochemical disease free survival, have been made possible by advances in treatment planning computers as well as improvement in linear accelerator technology. The higher radiation doses can be delivered to the prostate and peri-prostatic tissue while being able to spare normal tissues with the resultant reduction in toxicity. These advancements have been covered in great detail in previous papers of this special issue and will not be covered here.

Needless to say, however, the technologic improvements moving from 2D treatment planning and treatments to 3D treatments and finally intensity-modulated radiotherapy (IMRT) have resulted in higher costs per treatment course. In addition, the increased use of proton therapy in the treatment of prostate cancer has also resulted in a debate whether new technologies that are costlier be subjected to an in depth analysis, including cost-effectiveness, prior to routine incorporation into clinical practice.

Prostate cancer was the most frequent cancer site studied by cost-effectiveness analysis between 1977 and 2016 (1). The reason for this may be the number of treatments usually lasting over 7–8 weeks or the high cost of treatment, especially in the new healthcare reimbursement era we find ourselves today, or a combination of both. This review is divided into sections depending upon the comparisons between treatment modalities. The first section is economic analyses of different treatment delivery methods while the second section is comparisons of adjuvant treatments combined with radiotherapy. The third section outlines analyses of radiotherapy versus other treatment including watchful waiting or active surveillance and the fourth section reports on other economic analysis related to radiotherapy and prostate cancer.

Economic analysis of various radiotherapy treatment delivery methods

Treatment techniques have evolved over the course of many years as a result of the technologic advancement. Improvements in treatment planning software as well as linear accelerators have allowed treatment techniques to transition from 2-dimensional treatment plans and techniques to 3-dimenesional treatment plans and then to IMRT. The increased work necessary for physicians, dosimetrists, and physicists needed to design and perform quality assurance resulted in increased reimbursement, both on the professional and technical sides. The development and implementation of IMRT was made possible by the further improvements in treatment planning software and linear accelerators, with the advent of multi-leaf collimators. IMRT treatment techniques, as reported elsewhere in this issue, made it possible to escalate the delivered radiotherapy dose while reducing both acute and late toxicity. The increased in delivered radiotherapy dose resulted in higher biochemical disease-free survival (DFS). IMRT was rapidly adopted as the standard of care in the treatment of prostate cancer because of these results without randomized clinical trials comparing IMRT to 3D conformal radiotherapy (3DCRT). Reimbursements for IMRT, however, were considerable higher when compared to 3DCRT dramatically increasing the overall cost of care for prostate cancer. Economic analyses using decision models were performed to provide evidence of cost-effectiveness of IMRT compared to 3DCRT.

Three-dimensional radiotherapy compare to IMRT

Using a Markov model and from a payer perspective, Konski *et al.* compared 81 Gy delivered with IMRT to 78 Gy delivered with 3DCRT in a 70-year-old male with intermediate prostate cancer (2). The expected mean cost in US dollars and quality adjusted life years (QALY's) of IMRT and 3DCRT was $47,931 and $21,865 and 6.27 and 5.62 respectively. Therefore, the incremental cost-effectiveness ratio (ICER) was $40,101/QALY, below the generally accepted range of $50,000/QALY. A sensitivity analysis found IMRT would not be cost-effective if the utility values of IMRT were the same as the utility values of 3DCRT.

Yong and colleagues reported a similar analysis from the Canadian perspective (3). A Markov model was developed comparing IMRT and 3DCRT in the treatment of a 70-year-old male with localized prostate cancer. Reduced gastrointestinal toxicity in patients treated with IMRT was assumed with similar biochemical DFS between the two treatments. An ICER of CAN $26,768/QALY as a result of less toxicity experienced in patients treated with IMRT.

A similar analysis from the UK perspective was reported by Hummel *el al.* from a National Health Service (NHS) perspective (4). Using a discrete event simulation, IMRT resulted in an improvement in biochemical disease free relapse with IMRT favored over 3DCRT with an ICER of £ <20,000. But in comparison to the previous two studies, when survival was equivalent and only differences were seen in late gastrointestinal toxicity, IMRT was not found to be cost-effective.

