COST EFFECTIVENESS ANALYSES OF RADIATION THERAPY TREATMENTS

by

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The impact of radiation therapy in cancer treatments has shown great improvement in clinical outcomes. Recent radiation therapy advances with innovative technologies have changed the standard of care in cancer treatments rapidly. Evolution in radiation therapy has demanded highly specialized trained resources and comes at substantial increase in cost. Even though evidence based treatments have demonstrated the important role of advanced radiation therapy technologies in various cancer treatments, the sustainability of quality healthcare in an increasingly resource constrained environment has been ongoing challenge. Therefore, economic evaluation for new treatment technologies has been requested to make the most effective use of resources.

In this dissertation, we evaluated cost effectiveness analysis (CEA) for various disease sites with innovative technologies. First, we conducted CEA of 3-dimensional (3D) image guided brachytherapy (IGBT) compared to conventional 2-dimensional (2D) high dose rate (HDR) brachytherapy for the treatment of locally advanced cervical cancer. We found that 3D IGBT is a cost effective strategy compared to 2D HDR brachytherapy with a willingness to pay (WTP) threshold of $50,000/quality adjusted life years (QALY) gained, strongly supporting the routine use of 3D image guided brachytherapy. Second, we performed a CEA of single fraction of stereotactic body radiation therapy (SBRT) compared with single fraction of external beam radiation therapy (EBRT) for palliation of vertebral bone metastases. We found that SBRT is not a cost effective treatment strategy compared to conventional EBRT with a WTP threshold of

$100,000/QALY gained in patients with relatively short life expectancy. Finally, we performed a CEA of stereotactic body radiation therapy (SBRT) compared to radiofrequency ablation (RFA) for inoperable colorectal liver metastases. We found that SBRT is not cost effective compared to RFA with a WTP of $100,000/QALY gained unless large tumor size is treated.

In summary, given increasing attention placed on healthcare costs, a cost-effectiveness analysis can provide the appropriate platform to compare these treatment options. Therefore, the findings from the papers in this dissertation will identify the proper treatment choice to improve clinical outcomes at a reasonable cost, incorporating economic considerations into clinical decision making.

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PREFACE

I would like to thank my primary mentors, Drs. Saiful Huq and Kenneth Smith, for all of their support and encouragement. Also, I thank my dissertation committee members, Drs. Sushil Beriwal, Mark Roberts and Galen Switzer, for their guidance and insight. As a full time clinical physicist in a very busy clinic and also being out of graduate school for 12 years, it was a huge challenge to return to graduate school for study. However, my work place- Radiation Oncology department at UPMC Magee Womens Hospital- provided me a great supportive environment to pursue my study and research. Every single class at the institute for clinical research education has taught me both basic and advanced clinical research methodologies and has been greatly valuable. All the teaching staff was phenomenal. I have enjoyed clinical research using what I learned from classes and mentors.

My three papers in this dissertation are highlights from multidisciplinary efforts between the Radiation Oncology department in University of Pittsburgh Cancer Institute, Health Policy and Management in University of Pittsburgh School of Public Health and Institute for Clinical Research Education in University of Pittsburgh School of Medicine. Through our successful collaboration, we published two papers early this year. Those studies are cost effectiveness analysis of three-dimensional image-guided brachytherapy compared to two-dimensional brachytherapy in the treatment of locally advanced cervical cancer (the paper included in chapter 2; published in *Brachytherapy,* January 2015) and cost effectiveness analysis of stereotactic body

radiation therapy compared to single fraction of external beam radiotherapy for palliation of vertebral bone metastases (the paper included in chapter 3; published in *International Journal of Radiation Oncology Biology Physics*, March 2015). The publishers retain the copyright for these materials. Our most recent project, cost effectiveness analysis of stereotactic body radiation therapy compared to radiofrequency ablation in the treatment of inoperable liver metastases from colorectal cancer (the paper included in chapter 4), is under review in a peer review journal.

1.0 INTRODUCTION

Approximately sixty percent of cancer patients have an indication to receive radiation therapy (1). The results from prospective clinical trials, observational studies and retrospective reviews have shown the importance of radiation treatment for cancer patients (2, 3). Over the last decade, the evolution in radiation therapy technologies has led to rapid changes in the standard of care for cancer treatment. That is, new evidence based treatments through novel high precision technologies have demonstrated the crucial role and position of radiation therapy (4, 5). However, in an era of ever expanding health care costs globally, clinical effectiveness is no longer sufficient to request funding or reimbursement. Economic evaluation for innovative technologies is required in an attempt to have a more cost-conscious health care environment (6, 7).

Cost–effectiveness analysis (CEA) is an important tool for incorporating economic considerations into clinical decision making. It examines the relative value of new interventions to provide a guideline for clinical decision making with greater focus on health care costs. Therefore, we identified advanced radiation treatment technologies to compare with the standard of care for different disease sites and perform cost-effectiveness analyses (8-10).

In project 1, we evaluate the cost effectiveness of 3-dimensional image guided brachytherapy (IGBT) compared to conventional 2-dimensional high dose rate (HDR) brachytherapy for the treatment of locally advanced cervical cancer. In project 2, we perform a

CEA of single fraction of stereotactic body radiation therapy (SBRT) compared with single fraction of external beam radiation therapy (EBRT) for palliation of vertebral bone metastases. Lastly, in project 3, we conduct a CEA of SBRT compared to radiofrequency ablation (RFA) for inoperable colorectal cancer liver metastases.

These subjects have not been investigated before and will focus greater attention on health economics in radiation oncology, providing a clear reference point for cost-conscious decision making in the management of various cancers. Therefore, our studies will provide practical knowledge in economic evaluation for various radiation treatments which have been of interest nationwide.

2.0 COST EFFECTIVENENESS ANALYSIS OF 3D IMAGE GUIDED BRACHYTHERAPY COMPARED WITH 2D BRACHYTHERAPY IN THE TREATMENT OF LOCALLY ADVANCED CERVICAL CANCER

2.1 INTRODUCTION

Intracavitary brachytherapy is an integral component in the definitive management of locally advanced cervical cancer (10-13). High-dose rate (HDR) brachytherapy has been increasingly adopted in place of low-dose rate since it can be delivered as an outpatient treatment, results in decreased radiation exposure to personnel, and allows for the reproducible positioning of applicators with the opportunity for optimization of the treatment plan (14, 15). Until the early 2000s, HDR brachytherapy plans for cervical cancer were generated by 2D orthogonal X-rays films (2D conventional brachytherapy) (16).

The advent of 3D image-guided brachytherapy (IGBT) is a major step forward for the field. IGBT enables clinicians to accurately define the target at risk and surrounding crucial structures. With this volumetric information, brachytherapy plans can be optimized to ensure adequate coverage of the target while minimizing dose to bladder, rectum and sigmoid. The published prospective and retrospective literature has shown that these advantages translate into improved local control and reduced morbidities (17-22). Perhaps the best evidence supporting IGBT use is a non-randomized, multi-institutional prospective study from France (23). In this

study, centers could utilize either a 2D or IGBT approach depending on their practice pattern. The authors recruited 235 patients who were treated with definitive chemoradiation therapy (n=118 for IGBT and n=117 for 2D). They found grade 3-4 toxicity was substantially reduced from 22% to 2.6% ($p<0.002$). In addition, local control and overall survival were 74% vs. 79% and 65% vs. 74% for 2D and IGBT, respectively. In 2005, GEC-ESTRO group published guidelines recommending IGBT use for cervical cancer (24). The main advantage of IGBT is the opportunity for dose optimization, which enables alteration of size and the shape of the classical pear-shaped isodose lines to more accurately conform to the target volume. In small tumors, the irradiated volume can be reduced in order to decrease the dose to critical organs, and in larger tumors, the prescription isodose depth can be expanded for better coverage. This improvement in target coverage and reduction in dose to critical organs is responsible for the superior results.

However, IGBT use does carry added costs. Typically IGBT requires the acquisition of cross-sectional imaging for treatment planning with each fraction of brachytherapy (24, 25). This not only adds costs for imaging, but also additional time for image acquisition and simulation, the availability of imaging machines, longer treatment planning time, and their associated costs. Whether the benefits afforded by IGBT are cost effective has not been previously studied. Such studies become more relevant with the increasing cost scrutiny in health care. Herein, we sought to investigate the cost effectiveness of IGBT compared to conventional 2D HDR brachytherapy for the treatment of locally advanced cervical cancer.

2.2 METHODS

2.2.1 Decision Model

To estimate the cost-effectiveness of HDR IGBT compared to conventionally planned brachytherapy for FIGO stage IB2-IVA locally advanced cervical cancer, we constructed a Markov state transition model comparing IGBT and conventional brachytherapy strategies. In the model, identical hypothetical cohorts were treated with five fractions of HDR brachytherapy using the ring and tandem applicator after external beam radiation therapy. The treatment scheme delivered 5 fractions of HDR brachytherapy, once or twice a week. For IGBT, treatment was performed either CT based plan for all fractions (5 CT scans) or MRI based plan for all fractions (5 MRI scans). Cohorts were followed for 3 years; the Markov cycle length was 1 month. The Markov model is based on 3-year survival estimates and complication rates (RTOG late grade $\geq$ 3) obtained from the literature (Table 2.1). For our model calibration, Markov cohort probability analysis was performed for the expected survival rates for both IGBT and conventional brachytherapy cohorts. That is, mortality likelihood was calculated at one and three year intervals and our model produced clinically reasonable survival rates. Modeling for 3 years, rather than for the cohort's remaining lifetime, tacitly assumes that all cost and effectiveness values are equal after 3 years regardless of treatment strategy, which could bias the analysis against the more effective strategy.

Treatment occurred in the first cycle of the model. Complications could occur in the post treatment phase and were modeled with an onset in the month after treatment. If complications occurred, those patients transitioned to the survive with complications state, where the chronic loss of health utility due to complications and the likelihood of requiring retreatment for

complications were tracked. Patients surviving without complications were tracked separately. Utility for each survival state was derived from the likelihood of local control and its associated health utility. Transitions to the dead state were based on previously reported strategy-specific mortality rates (17- 23) and US life table data for females for mortality from other causes (26).

Costs included both hospital and professional costs associated with IGBT and conventional brachytherapy based on Medicare reimbursement in 2013 (Table 2.2). The effectiveness term was quality adjusted life years (QALYs), accounting for quality of life differences between treatment strategies using quality of life utility weights. These were obtained through literature review (27, 28). QALYs are the product of a health state's quality of life utility and time spent in that state. Both costs and utilities were discounted at an annual rate of 3%. The base case model was developed from the health care system perspective. TreeAge Pro Suite 2013 software (TreeAge Software, Williamstown, MA) was used to build the Markov model.

2.2.2 Model Assumptions

We assumed that, except for differences the frequency of RTOG late grade 3 or higher complications after brachytherapy between IGBT and conventional treatment strategies, other complications would occur at the same frequency, perhaps biasing against IGBT. The probabilities of survival, tumor local control and complications for both treatment strategies were obtained from the 3-year survival clinical outcome data (18, 20, 21, 23, 30-34), thus assuming that patients in study cohorts were similar to those seen in the general population.

2.2.3 Costs

Table 2 shows the cost estimates for brachytherapy treatment based on CPT codes for Medicare reimbursement unadjusted national rates in year 2013. The billing accounted for technical (hospital) and professional (physician) fees for 5 fractions of brachytherapy. Total reimbursement was $21,373 and $17,931 for IGBT-CT based and 2D X-ray film based conventional brachytherapy, respectively. Furthermore, we estimated total costs for IGBT-MR image based and it was estimated at $22,847. These costs were varied +/- 20% in 1-way sensitivity analyses based on regional variation in Medicare reimbursement. The treatment cost for complications and its variation was based on Healthcare Costs and Utilization Project (H-CUP) database using ICD-9 code (35). Our assumption for complication cost was based on a cost of surgical intervention for rectal bleeding (Proctitis; Table 2.1).

