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HOT TOPIC

Cost-Effectiveness of Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy: a Critical Review

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Abstract
Purpose of Review This review aims to summarize and appraise published cost-effectiveness studies on stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT).
Recent Findings We performed a Medline search of cost-effectiveness studies of SRS, SBRT, and other cancer treatment modalities such as surgery and systemic therapy from 2006 to 2016. We included studies that used both modeling and retrospective review techniques. We excluded studies of benign disease. We defined a strategy whose incremental cost-effectiveness ratio (ICER) is ≤$50,000/quality-adjusted life year (QALY) as "clearly cost-effective," a strategy whose ICER is ≤$100,000/QALY as "probably cost-effective," and a strategy ≤$200,000/QALY as "possibly cost-effective." We appraised modeling studies by determining whether or not they conform to the International Society for Pharmacoeconomics and Outcomes Research Good Research Practices (ISPOR) in modeling task force good research practices in model transparency and validation.
Summary We identified 24 studies that met inclusion criteria. Treatment sites included brain, bone, liver, lung, pancreas, and prostate. SRS and SBRT were clearly cost-effective strategies in 17 studies, probably cost-effective in 3 studies, and possibly cost-effective in 2 studies. Of the 16 modeling studies,15 conformed to transparency best practices; however, only 6 studies performed rigorous validation as described by the ISPOR guidelines.
Conclusions SRS and SBRT are likely to be cost-effective management strategies across a large variety of treatment sites and techniques. However, rigorous model validation techniques are lacking in these modeling studies.

Keywords Cost-effectiveness · Radiation therapy · Stereotactic · Radiosurgery

Introduction

Stereotactic radiosurgery (SRS) refers to the use of a single or small number of large doses of radiation delivered to small, precisely defined targets in the brain [1]. The technique often involves using multiple non-coplanar radiation beams that converge on the target lesion using rigid immobilization and image guidance. When these techniques are applied to body tumors outside of the brain, it is termed stereotactic body radiotherapy (SBRT) [2]. The efficacy and safety of SRS and SBRT have been validated in prospective trials [3–12].

Annual direct costs for cancer care in the USA are projected to rise by roughly 70 billion dollars from 2006 to 2020 [13]. Cost-effectiveness analyses (CEA) provide a formalized approach to determine the optimal use of available resources to maximize health benefits [14]. Stereotactic radiotherapy has the potential to be a cost-effective therapy because of the lower overall cost incurred by the use of fewer daily fractions, with equivalent efficacy and toxicity outcomes to conventional treatment [15].

The primary purpose of this article is to review the evidence regarding the cost-effectiveness of SRS and SBRT. A

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secondary aim of this article is to determine the extent to which modeling studies included in this review incorporate model calibration. Calibration is the process of confirming that the *actual* output of the model—survival rates, toxicities, etc.—mirrors the *expected* output of the model. Model calibration is an integral component of model development and is central to the validity of all analyses and conclusions drawn from the model [16].

Methods

We performed a Medline search of cost-effectiveness studies of SRS and SBRT as compared to other cancer treatment modalities such as surgery and systemic therapy from 2006 to 2016. Search terms included "stereotactic," "SRS," "stereotactic radiotherapy," "stereotactic body radiotherapy," "SBRT," "stereotactic ablative radiotherapy," "economic evaluation," "quality adjusted life year (QALY)," "cost," "cost-effectiveness," "cost-utility," and "cost analysis." We excluded studies of benign disease.

A treatment strategy is considered to be cost-effective if its overall cost is lower and its effectiveness higher relative to an alternative treatment. In this scenario, the cost-effective treatment is termed "dominant." If a treatment strategy is both costlier and more effective, its cost-effectiveness is assessed using the incremental cost-effectiveness ratio (ICER), which is defined as defined by the difference in cost between two treatment strategies, divided by the difference in their effectiveness. Effectiveness can be measured in life years, or more commonly, QALYs. A QALY represents a year of life lived in perfect health. QALYs are modified by utilities, which are preference scores on a 0 to 1 scale where 0 is equivalent to death and 1 is equivalent to perfect health. There are several ways to measure utilities. The most common methods involve direct elicitation from patients or the general population using the standard gamble, time trade-off, or visual analog scale techniques. If an ICER value is less than the societal willingness-to-pay (WTP), it is considered cost-effective. For instance, if a new technology is associated with increase in QALYs of 0.5 but at an increased cost of $80,000, its ICER would be $160,000/QALY. The new technology may or may not be considered cost-effective depending on societal WTP.

For this article, we defined a strategy whose ICER is ≤$50,000/QALY as "clearly cost-effective," a strategy whose ICER is ≤$100,000/QALY as "probably cost-effective," and a strategy ≤$200,000/QALY as "possibly cost-effective," as described previously [17]. We used the International Society for Pharmacoeconomics and Outcomes Research Good Research Practices (ISPOR) in modeling task force good research practices in model transparency and validation to appraise the studies [18]. The criteria are summarized in Table 1.

Results

We identified 24 studies that met inclusion criteria with site distribution as follows: brain [6], bone [3], liver [1], lung [7], pancreas [2], and prostate [5]. The majority of studies were modeling studies [16], of which 14 were Markov models and 2 used decision trees. The remaining eight studies were retrospective. The selected studies are summarized in Table 2. SRS and SBRT were clearly cost-effective strategies in 12 and probably cost-effective in 4 studies. In the remaining eight studies, other strategies were either cost-effective or the calculation of an ICER was not possible.