Shah and colleagues performed what was described as a cost-effectiveness study of over a thousand patients treated at a single institution between 1992 and 2008 comparing low dose rate brachytherapy, high dose rate brachytherapy and IMRT. They reported no difference in 5-year biochemical disease free survival between the treatments. The calculated reimbursement was lowest for low dose rate brachytherapy, $9,938, intermediate for high dose rate brachytherapy, $17,514, and highest for IMRT, $29,356.

Post-prostatectomy radiotherapy

IMRT compared to 3DCRT was evaluated in men having post-prostatectomy radiotherapy. Carter *et al.* compared IMRT to 3DCRT in a 65-year-old Australian male using a Markov model over a 20-year time horizon and undertaken from an Australian health care cost perspective (5). IMRT was found to produce an ICER of $41,572/QALY and after 20 years IMRT resulted in a mean incremental cost of $32,816 compared to $33,917 for 3DCRT. The authors report an approximate $1.1 million savings per 1,000 patients treated. Incremental gains in QALY were also reported with the use of IMRT. Therefore, IMRT was found to be dominant being more effective and less costly when compared to 3DCRT.

Showalter and colleagues investigated the cost-effectiveness of adjuvant post-prostatectomy radiotherapy compared to observation with the use of a Markov model using data from SWOG 8794. The perspective was from the payer perspective, Medicare, with the primary outcome measure being ICER per prostate-specific antigen success over a 10-year time horizon. As one would expect, immediate adjuvant radiotherapy results in a higher PSA success when compared to initial observation with an ICER of $26,983/PSA success (6).

Cost-effectiveness of proton beam radiotherapy in prostate cancer treatment

A relative lack of cost-effectiveness in the use of proton beam therapy (PBT) in the treatment of prostate cancer was reported recently in a systematic review of cost-effectiveness of PBT (7). There has been conflicting results as to the cost-effectiveness of PBT in the treatment of prostate cancer. Using a societal perspective, Lundkvist *et al.* used a Markov model to evaluate proton therapy against standard conformal radiotherapy in the treatment of a 65-year-old man with prostate cancer with no mention of the stage. The ICER was reported as €26,800/QALY (8). Another study however, had a different conclusion finding proton therapy not cost-effective in a 70-year-old man with prostate cancer with an ICER of $63,578/QALY and an ICER of $55,726 in a 60-year-old man with prostate cancer. One can argue today that the ICER should be $100,000/QALY and if so the results could be considered cost-effective. A nuance of this study was the authors' assumption that patients receiving PBT would receive 81 Gy because of the potential ability of PBT to spare normal tissue compared to IMRT. It was assumed the biochemical DFS would be improved because of the higher dose. There are no current studies utilizing a higher dose in patients receiving PBT when compared to patients receiving IMRT (9). A lifetime Markov model was used to evaluate the use of IMRT, PBT and stereotactic body radiotherapy (SBRT) in the treatment of a 65-year-old man with localized prostate cancer (10). A full description of SBRT in the treatment of localized prostate cancer can be found in other areas of this manuscript. Analyzing from a societal perspective, SBRT was the least expensive treatment with a lifetime cost of $24,873. IMRT was the second least expensive at $33,068 with PBT slightly more than double the cost of IMRT at $69,412. SBRT was found to be dominated treatment, i.e., cost less and was more effective than its comparators. Treatment with SBRT resulted in 8.11 QALY's while IMRT had the lowest with 8.05 and PBT slightly higher with 8.06.