2.2.4 Utilities

The quality of life utility values are listed in Table 2.1. For brachytherapy treatment, we used utilities for IGBT and 2D conventional brachytherapy as 0.8 and 0.7, respectively (27, 28), with the consideration of applicator insertion at the time of brachytherapy as well as procedure duration. Due to longer procedure time with 3D plan, IGBT has lower utility than 2D brachytherapy at the time of treatment. In addition, utility post treatment was estimated at 0.86 (28). We estimated utility for tumor local control and no control as 0.95 and 0.65, respectively. Utility for tumor local control was estimated based on the average of utility for no treatment without symptoms and utility post treatment from a study that elicited utilities for cervical cancer (28). For no tumor control utility, it was derived based on the average value of utility for local

recurrence and distant metastases using breast cancer as a proxy (29).For loss in quality of life with complications, the grade 3 rectal bleeding utility (36) was used as a base value.

2.2.5 Cost Effectiveness Analysis

Treatment strategies were compared using the incremental cost effectiveness ratio (ICER). That is, the ratio of the cost increment of one strategy over the other relative to the improvement in QALYs. There is no US consensus on a cost-effectiveness (C/E) criterion, however, interventions costing less than $100,000 per QALY gained are typically considered economically reasonable while those costing much more than this figure are felt to be an expensive use of health care resources (37, 38). A $50,000 per QALY gained criterion is commonly cited as the minimum of willingness-to-pay (WTP) (37, 39), thus we used WTP threshold of $50,000/QALY gained as our C/E criterion.

2.2.6 Sensitivity Analysis

We performed one-way, two-way and probabilistic sensitivity analyses to account for uncertainty in clinical assumptions. One way sensitivity analysis, where all parameters are varied individually, was examined to detect the effect of these variations on model results. A two-way sensitivity analysis varies two parameters simultaneously and denotes where a particular strategy is preferred. We performed a two-way sensitivity analysis to determine the optimal treatment strategy when cost and survival differences between 3D and 2D treatments are varied. The probabilistic sensitivity analysis using a Monte Carlo simulation was conducted to vary all parameters simultaneously. That is, distributions for each parameter (Table 2.1) were sampled at

random during 5000 trials and results reported as the percentage of trials in which a strategy is cost effective at a series of societal WTP (or acceptability) thresholds. Costs were modeled using a normal distribution with a standard deviation of 25% of the base case value, resulting in cost distributions varying from 50%-150% of the base cost, to account for the possibility of greater cost variation than the +/- 20% tested in 1-way sensitivity analyses. For utilities and probabilities, we used a beta distribution function for sampling (40).

Table 2.1 Model assumption-clinical parameters

Costs	Base Cost	Range *	Assumed distribution**
Cost for complication [a] (rectal bleeding/proctitis: ICD-9 569.49)	$8,394	±375	Normal
Cost for 2D treatment [b]	$17,177	± 20%	Normal
Cost for 3D treatment with CT plan [b]	$21,374	± 20%	Normal
Cost for 3D treatment with MR plan [b]	$22,847	± 20%	Normal
Utility and probability	**Base Estimate**	**Range**	**Assumed distribution**
Probability of complication with 2D [c]	0.1	0.07-0.15	Beta
Probability of complication with 3D [c]	0.05	0.02-0.07	Beta
Probability of survival with 2D [c]	0.65	0.55-0.7	Beta
Probability of survival with 3D [c]	0.7	0.65-0.85	Beta
Probability of local control (2D) [c]	0.8	0.65-0.85	Beta
Probability of local control (3D) [c]	0.9	0.85-0.95	Beta
Probability of retreatment of complication [c]	0.1	0.03-0.15	Beta
Disutility with acute complication [c]	-0.4	0.35-0.5	Beta
Utility of Complication [c] (for rectal bleeding complication)	0.6	0.55-0.65	Beta
Utility of local control [c]	0.95	0.9-0.97	Beta
Utility of not having local control [c]	0.65	0.6-0.7	Beta
Utility of post treatment [c]	0.86	0.8-0.9	Beta
Utility of survival [c,d]	calculate		
Utility of survival with complication [c,e]	calculate		
Utility of 2D treatment (at the time of brachytherapy)c	0.8	0.75-0.85	Beta
Utility of 3D treatment (at the time of brachytherapy)[c]	0.7	0.65-0.75	Beta

Note: ICD-9 = International Classification of Diseases, Ninth Revision; 2D = two-dimensional; 3D = three-dimensional.

a: Healthcare Costs and Utilization Project H-CUP

b: Medicare National unadjusted rate 2013

c: See references in text

d :(pLocalControl*uLocalControl)+(1-pLocalControl)*uNoLocalControl

e: ((pLocalControl*uLocalControl)+(1-pLocalControl)*uNoLocalControl)*uComp

*: For one-way sensitivity analysis

**: For probability sensitivity analysis

Table 2.2 Medicare reimbursement unadjusted national rate 2013 for hospital setting

CPT	Description	TC Quantity	PC Quantity	Total Medicare Reimbursement ($) 3D	Total Medicare Reimbursement($) 2D
77280	Simple simulation for X-ray	5	5	N/A	754.15
77014	CT scan for therapy guide	5	0	NOT REIMBURSABLE	N/A
76498	MR scan for therapy guide	5	0	1,473.90	N/A
77263	MD treatment plan complex	0	1	166.58	166.58
57155	Insert uteri tandem/ovoids	5	5	8,346.55	8,346.55
77295	3D treatment plan	5	5	6,296.05	N/A
77328	Brachytx isodose plan compl	5	5	N/A	2,099.55
77332	Radiation treatment aid(s)	1	1	241.79	241.79
77786	Hdr brachytx 2-12 channel	5	5	4,512.66	4,512.66
77336	Radiation physics consult	1	1	189.52	189.52
77370	Special physics consult	1	1	229.28	229.28
C1717	Brachytx, non-str,hdr ir-192	5	5	1,391.25	1,391.25
	TOTAL REIMBURSEMENT			**21,373.70 (CT) 22,847.60 (MR)**	**17,931.32**

Note: CPT= Current Procedural Terminology; TC = technical (hospital) charge; PC = professional (physician) charge; 3D = three-dimensional; 2D = two-dimensional;

N/A = not applicable; HDR= high dose rate; Ir-192=iridium 192 source

2.3 RESULTS

2.3.1 Base Case Analysis

In the base case analysis, the IGBT strategy cost $3003 more than 2D while gaining 0.16 QALYs, resulting in an ICER of $18,634 per QALY gained (Table 2.3). For MR imaging, rather than CT, IGBT cost $27,774 per QALY gained compared to 2D.

2.3.2 Sensitivity Analyses

In one-way sensitivity analyses, which varied all parameters individually, results were sensitive to variation of 3D and 2D treatment costs, survival rate with 3D and 2D treatment, tumor local control with 2D treatment and complication probability of 2D treatment in order (Figure 2.1). That is, our model is the most sensitive to variation of 3D treatment cost (range: ICER of -$9750 to $43,000/QALY gained), but the ICER remained <$50,000/QALY gained if IGBT costs were <$25,200 (the upper value in our clinical assumption for 3D cost range for CT planning; baseline point estimate $21,373). If IGBT cost is less than $18,375, IGBT would be a dominant strategy, i.e., a cost-saving, more effective treatment. A two way sensitivity analysis, using a $50,000 per QALY gained threshold showed that IGBT is always preferred when 1) the cost difference between 3D and 2D treatment is $5000 or lower regardless of the survival difference between 3D and 2D treatment, or 2) the survival difference between strategies is greater than 7.1% regardless of the cost difference (Figure 2.2). A Monte Carlo probabilistic sensitivity analysis, which varied all model parameters simultaneously 5000 times, demonstrated that IGBT-CT was favored in 63% of model iterations at a $50,000/QALY gained threshold and in 72% if a $100,000/QALY

threshold was used (Figure 2.3). In addition, IGBT-MR was favored in 62% of model iterations at a $50,000/QALY gained threshold and in 69% if a $100,000/QALY threshold was used.

Table 2.3 ICER for 3D IGBT compared with 2D brachytherapy

Strategy	Cost ($)	Incremental cost ($)	Effectiveness (QALY)	Incremental effectiveness (QALY)	ICER ($ per QALY gained)
2D	18,817	-	2.01	-	-
3D IGBT (CT)	21,820	3003	2.17	0.16	18,634
*3D IGBT (MRI)	23,293	4476	2.17	0.16	27,774

Note: ICER =incremental cost-effectiveness ratio; IGBT= image guided brachytherapy; QALY=quality adjusted life- year; * 3D IGBT (MRI) compared to 2D conventional brachytherapy

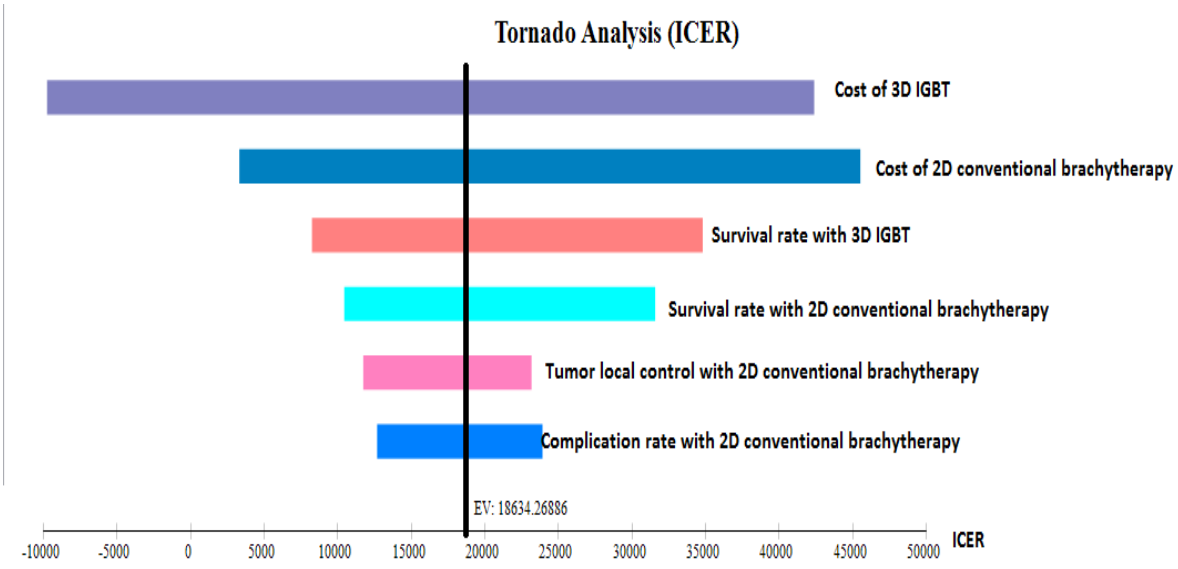

Figure 2.1 ICER Tornado diagram for one-way sensitivity analysis

Note: The central line represents the base-case value ($18,634). Costs of 3D and 2D treatment are top two most sensitive parameters to the model. ICER varies from $-9750 to $43,000 for the variation of 3D treatment cost. ICER = incremental cost-effectiveness ratio; 3D = three-dimensional; IGBT = image-guided brachytherapy; 2D = two-dimensional.

Figure 2.2 Two-way sensitivity analysis

Note: The x-axis represents the difference in costs between 3D and 2D treatments. The y-axis is the difference in survival between 3D and 2D treatments. The ‘‘X’’ on the graph represents the baseline values. Area above the line slope represents that 3D image-guided brachytherapy is a favored strategy.

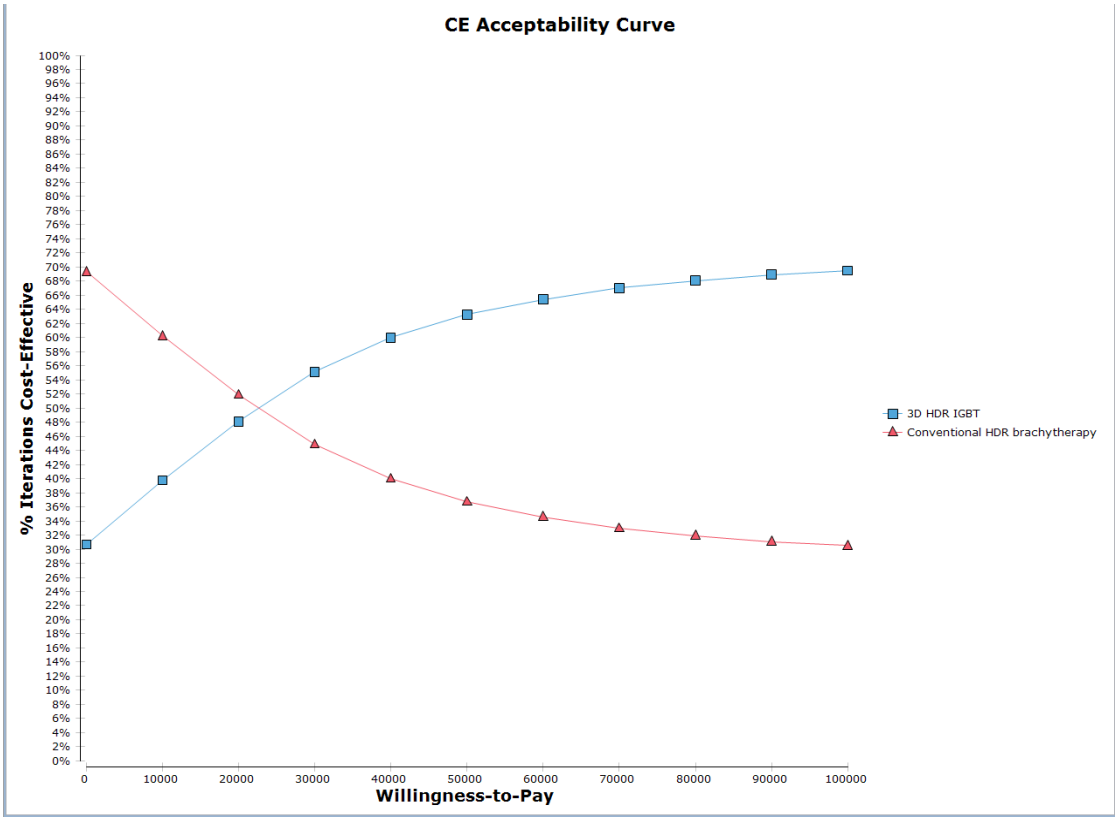

Figure 2.3 Probabilistic sensitivity analysis

Note: Cost effectiveness (CE) acceptability curve, showing the likelihood that strategies would be considered cost-effective (on the y-axis) over a range of willingness-to-pay (or acceptability) thresholds (the x-axis). Here, 3D IGBT has a 63% probability of being considered cost-effective at $50,000/QALY gained threshold.

2.4 DISCUSSION

This is the first study, to our knowledge, to evaluate the cost-effectiveness of 3D image-guided brachytherapy compared to conventional (2D) brachytherapy for locally advanced cervical cancer. Our analysis demonstrates that 3D IGBT for locally advanced cervical cancer is economically reasonable compared with 2D conventional brachytherapy, at a cost of about $18,634 per QALY gained for CT planning and $27,774 per QALY gained for MRI based plan. This finding was robust over a wide range of plausible clinical assumptions. In one-way sensitivity analyses, the ICER for 3D IGBT never exceeded $50,000 per QALY gained with variation of any individual model parameter. A probabilistic sensitivity analysis, varying all model parameters simultaneously, further supported 3D IGBT. These findings make a very compelling case for IGBT use in locally advanced cervical cancer based upon prior evidence of improved outcomes and our findings of economic reasonableness.

Even though interest in 3D IGBT for locally advanced cervical cancer has grown substantially, published outcome data has been limited. With greater focus on healthcare costs, cost-effectiveness analyses are important to identify treatment techniques that improve outcomes at a reasonable cost. Our study demonstrates that use of 3D IGBT with either cross-sectional imaging modality (CT or MR) was cost-effective.

There have been several other cost effectiveness analyses regarding locally advanced cervical cancer. Most have compared concurrent chemoradiation and adjuvant chemoradiation or chemoradiation and radiation alone (41-43). One study has assessed the cost effectiveness of intensity-modulated radiation therapy (IMRT) compared to conventional box-field radiation therapy (3D CRT) (34). In this analysis, IMRT cost >$100,000/QALY gained compared to 3D

CRT for locally advanced cervical cancer; extended field radiation treatment was on the borderline of cost effectiveness using a WTP threshold of $100,000/QALY.

There have been a number of other cost-effectiveness studies exploring new radiation technologies for other disease sites. Proton beam radiation was compared to IMRT for prostate cancer. The base cost of IMRT was $25,800 and proton therapy was $58,610. The authors found that for a 60-year old and 70-year old man, the ICER was $55,700/QALY and $63,600/QALY, respectively. Both were above the usual $50,000/QALY threshold (45). In contrast, our study found that the cost differential in absolute dollars between 3D and 2D brachytherapy was only about $3,400 and was associated with a greater reduction of toxicities, resulting in the favorable ICER.

There are several limitations in our study. First, as with most cost effectiveness analyses, the probabilities of survival, tumor local control and complications for both treatment strategies, were obtained from the available literature and primarily mainly retrospective studies. Also, quality of life utility values were extrapolated based on previously published values and tables with early stage cervical cancer who had chemotherapy and surgery, thus they may not precisely reflect the quality of life for HDR brachytherapy. Since this study model is limited to locally advanced cervical cancer patients, one way sensitivity analyses, varying these estimates, accounted for uncertainty. In addition, reported clinical follow up is 3 years or less, thus limiting our model time horizon to 3 years, which could overemphasize the contribution of acute toxicity and underestimate the disutility of long term complications. However, sensitivity analyses varying those factors did not appreciably change the favorability of IGBT. Similarly, through varying all parameters over wide ranges, we tested our model and consistently found that 3D IGBT-CT and MR are cost effective compared with conventional 2D brachytherapy. Finally,

while we assessed economic costs, other factors, such as added time, resources, education and availability of expertise for performing 3D image guided brachytherapy were not included in the model. The assessment in terms of societal perspective to include all other factors as well as economic costs is out of our study scope.

We used costs and utilities for treatment of rectal bleeding (grade 3; proctitis) as our baseline cost and utility for the treatment of complications. That is, we did not account for other grade 3-4 complications (vaginal or genitourinary) or for grade 1-2 complications. The exclusion of these other complications could bias the model against IGBT, since it assumes that those complications are identical between strategies. Were these other costs included, IGBT could be even more favorable than presented here. Additionally, there are a couple of different HDR fractionations used in routine practices. In USA, the most common fractionation schedule for HDR brachytherapy is 5 fractions, and we used it in this study (46). A final caveat is that costs were obtained from the Medicare reimbursement fee schedule and these may vary by region and with time. Despite these limitations, we found that the findings were robust and IGBT is the more cost effective treatment paradigm.

In conclusion, 3D IGBT for locally-advanced cervical cancer is a more cost effective option compared to 2D brachytherapy. These findings were robust to variation of parameter values, both individually and collectively, supporting the routine use of IGBT in locally-advanced cervical cancer.

3.0 COST EFFECTIVENESS ANALYSIS OF SINGLE FRACTION OF STEREOTACTIC BODY RADIATION THERAPY COMPARED WITH SINGLE FRACTION OF EXTERNAL BEAM RADIATION THERAPY FOR PALLIATION OF VERTEBRAL BONE METASTASES

3.1 INTRODUCTION

Back pain is the most common initial symptom of vertebral bone metastasis in late stage cancer (47, 48). It is often associated with neurological problems and decreased performance status (3). External beam radiotherapy (EBRT) has been an effective treatment for palliation of painful vertebral bone metastasis (50, 51). Conventional fractionated EBRT (largely 30 Gy in 10 fractions) has been mostly accepted for the palliative treatment even though dose-pain response is not well understood (52, 53). Radiation Therapy Oncology Group (RTOG) 97-14, which randomized patients to either 8Gy in a single fraction or 30Gy in 10 fractions for radiation treatment of bone metastases, has shown similar pain relief (the primary end point of this study) between the two study arms (47, 52). In addition, single fraction has proved more convenient for patients and caregivers. For this reason, 8 Gy in a single fraction is one of the acceptable options from the American Society for Radiation Oncology (ASTRO) consensus evidence-based standard of care for symptomatic bone metastases (48).

Recently, stereotactic body radiation therapy (SBRT) has demonstrated better pain control and neurological function as compared to historic results with conventional EBRT for spine

metastases (54-56). Unlike with EBRT, where concerns of spinal cord myelopathy have limited dose-escalation due to the proximity of the spinal cord to the vertebral body, improved precision of dose delivery with SBRT creates a sharp dose fall-off between the target and adjacent spinal cord. This high targeting accuracy allows a higher single fraction radiation doses to the vertebral target, while maintaining a safe spinal cord dose previously not feasible with EBRT (56). Clinical dose-response studies have reported that SBRT dose escalation to ≥ 16 Gy is associated with a strong trend toward improved pain relief (57-63).

RTOG 0631, a Phase III clinical trial comparing SBRT (16 or 18 Gy in 1 fraction) to EBRT (8Gy in 1 fraction) is an ongoing cooperative group trial which will lend further clarity about differences in efficacy between these two treatment modalities (49). The trial hypothesis is that SBRT can improve pain relief by 40%, in relative difference, compared to EBRT (SBRT 0.7 and EBRT 0.51; absolute difference 19%). In this study, we performed a cost effectiveness analysis of SBRT compared to EBRT in the palliative treatment of painful vertebral bone metastases assuming 20% absolute difference in pain control.

3.2 METHODS

3.2.1 Decision Model

We constructed a Markov state transition model comparing SBRT with single fraction EBRT for palliative treatment of painful vertebral bone metastases. In the model, identical hypothetical cohorts were treated with single fraction SBRT (16 or 18Gy) or EBRT (8Gy). Patients with spinal cord compression were excluded. Cohorts were followed over their remaining life time; the Markov cycle length was 1 month. The Markov model is shown in Figure 3.1 representing transition probabilities between health states based on medical literature-based treatment outcome and survival rates (Table 3.1) (47, 63-67). For our model calibration, Markov cohort probability analysis was performed for the expected survival rates for both SBRT and EBRT cohorts. That is, mortality likelihood was calculated and our model produced clinically reasonable survival rates. With a lifetime time horizon, our model cycled until the entire cohort had died.

Initial treatment occurred in the first cycle of the model. Patients who were alive had either pain relief or no pain relief after initial treatment. Patients who had pain relief after initial treatment could have continued pain relief over time, or could develop pain later. Those developing pain later and those with unrelieved pain after initial treatment could be retreated with the same radiation regimen or treated with pain medicine alone. Retreated patients could not receive any further radiation and stayed as unrelieved pain or pain relief state. Death was the absorbing state. Transitions to dead were based on previously reported survival rates (47, 63-67).

Costs included both hospital and professional costs associated with SBRT and EBRT based on Medicare reimbursement in 2014 (Table 3.2). The effectiveness term was quality adjusted

life years (QALYs), accounting for quality of life differences between treatment strategies using quality of life utility weights. These were obtained through literature review (68-74). QALYs are the product of a health state's quality of life utility and time spent in that state. Both costs and utilities were discounted at an annual rate of 3%. TreeAge Pro Suite 2013 software (TreeAge Software, Williamstown, MA) was used to build the Markov model. The base case model was developed from a payer's perspective for health care services, using Medicare reimbursement.

3.2.2 Costs

Table 3.2 shows the cost estimates for SBRT and EBRT based on CPT codes for Medicare reimbursement unadjusted national rates in year 2014. The billing accounted for technical (hospital) and professional (physician) fees for single fraction of each treatment strategy. Total reimbursement was $9,000 and $1,087 for SBRT and EBRT, respectively. Reimbursement rate varies geographically, thus sensitivity analyses were performed to include this variation.

3.2.3 Utilities

The quality of life utility values are listed in Table 3.1. For treatment state, we used utility values for both SBRT and EBRT as 0.45 (68-70). In addition, utility of post treatment was estimated at 0.55 for pain relief (69, 70) and 0.3 for unrelieved pain (69, 70). The utility for the retreatment state assumed to be less than initial utility of treatment (0.35). Sensitivity analyses were used to test utility value assumptions.

3.2.4 Cost Effectiveness Analysis

Treatment strategies were compared using the incremental cost effectiveness ratio (ICER) - the ratio of cost and QALY differences between strategies. There is no US consensus on cost-effectiveness (C/E) criterion, however, interventions costing less than $100,000 per QALY gained are typically considered economically reasonable while those costing much more than this figure are often felt to be an expensive use of health care resources (75-77). Thus we used willingness to pay (WTP) threshold of $100,000/QALY gained as our C/E criterion. In a sensitivity analysis, we also examined a $50,000 per QALY gained threshold, a commonly cited prior benchmark (78).