Hypofractionated radiotherapy

Standard radiotherapy for prostate cancer consists of daily radiotherapy treatments Monday through Friday for 7–8 weeks. This can cause a strain on patients and families and increased the indirect cost of care because of travel costs and loss of work. These costs are bourn directly by the patient and family. As described previously in this issue, hypofractionated radiotherapy has been found to provide equivalent results with fewer treatments. A Markov model was used to compare high-dose IMRT and hypofractionated IMRT (HFIMRT) to 3DCRT in a model cohort with an average age of 70 years of men in Hungary diagnosed and treated with a time horizon of 10 years (11). The analysis was performed from the perspective of the public payer in Hungary. Transition probabilities were calculated for men with low, intermediate and high-risk prostate cancer. The model cohort transition probabilities were similar to men with intermediate-risk prostate cancer. The authors reported a total discounted cost of IMRT of €329 lower than 3DCRT with IMRT provided an additional 0.203 QALY's resulting in IMRT being the dominant strategy. HFIMRT was €1,141 lower than 3DCRT with an almost equivalent improvement in quality adjusted survival of 0.204 QALY's.

Cost-effectiveness of SBRT in the treatment of localized prostate cancer

A cost-effectiveness analysis comparing SBRT to IMRT in the treatment of a 65-year-old man with low-risk prostate cancer was performed using a Markov model with a Monte Carlo simulation by Sher *et al.* IMRT to a total dose of 75.6 Gy in 1.8 Gy fractions was compared to a 5-fraction SBRT regimen. A payer perspective was taken in the analysis with both a robotic and a non-robotic SBRT treatment evaluated as Medicare is the only payer to distinguish between the two treatment platforms. Since worse toxicity was assumed for SBRT the QALY life expectancy was worse for SBRT. The ICER for IMRT when compared to robotic and non-robotic SBRT were $285,000 and $591,100/QALY respectfully (12). This is a result of the IMRT being more expensive when compared to SBRT. SBRT is the more cost-effective even in sensitivity analysis because of the cost of IMRT in relation to SBRT. SBRT was the most cost-effective in this analysis and probably would have even been more cost-effective had the authors performed the analysis from a societal perspective and included the indirect costs of travel and the opportunity costs of missing work for treatment.

A cost-utility analysis was performed from the Canadian perspective comparing SBRT with low dose-rate brachytherapy in the treatment of localized low-risk prostate cancer in a 66-year-old man using a Markov model. SBRT was found to be the dominant strategy with an improvement in 0.029 QALY's at a cost savings of

CAN$2,615 (13). The results of the study were sensitive to the biochemical recurrence probability with low-dose rate brachytherapy being marginally more effective if the assumption was made of similar biochemical recurrence for both treatments with the ICER being CAN$272, 848/QALY.

A SEER-Medicare study was performed investigating SBRT, brachytherapy, IMRT and PBT in the treatment of Medicare-aged men, 65 years and older, with prostate cancer between 2004–2011 (14). A total of 542 men were treated with SBRT, 800 treated with PBT, 9,647 treated with brachytherapy, and the vast majority of men were treated with IMRT, 23,408. A significant increase in the use of PBT and SBRT was noted over the study period while the use of brachytherapy decreased. Cost of treatment was calculated by summing the total amount paid for inpatient, outpatient and physician services during the year prior to and following prostate cancer diagnosis. The median cost of SBRT was $27,145, while brachytherapy cost was the cheapest at $17,183. IMRT was the second most expensive at $37,090 and PBT being the most expensive at $54,706. The cost of treatment of late complications occurring more than 1 year after completion of treatment was not captured in this analysis. The side effect profile differed for each treatment which would have affected the QALY had a cost-utility analysis been performed. SBRT was associated with more urinary incontinence when compared to IMRT and PBT. SBRT was also associated with more erectile dysfunction as well. Clinical outcomes were not reported in this analysis.

Hodges *et al.* performed a cost-utility analysis using a Markov model comparing SBRT and IMRT in a 70-year-old male with organ confined prostate cancer. The patient was assumed to have a PSA ≤15 and ≤ T2b disease. The analysis had a 10-year time horizon and was performed from a payer perspective. The authors assumed equal effectiveness between the treatments. SBRT was found to dominate IMRT with an ICER of <$50,000/QALY (15). The results of the probabilistic sensitivity analysis found the results to be sensitive to the effectiveness and quality of life assumptions.