3.2.5 Sensitivity Analysis

We performed one-way, two-way and probabilistic sensitivity analyses to account for uncertainty in decision model assumptions. One-way sensitivity analysis, where all parameters are varied individually, was examined to detect the effect of these variations on model results. A two-way sensitivity analysis varies two parameters simultaneously and denotes where a particular strategy is preferred. We performed a two-way sensitivity analysis to determine the optimal treatment strategy when median survival rate and pain relief difference are varied. The probabilistic sensitivity analysis using a Monte Carlo simulation was conducted to vary all parameters simultaneously. That is, distributions for each parameter (Table 3.1) were sampled at random during 5000 trials and results reported as the percentage of trials in which a strategy is cost effective at a series of WTP (or acceptability) thresholds. Costs were modeled using a normal

distribution with a standard deviation of 25% of the base case value. For utilities and probabilities, we used a beta distribution function for sampling (79).

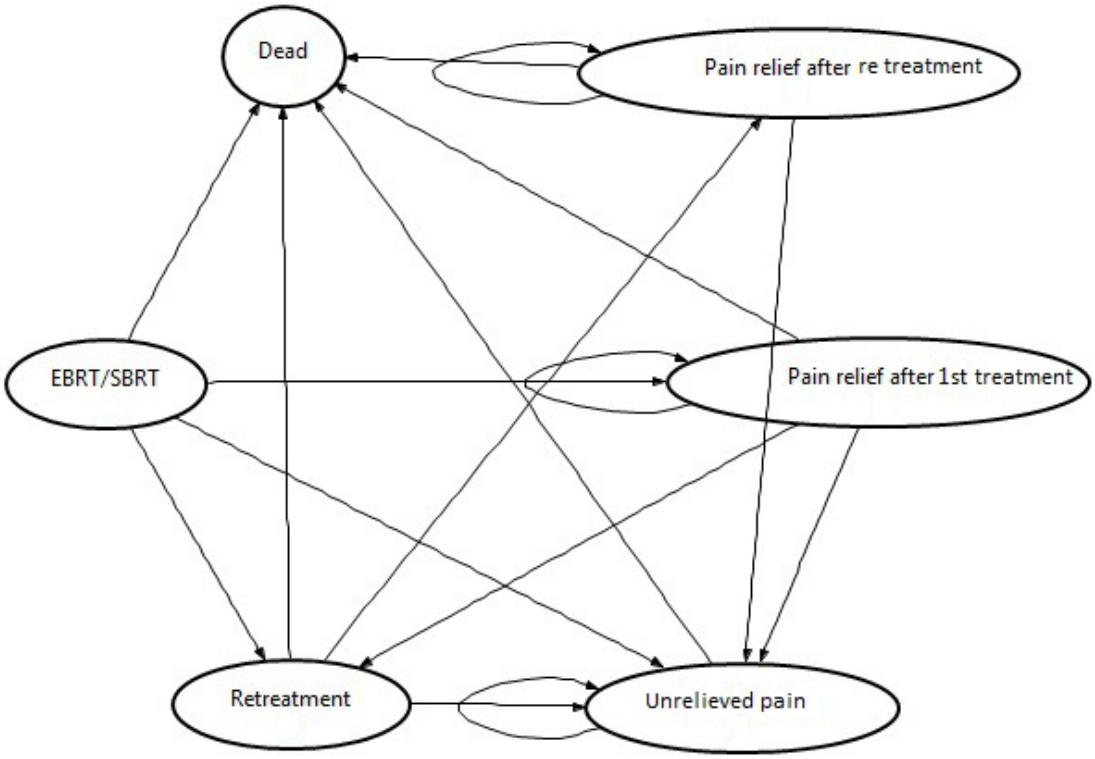

Figure 3.1 Markov transition model

Note: Arrows represent transition between health states. EBRT = external beam radiation therapy; SBRT = stereotactic body radiation therapy

Table 3.1 Model assumption-clinical parameters

Cost	**Base cost ($)**	**Range**	**Assumed distribution**
Cost for EBRT	1087	870-1304	Normal
Cost for SBRT	9000	7200-10800	Normal
Cost of retreatment with EBRT	1087	870-1304	Normal
Cost of retreatment with SBRT	9000	7200-10800	Normal
Cost of pain medication	200	100-400	Normal
Probabilities	**Base estimate**	**Range**	**Assumed distribution**
Median survival for both treatment strategy	9 months	7-24 months	Beta
Probability of pain relief after initial EBRT	0.6	0.45-0.77	Beta
Probability of pain relief after initial SBRT	0.8	0.75-0.85	Beta
Probability of retreatment after initial EBRT	0.15	0.12-0.28	Beta
Probability of retreatment after initial SBRT	0.05	0.03-0.1	Beta
Probability of pain relief after retreatment from EBRT	0.8	0.66-0.87	Beta
*Probability of pain relief after retreatment from SBRT	0.95	0.9-1	Beta
Probability of getting pain later after pain relief from initial EBRT	0.1	0.05-0.2	Beta
Probability of getting pain later after pain relief from initial SBRT	0.05	0-0.07	Beta
Probability of getting pain later after pain relief from retreatment of EBRT	0.1	0.05-0.15	Beta
Probability of getting pain later after pain relief from retreatment of SBRT	0.006	0-0.01	Beta
Probability of retreatment later time after initial EBRT	0.07	0.05-0.15	Beta
*Probability of retreatment later time after initial SBRT	0.03	0-0.05	Beta
Utilities	**Base estimate**	**Range**	**Assumed distribution**
Utility for EBRT	0.45	0.4-0.5	Beta
**Utility for SBRT	0.45	0.4-0.5	Beta
Utility for Retreatment	0.35	0.3-0.4	Beta
Utility for pain medication	0.3	0.2-0.5	Beta
Utility for pain relief after initial EBRT	0.55	0.4-0.7	Beta
**Utility for pain relief after initial SBRT	0.55	0.4-0.7	Beta
Utility for pain relief after retreatment with EBRT	0.55	0.4-0.7	Beta
**Utility for pain relief after retreatment with SBRT	0.55	0.4-0.7	Beta

Note: * Estimation from experts' opinions, ** same value as EBRT utility

Table 3.2 Medicare reimbursement unadjusted national rate 2014 for hospital setting

EBRT 1 fraction

CPT code	Description	TC Quantity	PC Quantity	Medicare Tech Reimbursement / Unit ($)	Medicare Prof Reimbursement / Unit ($)	Total Medicare Reimbursement ($)
77014	CT image guided treatment fields	1	0	0.00	0.00	0
77261	MD treatment plan (simple)	0	1	0.00	75.23	75.23
77280	Confirmation simulation	1	1	114.65	36.19	150.84
77305	Isodose plan	1	1	114.65	36.18	150.83
77332	Treatment device (simple)	1	1	213.49	28.30	241.79
77300	Basic dose calculation	1	1	114.65	32.24	146.89
77404	Treatment delivery	1	0	104.26	0.00	104.26
77336	Weekly physics	1	0	114.65	0.00	114.65
77431	Radiation treatment management	0	1	0.00	102.09	102.09
TOTAL						**1,086.58**

SBRT 1 fraction

CPT Code	Description	TC Quantity	PC Quantity	Medicare Tech Reimbursement / Unit ($)	Medicare Prof Reimbursement / Unit ($)	Total Medicare Reimbursement ($)
77014	CT image guided treatment fields	1	0	0.00	0.00	0
77263	MD treatment plan (complex)	0	1	0.00	166.58	166.58
77290	Simulation with SBRT	1	1	311.37	80.96	392.33
77295	3D simulation	1	1	1,036.39	222.02	1,258.41
77334	Treatment device (complex)	11	11	213.49	64.12	3,053.71
77300	Basic dose calculation	10	10	114.65	32.24	1,468.90
77373	Treatment delivery	1	0	1,921.30	0.00	1,921.30
77336	Weekly physics	1	0	114.65	0.00	114.65
77435	SBRT management course	0	1	0.00	633.71	633.71
TOTAL						**9,009.59**

Note: CPT = Current Procedural Terminology codes; CT = computed tomography; EBRT = external beam radiation therapy; MD = physician; PC = professional (physician) charge; SBRT = stereotactic body radiation therapy; TC = technical (hospital) charge.

3.3 RESULTS

3.3.1 Base Case Analysis

In the base case analysis, pain relief after the initial treatment was assumed to be 80% for SBRT and 60% for EBRT. In the model, total strategy costs, including all medical care costs, were $7380 greater for SBRT, which gained 0.06 more QALYs than EBRT, resulting in an ICER of $124,552 per QALY gained.

3.3.2 Sensitivity Analyses

In one-way sensitivity analyses, results were most sensitive to variation of the utility of unrelieved pain (range: $89,330 to $592,720/QALY gained). The utility of relieved pain after initial treatment and median survival were also sensitive to variation (Figure 3.2). If median survival is ≥11 months (base case estimate: 9 months), SBRT cost <$100,000/QALY gained. If median survival is ≥18 months, SBRT cost <$50,000/QALY gained. A two way sensitivity analysis, using a $100,000 per QALY gained threshold (Figure 3.3) showed that SBRT is always preferred when the median survival is more than 22 months regardless of difference in the likelihood of pain relief between strategies. In addition, if the absolute difference in the likelihood of pain relief is more than 28% with a base case 9 month median survival (relative difference 47% or higher: SBRT 88% or higher and EBRT 60%), SBRT could be a cost effective option. Probabilistic sensitivity analysis, which varied all model parameters simultaneously 5000 times, demonstrated that SBRT was favored in 30% of model iterations at a WTP threshold of $100,000/QALY gained (Figure 3.4).

In addition, we performed two scenario analyses based on current practice patterns. One assumed that retreatment was with SBRT regardless of initial therapy. Total costs were $6924 more for SBRT with 0.06 QALYs gained compared to EBRT, resulting in ICER of $ 116,871 per QALY gained. In the other, we compared EBRT 30Gy in 10 fractions to SBRT. Total costs were $5802 more for SBRT with 0.06 QALYs gained compared to EBRT, resulting in an ICER of $ 92,437/QALY gained.

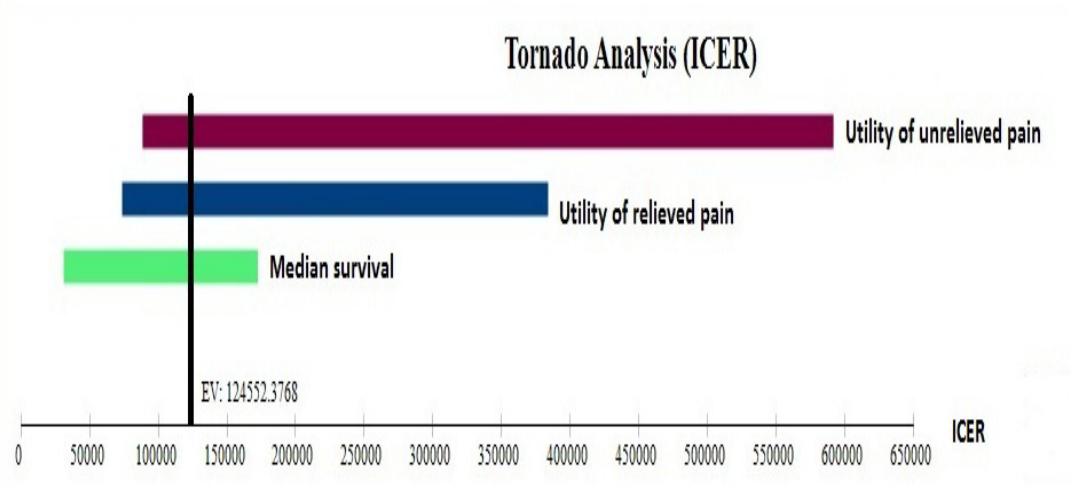

Figure 3.2 One-way sensitivity analysis

Note: Incremental cost-effectiveness ratio (ICER) Tornado diagram for 1-way sensitivity analysis. The vertical line represents the base case value of ICER ($124,552). Utility of unrelieved pain (range, $89,330 to $592,720/QALY gained), utility of relieved pain after the initial treatment (range, $74,339 to $384837/QALY gained), and median survival rate (range, $31,828 to $173269/QALY gained) were the parameters whose variations caused the greatest changes in model results.

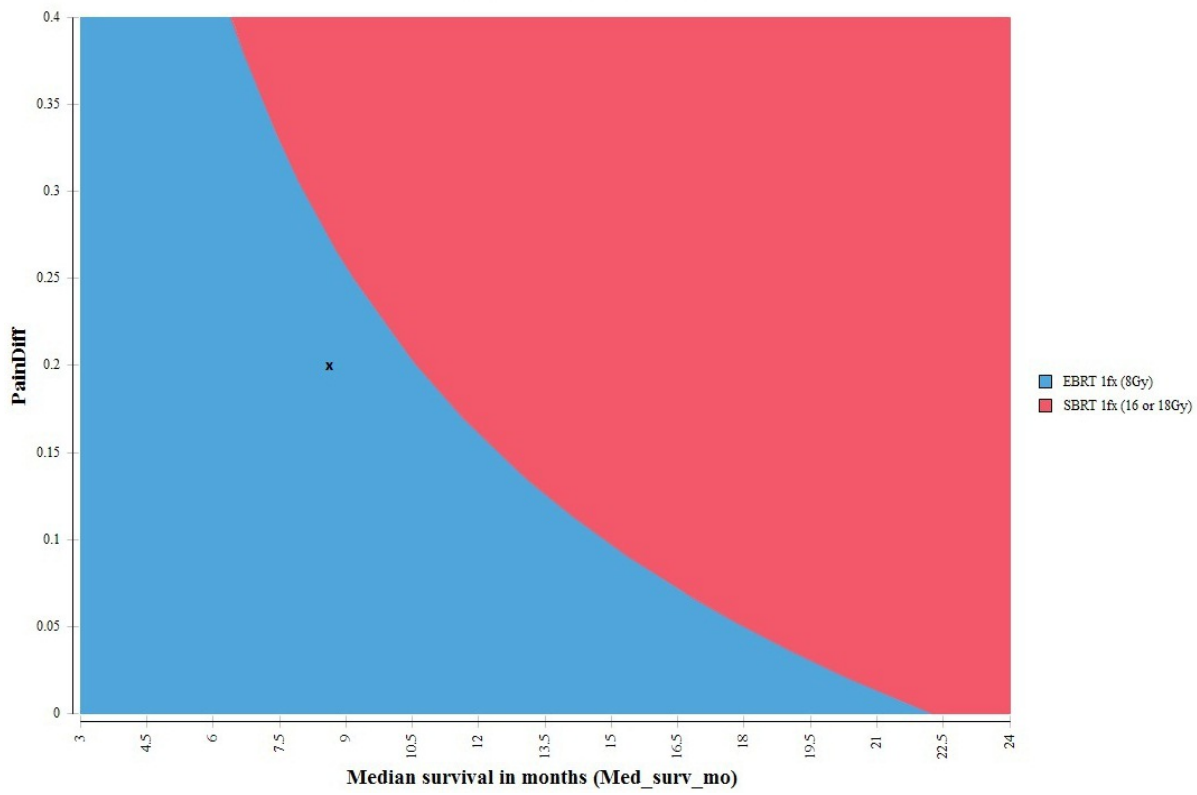

Figure 3.3 Two-way sensitivity analysis

Note: The x axis represents the median survival in months (3-24 months). The y axis is the absolute difference in pain relief between stereotactic body radiation therapy (SBRT) and external beam radiation therapy (EBRT). Likelihood of pain relief from SBRT is set as 0.8 and 0.6 for EBRT as a base case; the absolute pain relief difference is 0.2. The x on the graph represents the base case values for these parameters.

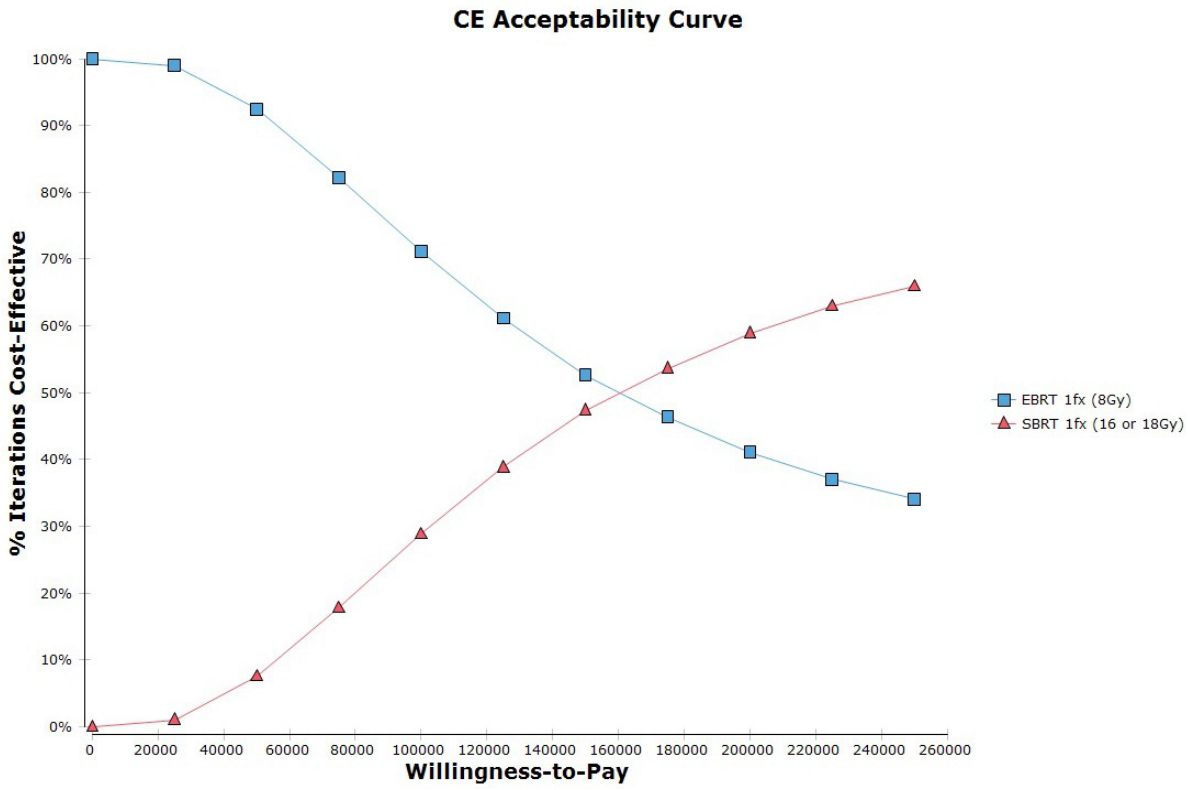

Figure 3.4 Probabilistic sensitivity analysis

Note: Cost-effectiveness (CE) acceptability curve, showing the likelihood that strategies would be considered cost-effective (on the y axis) over a range of willingness to pay (WTP) threshold. Here stereotactic body radiation therapy (SBRT) has a 30% probability of being considered cost-effective at $100,000 per quality-adjusted life year (QALY) gained threshold. SBRT becomes a favored treatment strategy above a WTP $160,000/QALY gained.

3.4 DISCUSSION

This is the first study, to our knowledge, to evaluate cost-effectiveness of single fraction of stereotactic body radiotherapy compared to single fraction external beam radiotherapy for palliation of painful vertebral bone metastases. We found that SBRT is not cost effective compared to single fraction EBRT at the WTP threshold of $100,000/QALY gained.

Cost effectiveness analyses can identify treatment strategies that improve outcomes at a reasonable cost in an environment with a greater focus on health care expenditures. Our study demonstrates that SBRT can be economically reasonable if 1) the quality of life utility value of unrelieved pain is worse than the base case (base case: 0.3), 2) the utility of relieved pain is better than the base case (base case: 0.55), or 3) median survival ≥ 11 months (base case: 9 months) compared to single fraction EBRT. In this regard, obtaining accurate quality of life utility values is challenging. Published utility values for unrelieved and relieved pain vary widely (68-72). This is because quality of life surveys often combine all types of bone metastases, not just vertebral metastases, and variation in complications and life expectancy. Thus, variation of the expected median survival rate is likely a more concrete parameter than utilities for projecting strategy cost effectiveness. Based on our model results, SBRT is economically reasonable in patients whose expected median survival is at least 11 months. Moreover, if median survival is ≥ 18 months SBRT costs $50,000/QALY or less, which is a commonly cited as a benchmark of a "good buy" for medical interventions (71, 73).

These findings make the case that the most economically feasible approach would involve the judicious use of SBRT for spine metastases in patients with relatively long predicted survival. Patients with breast or prostate cancer, bone metastasis, and good performance status

have a median survival of ≥18 months (80, 81) and thus may be good candidates for this approach.

Other studies report cost effectiveness analyses of palliative treatment for painful bone metastases (66, 68-70). Those studies, including RTOG 97-14 clinical trials comparing a single fraction of EBRT to conventional fractionated EBRT, have shown that a single fraction of EBRT was cost effective compared to fractionated EBRT. They reported that utility of pain relief post treatment was a sensitive parameter in their model; our study results are consistent with theirs. However quality of life utility value of pain relief from each strategy in our study was set to be same while other studies set this value differently between strategies (68, 69). Because quality of life assessment measures mainly whether pain was relieved or not, we used the same utility values post treatment when pain was relieved regardless of strategy.

Papatheofanis et al. (68) assessed the cost effectiveness of SBRT using Cyberknife system compared to conventional fractionated EBRT for spinal metastases. In this analysis, SBRT was cost effective, costing $41,500/QALY gained compared to fractionated EBRT. However, this study did not include retreatment and their primary assessment end point was pain relief after initial treatment. Also, their transition probabilities were mainly from studies reporting retreatment: EBRT as an initial treatment and SBRT as retreatment. In addition, their model includes spinal cord compression and spinal instability, while ours did not, perhaps explaining the difference in results.

There are several limitations in our study. First, as with most cost effectiveness analyses, transition probabilities for both treatment strategies were obtained from a few prospective studies, but mainly from retrospective studies and reviews. There is a lack of prospective studies and clinical trials related to SBRT for painful vertebral bone metastases. Thus, our clinical

assumptions for SBRT may not accurately reflect reality. Results are sensitive to assumptions regarding patient survival and the effectiveness of pain relief following radiation treatment, so the model estimates for the cost effectiveness of SBRT will be strengthened by results from ongoing prospective clinical trials such as RTOG 0631. However, one-way sensitivity analyses were performed to take our model assumptions into account. Due to scant data on duration of pain relief in relation to observed survival, we could not model pain relief as a time-based function, which could similarly affect results. In addition, we did not include treatment-related adverse effects such as fracture, toxicity and surgical intervention for both strategies. This modeling choice tacitly assumes that the likelihood of these events is the same, regardless of strategy, perhaps biasing our analysis against SBRT. A number of published papers reported that pathological fracture related to EBRT is about 5% (52, 57). However, adverse events from only SBRT have not been reported well in literature because SBRT is commonly used for retreatment after initial EBRT treatment for painful vertebral bone metastases. Since RTOG 0631 – a Phase III clinical trial comparing SBRT (16 or 18 Gy in 1 fraction) to EBRT (8Gy in 1 fraction) – is now ongoing, the results from this trial may provide adverse effects data for SBRT. Treatment costs were based on Medicare reimbursement. Reimbursement rates are different among various payers, but Medicare reimbursement data is commonly used as a proxy for true costs in cost effectiveness analysis. Finally, although we assessed economic costs, other factors such as time away from home, travel costs, lost productivity costs, education, resources were not accounted in this analysis, since our analysis is from a third party payer perspective. Not including those costs could also bias our analysis against SBRT.

In conclusion, SBRT for palliation of vertebral bone metastases is not cost-effective compared to EBRT when a WTP threshold of $100,000/QALY gained is used. However, if

median survival is ≥11 or ≥ 18 months, SBRT costs ≤$100,000/QALY or ≤$50,000 /QALY gained respectively, suggesting that selective SBRT usage in patients with longer expected survival may be the more cost-effective approach. This approach will need to be further supported by RTOG 0631 results.