Economic analysis of adjuvant therapy with radiotherapy

Konski *et al.* investigated the cost-effectiveness by means of a Markov model of the addition of total androgen suppression in men with locally advanced prostate cancer treated on Radiation Therapy Oncology Group trial 86–10. This trial treated men with conformal radiotherapy with half receiving total androgen suppression consisting of 4 months of goserelin every 4 weeks and flutamide 2 months prior to and during the radiotherapy and the other half to radiotherapy alone. The analysis was from a payer's perspective, i.e., Medicare. The ICER for the use of radiotherapy and total androgen suppression was well within the range of cost-effectiveness of $2,153/QALY with a >80% probability of cost-effectiveness on the cost-effectiveness acceptability curve (16).

Neymark and colleagues performed an economic analysis of a very similar EORTC trial, EORTC 22863 which compared radiotherapy to radiotherapy plus adjuvant hormonal therapy. This study differed to the one published by Konski *et al.* in that the authors collected costs for the 90 patients randomized and treated at the Centre Hospitalier Universitaire (CHU) of Grenoble, France. Resource use was abstracted from radiotherapy, urology and other hospital charts and the analysis performed from the French health insurance perspective. The addition of hormone therapy increased the mean survival time by about 1 year while reducing the cost per patient for the French health insurance by 12,700 FF (17).

Economic analysis comparing radiotherapy with other treatments

There have been numerous studies investigating active surveillance to treatment in patients with low-risk prostate cancer given the controversy of whether treatment is actually beneficial in these patients. Hummel *et al.* investigated a number of treatment options via a Markov analysis in the treatment of a 65-year-old man with a well differentiated prostate cancer from the UK NHS perspective. The treatments were watchful waiting, radical prostatectomy, cryotherapy, brachytherapy, 2D and 3D radiotherapy. Brachytherapy had the highest QALY's, 9.28, while watchful waiting had the lowest cost, £1,714. The authors used 2D radiotherapy as a reference case. The ICERs for 3DCRT was £683, brachytherapy £8,575 and cryotherapy £111,316 (18). 3DCRT and brachytherapy was considered cost-effective whereas cryotherapy was not. This study was published in 2003 so it is hard to imagine the relevance of these conclusions in today's current environment.

Ollendorf *et al.* performed an analysis of the cost-effectiveness of active surveillance, brachytherapy, IMRT, PBT and radical prostatectomy in the treatment of a 65-year-old man with low risk prostate cancer from a payer's perspective, i.e., Medicare. Using radical prostatectomy as a base case, the ICERs for active surveillance was $1,803, IMRT $35,233 and PBT $169,867 (19). Brachytherapy was found to provide the highest value costing less than active surveillance, $25,484 versus $30,422.

A similar study was reported by Hayes and colleagues. Watchful waiting or active surveillance was compared to brachytherapy, IMRT, and radical prostatectomy in a 65- and 75-year-old with low-risk prostate cancer. A US societal perspective was taken for the analysis. Watchful waiting was the least expensive in both the 65- and 75-year-old, $24,000 and $18,302 respectively, and provided the highest QALY in both as well (20). Brachytherapy once again provided the best value among the treatments evaluated having the highest QALY's, 8.14, and being the least costliest, $35,374.

Cooperberg *et al.* compared three different types of radical prostatectomy, open, laparoscopic or robotic, with 3DCRT, brachytherapy, IMRT or a combination of external beam radiotherapy with brachytherapy in a 65-year-old male with low, intermediate and high risk prostate cancer (21). A Markov model was used with Monte Carlo probabilistic sensitivity analysis from a US payer perspective, i.e., Medicare. Brachytherapy was consistently less expensive amongst the radiotherapy treatment options and IMRT the most expensive. Robotic prostatectomy was the least expensive and provided the greatest QALY's of all the treatment options across all of the disease sites evaluated.