4.0 COST EFFECTIVENSS ANALYSIS OF STEREOTACTIC BODY RADIATION THERAPY COMPARED WITH RADIOFREQUENCY ABLATION FOR INOPERABLE COLORECTAL LIVER METASTASES

4.1 INTRODUCTION

Colorectal cancer (CRC) is the third leading cause of US cancer mortality (82). Typically, the first detected site of metastatic disease is within the liver. Approximately half of CRC patients develop liver metastases within 2 years after initial diagnosis (83, 84). With a relatively prolonged survival in patients with CRC metastases limited to the liver, adequate local control of liver metastases may be beneficial not only to decrease morbidity but also to potentially prolong disease-free and overall survival (85, 86).

In this subset of patients, surgical resection is the therapeutic choice and improves prognosis and quality of life, but only 15-20% of patients with liver metastases are suitable for resection (87, 88). Alternative local therapies for unresectable liver metastases include radiofrequency ablation (RFA), cryotherapy, hepatic arterial chemotherapy infusion and laser-induced thermotherapy. Among these, RFA is the favored treatment based on favorable local control and survival rates with fewer required treatments and less invasiveness compared to other options (85, 86, 89). However, RFA presents some limitations when lesions are larger than 3.0 cm in diameter or in proximity to major blood vessels, adjacent to the main biliary tract or

gallbladder, or beneath the diaphragm. RFA to lesions with these characteristics yields suboptimal local control and progression-free survival rates (90, 91).

Stereotactic body radiation therapy (SBRT) is a newer, non-invasive technique for the delivery of conformal high radiation doses to the tumor with sub-millimeter accuracy. Due to rapid dose falloff, the SBRT technique is superior to three dimensional conformal radiation therapy (3D CRT) technique. The normal liver tissue surrounding the target receives significantly lower radiation dose in the SBRT treatment compared to the 3DCRT treatment thereby, decreasing the potential for radiation-induced liver disease for the former treatment technology. In contrast to 3D CRT, SBRT entails precise delivery of a high dose in fewer fractions (3-5 fractions; most commonly 3 fractions), resulting in tumor ablation and maximal normal tissue sparing (92-97). Based on retrospective and prospective results, SBRT for inoperable liver metastases from CRC is safe, non-invasive and has been proved effective, leading to comparable results to RFA despite often treating less favorable lesions (92, 97). Yet SBRT can be both expensive and resource intensive based on requirement of advanced treatment planning, real-time motion management, and three-dimensional multimodal image acquisition systems needed to track target position (97). Whether the benefits afforded by SBRT are cost effective compared to RFA has not been previously studied.

With rapidly evolving modalities in radiation therapy, new sophisticated cutting edge technologies such as SBRT have demanded highly specialized resources, but an increasingly resource constrained health care environment has challenged the sustainability of these technologies. Decreasing reimbursement and cost scrutiny from insurers further stresses the need to rationalize therapies (98). Despite the potentially more favorable toxicity profile of SBRT compared to RFA for unresectable liver lesions, justification is needed to determine which

modality provides not only more favorable outcomes but employs a cost effective approach. A cost effectiveness analysis was therefore conducted to determine whether SBRT is a cost effective therapy compared to RFA for patients with unresectable CRC liver metastases.

4.2 METHODS

4.2.1 Decision Model

A Markov state transition model was constructed, comparing SBRT with RFA for liver metastases from CRC. In the model, identical hypothetical cohorts were treated with RFA (single treatment) or SBRT (utilizing 3 fractions) (97). Cohorts were followed over their remaining lifetime; the Markov cycle length was 1 month. The Markov model is shown in Figure 4.1, with arrows representing transition probabilities between health states based on comprehensive review of medical literature-based treatment outcome, survival estimates and complication rates (Table 4.1) (85-92, 94-97, 99-120). For our model calibration, Markov cohort probability analysis was performed for the expected survival rates for both RFA and SBRT cohorts. That is, mortality likelihood was calculated and our model produced clinically reasonable survival rates. With a lifetime time horizon, our model cycled until the entire cohort had died.

The seven main health states in this model were: treatment, no disease progression, local recurrence, regional/distant failure, disease progression (prompting initiation of palliative chemo), disease controlled after retreatment, and death. Death was the absorbing state. Transitions to death were based on previously reported survival rates. All patients entered the treatment state in the first cycle of the model. Patients who were alive had either no disease

recurrence or disease recurrence, which could be either as local or regional/distant failure. Those with local recurrence received salvage treatment with the same therapy as initially given. After local retreatment, patients could either have a repeat recurrence or no further recurrence. Patients who had regional/distant failures or a third local recurrence were transitioned to a palliative chemotherapy state. The likelihood of developing complications from either therapy was accounted for.

Both costs and utilities were discounted at an annual rate of 3%. TreeAge Pro Suite 2015 software (TreeAge Software, Williamstown, MA) was used to build the Markov model. The base case model was developed from a payer's perspective for health care services, using 2014 Medicare reimbursement rates.

4.2.2 Costs

Cost estimates for SBRT and RFA were based on Medicare reimbursement unadjusted national rates, derived from current procedural terminology (CPT) codes in the year 2014. Medicare reimbursement data account for technical (hospital) and professional (physician) fees for each treatment strategy. Total costs were estimated from Center for Medicare and Medicaid Services (CMS) and Agency for Healthcare Research and Quality/Healthcare Cost and Utilization Project (AHRQ/HCUP) data (121). Costs included the total course of treatment for each strategy, costs of potential complications, inpatient hospital stay, retreatments, and palliative chemotherapy (estimated from the cost of 6 cycles of FOLFOX). Total Medicare reimbursement for SBRT and RFA were $13,000 and $2,240, respectively (Table 4.2), accounting for differences in treatment episodes between strategies. For treatment related complications, RFA complication-related costs were based on hospital stays. Only severe toxicities (grade 3 or higher) prompting the need

for procedural intervention or hospital stay were accounted for in patients treated with SBRT. The cost of each event was estimated from inpatient hospital stays (122) and the event rate was assumed from SBRT studies for pancreatic cancer (123). Reimbursement varies geographically, thus sensitivity analyses were performed to evaluate the impact of this variation.

4.2.3 Utilities

The effectiveness term is quality adjusted life years (QALYs), the product of a health state's quality of life utility and time spent in that state, accounting for quality of life differences between treatment strategies using quality of life utility weights. Quality of life utility values for each health status were acquired through Tufts CEA registry as well as literature search (124-127) and listed in Table 4.1. Sensitivity analyses were used to test utility value assumptions.

4.2.4 Cost Effectiveness Analysis

Treatment strategies were compared using the incremental cost effectiveness ratio (ICER), the ratio of cost and QALY differences between strategies. There is no consensus on cost effectiveness (C/E) criterion in United States; however, interventions costing less than $100,000 per QALY gained are typically considered economically reasonable from a societal perspective, while those costing much more than this figure are often felt to be an expensive use of health care resources (128-130). The present analysis is based on payer's perspective (direct medical costs) with a willingness to pay (WTP) threshold of $100,000/QALY gained. Sensitivity analysis using a WTP threshold of $50,000/QALY gained was also completed, as this is another commonly cited benchmark (131). Markov states tracked costs as a patient traversed the model.

Treatment strategies were compared using the ICER to determine which provides a more cost effective therapy based on the $100,000/QALY WTP threshold.

4.2.5 Sensitivity Analysis

One-way, two-way and probabilistic sensitivity analyses were utilized to account for uncertainty in decision model assumptions. The ranges of clinical parameters were assumed based on data obtained from the comprehensive literature review (85-92, 94-97, 99-120). One-way sensitivity analysis, where all parameters are varied individually, was examined to detect the effect of these variations on model results. A two-way sensitivity analysis was completed to determine the optimal treatment strategy when median survivals from RFA and SBRT were varied. The probabilistic sensitivity analysis using Monte Carlo simulation was performed to vary all parameters simultaneously. That is, distributions for each parameter were sampled at random during 5000 trials and results reported as the percentage of trials in which a strategy is cost effective at a series of WTP (or acceptability) thresholds. Costs were modeled using a normal distribution with a standard deviation of 25% of base case value. For utilities and probabilities, a beta distribution function was used for sampling (132).

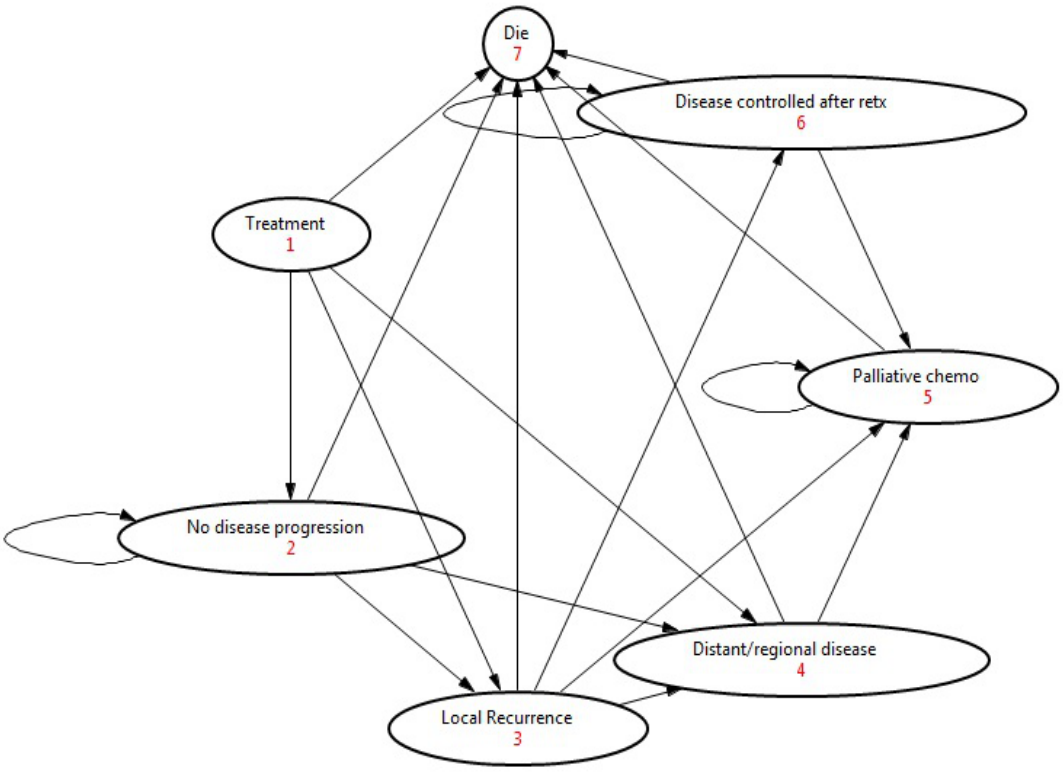

Figure 4.1 Markov state transition model

Note: Arrows represent transition between health states (see text for details).

Table 4.1 Model assumption- clinical parameters

Cost	Base cost ($)	Range ($)	Assumed distribution
Cost for RFA	2240	1790-2700	Normal
Cost for SBRT (3 fractions)	13000	11000-15000	Normal
Cost of hospital stay (per day)	2157	1600-3000	Normal
Cost of retreatment with RFA	2240	1790-2700	Normal
Cost of retreatment with SBRT (3 fractions)	13000	11000-15000	Normal
Cost of chemotherapy (6 cycle)	7542	6033-9050	Normal
Cost of complication for RFA	Calculate *		
Cost of complication for SBRT	Calculate *		
Probabilities	**Base estimate**	**Range**	**Assumed distribution**
Median survival for both treatment strategies	25 months	20-30 months	Beta
i) Probability of local recurrence for RFA ii) Probability of local recurrence for RFA (only for tumor size > 4.0cm)	i) 0.3 ii) 0.6	i) 0.16-0.44 ii) 0.5-0.7	Beta
Probability of local recurrence for SBRT	0.2	0.08-0.32	Beta
i) Probability of any recurrence for RFA ii) Probability of any recurrence for RFA ** (only for tumor size > 4.0cm)	i) 0.7 ii) 0.85	i) 0.55-0.85 ii) 0.75-0.95	Beta
Probability of any recurrence for SBRT	0.6	0.5-0.7	Beta
Probability of retreatment for RFA	0.45	0.25-0.65	Beta
Probability of retreatment for SBRT	0.1	0.02-0.2	Beta
¶Probability of any recurrence after retreatment for RFA	0.7	0.55-0.85	Beta
¶Probability of any recurrence after retreatment for SBRT	0.7	0.55-0.85	Beta
Probability of complication after RFA	0.06	0.03-0.1	Beta
Probability of complication after SBRT	0.02	0-0.05	Beta
Utilities	**Base estimate**	**Range**	**Assumed distribution**
Utility for RFA	0.7	0.6-0.8	Beta
Utility for SBRT	0.8	0.7-0.9	Beta
Utility for disease free after treatment	0.75	0.7-0.8	Beta
Utility for retreatment with RFA	0.7	0.6-0.8	Beta
Utility for retreatment with SBRT	0.8	0.7-0.9	Beta
Utility for local recurrence	0.74	0.64-0.84	Beta
Utility for regional/distant disease	0.19	0.15-0.3	Beta
Utility for chemotherapy	0.6	0.5-0.7	Beta
Utility for complication after RFA	0.47	0.4-0.6	Beta
Utility for complication after SBRT	0.47	0.4-0.6	Beta

Note: *: (probability of complication from either strategy)*(days of hospital stay)* (cost per one hospital stay)

**: Consensus estimate based on limited reported data.

¶ : Consensus estimate based on limited reported data.

Table 4.2 Medicare reimbursement rates 2014 for professional and technical services related to RFA

For one RFA procedure

CPT code	Description	Medicare Reimbursement ($)
47380	Radiofrequency ablation	1469.45
36481	Insertion of catheter vein	369.7
75887	Vein x-ray liver w/o hemodyn	169.8
36011	Place catheter in vein	163.4
75894	X-rays transcath therapy	67.7
TOTAL		**2,240**

For SBRT 3 fractions

CPT code	Description	TC Quantity	PC Quantity	Medicare Tech Reimbursement / Unit ($)	Medicare Prof Reimbursement / Unit ($)	Total Medicare Reimbursement ($)
77014	CT image guided treatment fields	1	0	0	0	0
77263	MD treatment plan (complex)	0	1	0	166.58	166.58
77290	Simulation with SBRT	1	1	311.37	80.96	392.33
77293	Motion Management	1	1	0	103.89	103.89
77295	3D simulation	1	1	1,036.39	222.02	1,258.41

For SBRT 3 fractions (continued)

77334	Treatment device (complex)	11	11	213.49	64.12	3,053.71
77300	Basic dose calculation	10	10	114.65	32.24	1,468.90
77373	Treatment delivery	3	0	1,921.30	0	5,763.90
77336	Weekly physics	1	0	114.65	0	114.65
77435	SBRT management course	0	1	0	633.71	633.71
TOTAL						**12,956.08**

Note: TC: technical charge, PC: professional charge, MD: physician

4.3 RESULTS

4.3.1 Base Case Analysis

Cost effectiveness analysis demonstrated that SBRT costs $7,949 more than RFA while gaining 0.04 QALYs, resulting in an ICER of $185,515 per QALY gained. Assuming similar patients treated with either modality, both treatment strategies were assumed to have the same median survival (25 months).

4.3.2 Sensitivity Analysis

In one-way sensitivity analyses, results were most sensitive to variation of the median survival (ICER range, -$240,000 to $185,515 per QALY gained: Figure 4.2). Results were additionally sensitive to the following parameters: quality of life utility value of chemotherapy, any tumor recurrence rate after RFA, and any tumor recurrence rate after SBRT. If median survival of

SBRT was ≥26 months and ≥27 months, SBRT costs ≤$100,000 and ≤$50,000 per QALY gained, respectively. However, if median survival of SBRT was ≤ 24 months, RFA led to a dominant strategy (less costly and more effective treatment). Noticeably, any variation of clinical parameters used, except for median survival rates, within the limits of previously published ranges did not lead to SBRT becoming favored based on the ICER threshold of $100,000/QALY gained (Figure 4.2). Median survival variations of both treatment strategies were not performed simultaneously to reflect the median survival change of one strategy compared to the other. In the analysis, median survival relative risk, the ratio of the two median survivals, was used to represent the median survival change of the two strategies dependently. The range of median survival relative risk was 0.8-1.2; one strategy survival varied between 20 and 30 months, while the other strategy kept base case 25 months.

A two-way sensitivity analysis was conducted varying median survival and tumor recurrence rate from RFA, the parameters whose variation had the great effects on model results. As shown in Figure 4.3, median survival change dramatically influenced the decision of treatment strategy preference based on cost effectiveness, regardless of tumor recurrence rates.

Probabilistic sensitivity analysis, which varied all model parameters simultaneously, demonstrated that SBRT was favored in 47% of model iterations and RFA favored in 53% at a WTP threshold of $100,000 per QALY gained (Figure 4.4).

In a separate scenario analysis, RFA and SBRT were compared for large tumor sizes (>4 cm) due to established inferiority of local control rates with RFA in this population. Total costs remained higher with SBRT at $7,326 with 0.07 QALYs gained compared with RFA, yielding an ICER of $101,052 per QALY gained.

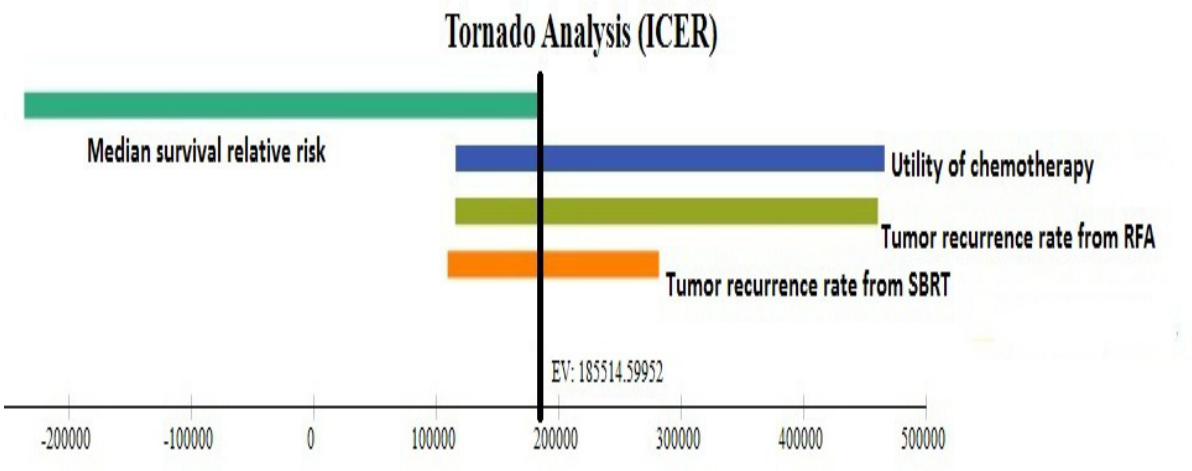

Figure 4.2 One way sensitivity analysis.

Note: ICER Tornado diagram for one way sensitivity analysis. The vertical line represents the base case value of ICER (base case median survival is 25 months for both strategies and ICER is $185,515 per QALY gained).

Median survival relative risk is defined as a ratio of the two median survivals (ranges: 0.8-1.2, ICER -$240,000 to 185,515/QALY gained). Utility value of chemotherapy (ICER ranges: $ 115,800 to $466,288/QALY gained), any tumor recurrence rate from RFA ($115,362 to 460,823/ QALY gained) and any tumor recurrence rate from SBRT (ICER ranges: $ 110,000 to 282,000/QALY gained) are also sensitive to model results.

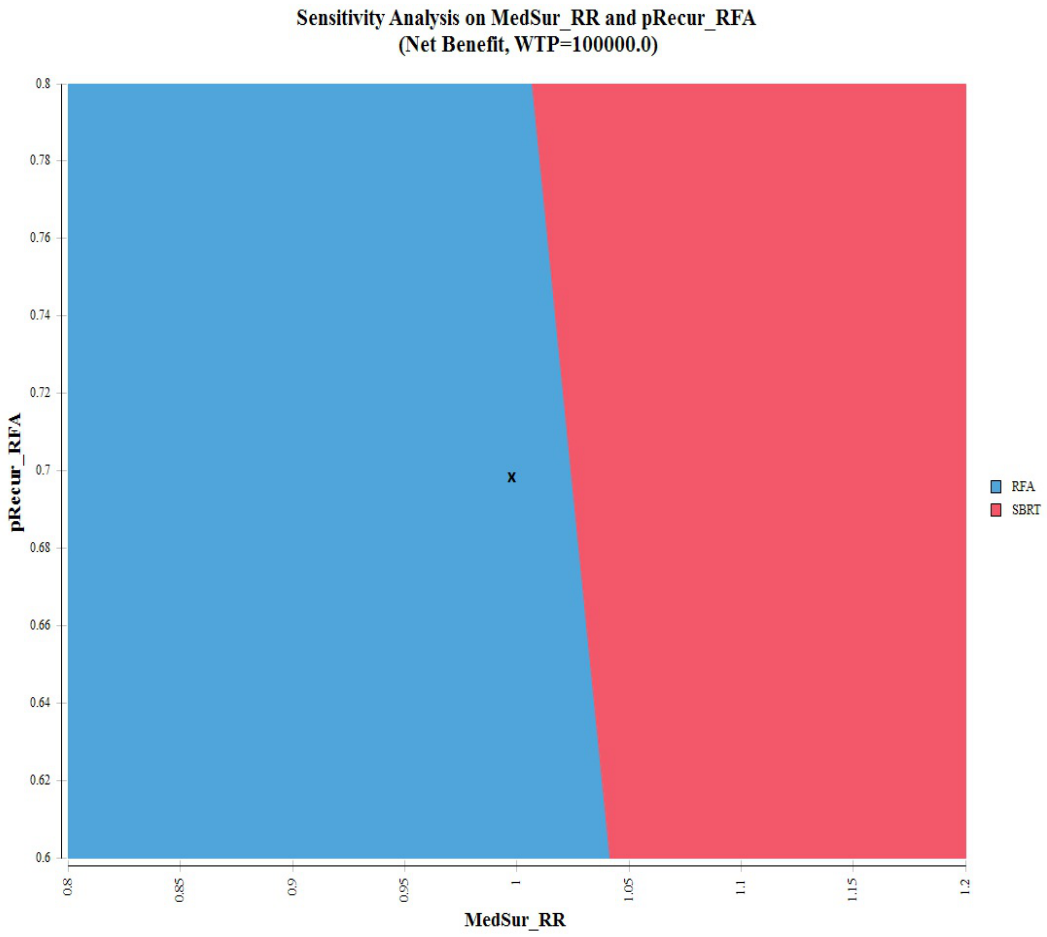

Figure 4.3 Two way sensitivity analysis.

Note: The x axis represents median survival risk ratio (range: 0.8-1.2 reflecting that one of the two strategies is varying between 20-30 months, while the other is holding constant as 25 months). The y axis represents any tumor recurrence rate from RFA. The" x"on the graph represents the base case value (median survival 25 months and recurrence rate as 70%) showing RFA as a preferred strategy at a WTP of $100,000 /QALY gained.