Miscellaneous economic analyses pertaining to radiotherapy and prostate cancer

Rectal toxicity remains an important concern in the use of radiotherapy in the treatment of men with prostate cancer. The prostate is directly anterior to the rectum with the anterior rectal wall receiving the given dose of radiotherapy. Strategies have been developed to try and increase the distance between the anterior rectal wall and the prostate. The use of spacers made of hydrogel injected between the prostate and rectum has been developed in an attempt to increase the therapeutic ratio between normal tissue and the prostate. The use of these spacers has increased the incremental cost and has been evaluated in two cost-effectiveness analysis. Vanneste *et al.* used a Markov model investigating the use of spacers in the treatment of patients with prostate cancer over a 5-year time horizon. The age and stage of the base case was not specifically mentioned. The analysis was performed from the Netherland government perspective. Patients treated with a spacer had lower rectal toxicity when compared to men treated without the spacer. Treatment follow-up and toxicity costs where €160 less in men treated with the spacer incurred a higher cost of €1,700 for spacer placement. The ICER for spacer use was €55,880QALY which was below the €80,000/QALY threshold for cost-effectiveness in the Netherlands resulting in a 77% probability of cost effectiveness (22).

This Markov model was used to test a virtual implantable rectum spacer (IRS) in 16 patients, 8 with a rectal balloon implant (RBI) and 8 with a hydrogel spacer. Patients were planned to receive 70 Gy with toxicity accessed using externally validated normal tissue complication probability models. Both the implantable rectal spacer and the virtual implantable rectal spacer improved the rectal volume receiving 75 Gy. The RBI was cost-effective in only 1 of 8 patients whereas the spacer was only cost-effective in 2 of 8 patients. The authors found the classification of the model, regarding the cost-effectiveness, to be 100% (23). They concluded the virtual approach when combined with toxicity prediction and cost effectiveness analysis to be a promising basis for decision support (23).

Another study of the cost-effectiveness of the use of a spacer in men with cT1–cT2c prostate cancer undergoing radiotherapy was performed from a US perspective with a decision tree model (24). The exact perspective of the analysis was not explicitly mentioned but the authors included direct and indirect costs in the analysis. The authors investigated conformal radiotherapy, IMRT and SBRT, both low and high dose. The use of a spacer was reported to be cost-effective for high-dose SBRT.

Daily imaging with an on-board imaging device is another technique used to attempt to minimize radiotherapy dose to normal structures in an attempt to reduce toxicity and improve quality adjusted survival. The hypothesis is reduced treatment margins could be used, and therefore less normal tissue irradiated, if daily imaging can be used to reduce set-up uncertainty. Das *et al.* reviewed the literature to assess cost of image guided radiotherapy strategies (25). The imaging modalities used to image the prostate include using daily ultrasound guidance, implanted fiducial markers, daily cone beam CT, implantable electromagnetic transponders, and cine MRI. Cost for fiducial marker placement was reported at $391 while electromagnetic transponder placement was $1,200/patient. The least expensive capital cost technique was ultrasound while the most expensive was MRI cine. Using a Medicare fee schedule for reimbursement, the daily cost for each modality was $67/day, $87/day, $143/day, $64–141/day and $3,000–4,000/scan for ultrasound, fiducial, cone-beam CT, electromagnetic transponders and cine MRI respectively.

Conclusions

Radiotherapy treatment of patients with prostate cancer has evolved with technologic advances. These advances, however, have increased the cost of treatment. Some treatment techniques have sought to minimize cost by reducing the number of treatments or improving the quality of life for the survivors by minimizing irradiation of sensitive surrounding normal tissue. Cost-effectiveness analyses have been used to justify the increased cost by comparing the newer treatment modalities to the standard of care at the time. These analyses were a proxy to show value as the overall cost of medical care has risen. Cost-effectiveness analyses of newer therapies, however, may need to morph into value evaluations as healthcare systems evaluate adopting value based payment models that use disease specific reimbursement.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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