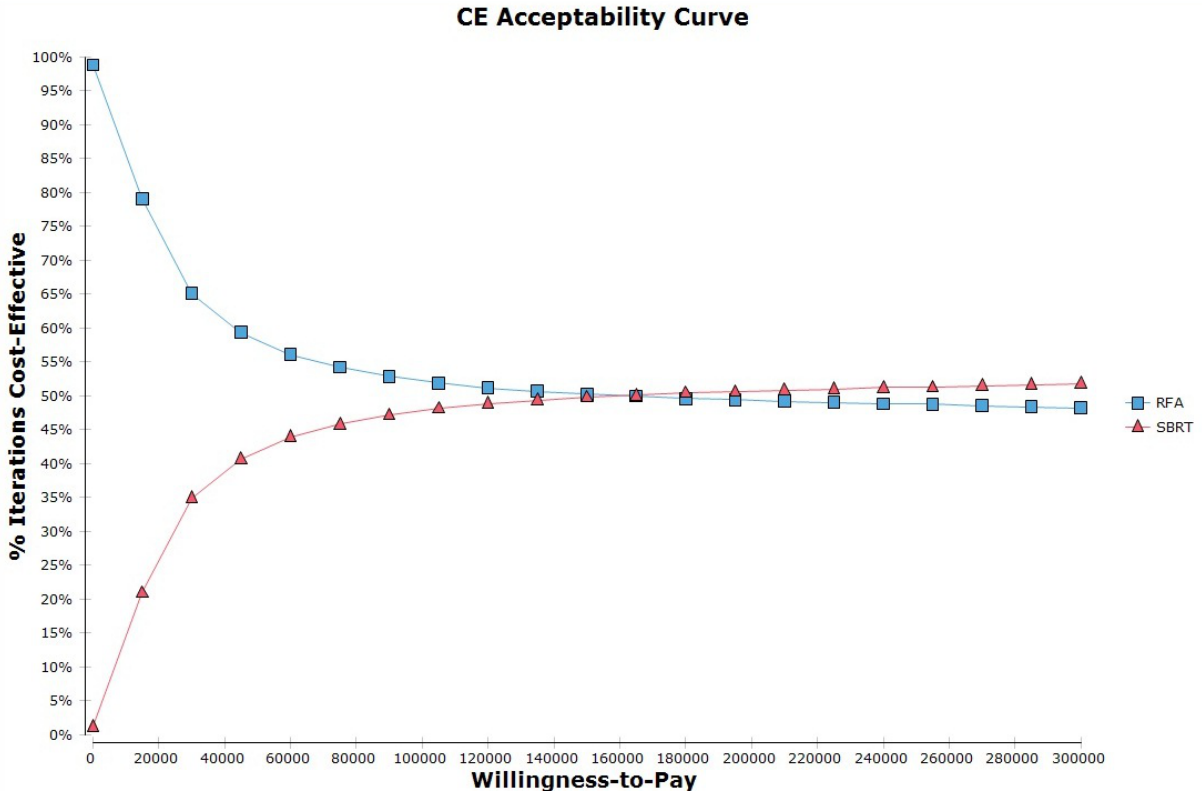

Figure 4.4 Probabilistic Sensitivity Analysis

Note: Cost- effectiveness acceptability curve, showing the likelihood that strategies would be considered cost-effective (on the y axis) over a range of willingness to pay (WTP) threshold. Here SBRT has a 47% probability of being considered cost-effective at $100,000/QALY gained threshold. SBRT becomes a favored treatment strategy above a WTP $200,000/QALY gained.

4.4 DISCUSSION

To our knowledge, this is the first study to conduct a cost effectiveness analysis of SBRT and RFA for the treatment of liver metastases resulting from CRC. Results from the analysis confirmed that SBRT is not a cost effective strategy compared with RFA using a WTP threshold of $100,000 per QALY gained when equal survival between strategies is assumed.

Existing literature evaluating cost effective approaches for CRC liver metastases have not yet addressed the role of SBRT. Roberts et al (127) completed a cost-utility analysis of operative versus non-operative approaches for colorectal liver metastases, incorporating outcomes from institutional observational data. This analysis demonstrated that an operative approach was both cheaper (€22,200 vs. €32,800) and more effective (4.017 vs. 1.111 QALYs gained) than non-operative strategies, with results found to be robust in sensitivity analyses. These findings may reflect the distinct, nearly two-fold, median survival difference seen with an operative approach. One critical difference with our study was evaluation of SBRT, which was not considered in that prior study. Additionally, patients treated with non-operative approaches were typically deemed surgically unresectable, thus leading to inherent imbalances in patient characteristics between the two arms (operative and non- operative cohorts).

For non-operative candidates, data supporting both RFA and SBRT are limited to retrospective and non-comparative prospective trials, leading to difficulties in comparing efficacy. Local control rates in literature using SBRT range from 66-92% (94-97, 113-120) versus those with RFA, which range from 56-84% (90, 91, 99-120). The base case assumption for local control rate in the present study was 80% and 70% for SBRT and RFA, respectively. Additionally, rates of severe toxicity appear slightly lower with SBRT (0-3 vs. 5-10 %). Despite these potential gains, these findings suggest these benefits come at a substantial increase in cost.

One significant challenge in the present study is the heterogeneity of results from previously established studies. Compared to RFA studies, a majority of reported literature using SBRT includes patients with higher rates of comorbidities, larger tumor sizes and suboptimal tumor locations (proximity to large vessels). Presumably these patients would have inferior outcomes with RFA. Such variability and issues with selection imbalances underscore the need for a randomized trial. Unfortunately, a prior attempt at a randomized clinical trial (RAS01: RFA vs. SBRT in CRC liver metastases) failed due to poor accrual. Accepting this limitation and using existing outcomes for SBRT and RFA, the results of this study suggest SBRT is a less cost effective modality for treatment of CRC liver metastases if survival is equal in comparable patient cohorts.

One notable caveat to this conclusion was the finding of a high degree of sensitivity to changes in survival for both treatment strategies. Based on model results, if median survival of SBRT was $\leq$ 24 (base case 25 months), RFA led to a dominant strategy. However, SBRT is economically sound at the WTP threshold of $100,000 per QALY gained if median survival of SBRT is $\geq$26 months. Moreover, if median survival is $\geq$ 27 months, SBRT costs $50,000 per QALY or less, which is commonly cited as a benchmark of a "good buy" for medical interventions (131). That is, the small absolute survival benefit of SBRT can lead to justify this treatment from a cost effectiveness standpoint. However, existing data do not support the survival difference between strategies. Based on the lower rates of toxicity and higher local control with SBRT, one would expect in appropriately selected patients, survival may be improved compared to RFA. If indeed this is assumed, even with as small as a month median survival gain, SBRT becomes a more cost effective approach than RFA. These findings should

emphasize the critical need for a randomized comparison between these two approaches to avoid cohort imbalances.

In order to better correct for these imbalances in prior studies, a separate scenario analysis was completed for patients with larger tumor sizes (>4 cm). Tumor size has been known as a significant predictor for tumor control and survival with RFA (101, 103, 106, 108). In this patient subset, SBRT resulted in an ICER of $101,052 per QALY gained with equal survival between treatment strategies, while local control rate was assumed as 80% and 40% for SBRT and RFA, respectively (94, 96, 101, 103, 106, 108, 113, 114, 117, 119). Therefore, with appropriate dose delivery when feasible, SBRT may indeed be a more suitable and cost effective approach for these challenging cases.

A predominant challenge of cost effectiveness analyses lies in the definition of financial costs. In this study, direct medical costs based on a payer's perspective (Medicare in this example) were utilized for several reasons. First, $100,000/QALY threshold is usually considered as a societal perspective including both direct medical, direct non-medical, and time costs. Direct non-medical costs (costs incurred by the patient for seeking or receiving care) and time costs (time for a caregiver or patient seeking or receiving care) are particularly complex to calculate for each patient due to a lack of accepted standards of measurement (133). Furthermore, these costs are relatively small in comparison to direct medical costs. Therefore, ICER results between payer's perspective and societal perspective will likely not differ substantially. Secondly, results based on payer's perspective can provide a better representation of reimbursement-related policy because estimation of direct medical costs has been calculated from resource use and separate cost per each unit of resource expanded. Due to its standard quantification method based on the resource use across health care setting, medical care policy

makers take cost- effectiveness analysis that encompass a payer's perspective to reflect reimbursement insurance policy (134).

Aside from those previously discussed, further challenges and limitations exist in our study. Treatment-related complications rates for SBRT were limited to severe toxicities (grade 3 or higher). While such toxicities are generally uncommon with SBRT (zero to 3%), lesser toxicities (grade 1 and 2) are common. Differing rates of low-grade toxicity between treatment strategies could bias results and fail to capture the added cost of care. However, sensitivity analyses suggested that assumptions about toxicity rates did not change the results. Next, the assumption was made that after local recurrence, either the same local therapy, based on prior re-treatment rates, or palliative chemotherapy was delivered (96, 106, 110-112, 114, 116, 119). A number of alternative salvage regimens exist for these patients such as additional systemic therapy, palliative external beam radiotherapy and surgical resection. Establishing exact probability rates of receiving any of these other salvage options is challenging due to the complexities of such cases. Lastly, treatment costs were based on Medicare reimbursement rates. While reimbursement rates vary among payers, Medicare reimbursement data is commonly a model for other payers. Other published cost effectiveness analyses have employed this data set as a proxy for true costs in cost effectiveness analysis.

In conclusion, SBRT was found to not be a cost effective treatment option compared to RFA using a WTP of $100,000/QALY gained when equal survival is assumed between strategies. However, considerable variability and selection bias exists in reported outcomes for each approach. In patients with larger tumor sizes (>4 cm), SBRT was found to be a more cost effective choice. Subtle variations in median survival, even as small as a 1-month gain, achieved

the threshold where SBRT became more cost effective. Such findings emphasize the need for a comparative clinical trial to guide appropriate and cost-conscious management.

5.0 CONCLUSION

The studies in this dissertation evaluated cost effectiveness analyses in radiation therapy treatments. Recent advances in radiation therapy technologies have led to rapid changes in the standard of care for cancer treatment. New, innovative therapies are more effective than therapies developed previously. However, these therapies come at a high cost. In current daily practice, we are continuously asked to demonstrate cost- effectiveness and value so that the most appropriate management decisions can be performed.

My dissertation addresses this critical question of cost-effectiveness using quantitative analysis methods. The projects in this dissertation investigated whether the clinical benefit from innovative radiation treatment technology is worth the higher costs when compared with lower cost alternatives. First, we compared 3-dimensional (3D) image guided brachytherapy (IGBT) compared to conventional 2-dimensional (2D) high dose rate (HDR) brachytherapy for the treatment of locally advanced cervical cancer. We found that 3D IGBT is a more cost effective option compared to 2D HDR brachytherapy with a willingness to pay (WTP) threshold of $50,000/quality adjusted life years (QALY) gained. These findings were robust to variation of parameter values, both individually and collectively, strongly supporting the routine use of 3D image guided brachytherapy for the treatment of locally advanced cervical cancer. Second, we compared a single fraction of stereotactic body radiation therapy (SBRT) to a single fraction of external beam radiation therapy (EBRT) for palliation of vertebral bone metastases. We found

that SBRT is not a cost effective treatment strategy compared to conventional EBRT with a WTP threshold of $100,000/QALY gained in patients with relatively short life expectancy. This finding suggests that selective SBRT usage in patients with longer expected survival may be the more cost-effective approach. Finally, we compared SBRT with radiofrequency ablation (RFA) for inoperable colorectal liver metastases. We found that SBRT is not cost effective compared to RFA with a WTP of $100,000/QALY gained when equal survival is assumed between treatment strategies. However, interestingly, SBRT was found to be a more cost effective choice in patients with larger tumor sizes (>4 cm).

The conclusion of each study, however, has to be taken with caution, as there were inevitable limitations in conducting the studies. For example, in the three studies presented here, model assumptions with clinical parameters were obtained mainly from retrospective studies and reviews. This was because there is a lack of prospective studies and clinical trials related to these studies. Furthermore, randomized clinical trial and Meta-analysis were not available for these studies. In the first study, a randomized clinical trial between 3D IGBT and 2D conventional brachytherapy was not feasible due to an ethical issue. In the second study, RTOG 0631, a Phase III clinical trial comparing SBRT (16 or 18 Gy in 1 fraction) to EBRT (8Gy in 1 fraction) is still an ongoing cooperative group trial to clarify the clinical effectiveness between the two arms. In the third study, a randomized clinical trial (RAS01: RFA vs. SBRT in CRC liver metastases) failed due to poor accrual. Moreover, model assumption in this study had a significant heterogeneity of results from previously established data, underscoring a need for prospective studies for a direct comparison in efficacy between treatment strategies. Also in the second and third studies, results were highly sensitive to assumptions regarding patient survival rates and quality of life utility values. This highlights that the model estimates for the cost effectiveness

should be confirmed with results from comparative prospective trials to increase the robustness of model analysis.

Despite these challenges, the results demonstrate general usefulness of cost effectiveness studies in drafting clinical decision guidelines in terms of 1) providing payers with clear picture on the cost-benefit relationship; 2) consequences of treatment choices; and 3) making the use of resources most efficiently. In addition, these studies provide a practical frame work for constructing cost effectiveness analysis models that incorporate data from future prospective clinical trials and observational studies.

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