Brain

We identified six studies that have evaluated the cost-effectiveness of SRS for treating brain metastases. Lal et al. constructed a decision tree populated with data from a randomized controlled trial that compared SRS alone to SRS and upfront whole brain radiation therapy (WBRT) in patients with one to three brain metastases [6, 21]. SRS alone yielded an ICER of $41,783 per QALY, which is clearly a cost-effective strategy. A recent study by Lester-Coll et al. found a similar, albeit higher, and probably cost-effective ICER of $51,348 per QALY for SRS compared to SRS and WBRT for one metastasis and $58,903 for two to ten metastases. This model was informed by data from the JLGK0901 prospective study [12, 22••]. One notable difference that could explain the differences in these two studies are the utilities employed. Lal et al. used patient-elicited utilities ($n = 58$) using a variation of the time trade-off method. However, the actual utilities values used in the model are not reported in this manuscript, but overall quality-adjusted life expectancy (QALE) ranged from 1.48 to 1.64 for SRS alone [21]. In contrast, Lester-Coll used utilities elicited from a combination of patients and nurses ($n = 51$) using the standard gamble technique and reported overall QALE of 0.78–0.94 with SRS [22••, 43]. In addition to differences instruments used to elicit these utilities, it has been shown that populations that have direct knowledge of the health states in question, such as patients, perceive the same health states differently [44]. Indeed, Lal et al. write in their discussion that their instrument "seems to be capturing the preference of the patient for being alive versus dead, rather than their preference for being at a higher physical and/or mental functional state (19)." The primary limitation of Lester-Coll et al. is the lack of direct randomized data comparing SRS alone to WBRT alone.

Kimmel et al. compared six treatment strategies (WBRT, SRS, surgery, SRS + WBRT, surgery + WBRT, surgery + SRS) using a decision tree and also found SRS + WBRT to be clearly cost-effective compared to WBRT with an ICER of $39,117/QALY [20]. The study also found SRS alone to be clearly cost-effective relative to WBRT with an ICER of only

Table 1 ISPOR criteria

Best practice criteria
1 Every model should have non-technical documentation that should be freely accessible to any interested reader. At a minimum, it should describe in non-technical terms the type of model and intended applications; funding sources; model structure; inputs, outputs, other components that determine the model's function, and their relationships; data sources; validation methods and results; and limitations
2 Every model should have technical documentation, written in sufficient detail to enable a reader with the necessary expertise to evaluate the model and potentially reproduce it. The technical documentation should be made available openly or under agreements that protect intellectual property, at the discretion of the modelers
3 Validation should include an evaluation of face validity of a model's structure, evidence, problem formulation, and results. A description of the process used to evaluate face validity should be made available on request. To the greatest extent possible, evaluation of face validity should be made by people who have expertise in the problem area, but are impartial, and preferably blinded to the results of the analysis. If face validation raises questions, these issues should be discussed in the report
4 Models should be subjected to rigorous verification. The methods should be described in the model's non-technical documentation. Pertinent results of verification should be made available on request
5 Modelers should search for modeling analyses of the same or similar problems and discuss insights gained from similarities and differences in results
6 There should be a formal process for conducting external validation that includes:
– Systematic identification of suitable data sources; justification of the selection; specification of whether a data source is dependent, partially dependent, or independent; description of which model parts are evaluated by each source
– Simulation of each source
– Comparison of results, including descriptions of
– Data source
– Simulation setup
– Discrepancies between source and simulation, and their implications
– Discrepancies between simulation and observed results
– Sensitivity analyses
– Quantitative measures of how well the model's results match the source outcomes

ISPOR international society for pharmacoeconomics and outcomes research

$7377/QALY. However, there are significant limitations to this study. Kimmel et al. used a large variety of sources for estimates of treatment efficacy that resulted in a mean life expectancy of 28.9 weeks with WBRT compared to 47 weeks for SRS and 50.9 weeks for SRS + WBRT. There is considerable selection bias when comparing outcomes of older WBRT trials to contemporary cohorts of favorable prognosis patients selected for SRS. With the exception of one trial [6], the majority of randomized controlled trials data have not demonstrated differences in survival between SRS and WBRT when patients are properly stratified and randomly assigned treatment [3–5, 10]. The authors did not test their assumptions of these differences in survival outcomes on sensitivity analyses. This study used Karnofsky performance scale rather than utilities to adjust for quality-of-life. Kimmel et al. also did not take into account costs of surveillance, complications, or end-of-life care into their cost estimates. Finally, the manuscript does not include a figure of the actual decision model employed in the paper, and the lack of model transparency limits the interpretation of the results. The only other only cost-effectiveness study to date that has strictly compared SRS alone to WBRT found SRS to be with possibly cost-effective ICERs of $117,418 to $123,256 [22••].

Two published cost-effectiveness studies of SRS for brain metastases retrospectively compared the costs and outcomes of individual patients. Hall et al. reviewed the records of 289 patients treated at a single institution and found no differences in survival across treatment groups [19]. However, there were differences in the average cost per month of median survival: $2412 per month for SRS alone, $3220 per month for SRS + WBRT, and $4360 per month for surgery + SRS ($P < 0.03$). Compared with SRS + WBRT, SRS alone had an average incremental cost savings of $110 per patient. A strength of this study is the capturing of all costs related to primary therapy of brain metastases, including salvage treatment. However, other cancer costs, such as subsequent systemic therapies and end-of-life care, are not captured. In addition, the study does not consider quality-of-life and therefore QALYs as an endpoint, which is a crucial consideration in focal versus whole brain treatment.

Table 2 Selected studies

Reference	Site	Country/payer	Type of study	Arms	Result/ICER
Hall et al. [19]	Brain	USA/Medicare	Retrospective	1. SRS 2. SRS + WBRT 3. S + SRS	SRS dominant
Kimmel et al. [20]	Brain	USA/multiple	Decision tree	6 combinations of surgery, SRS, and WBRT	SRS vs. WBRT $7377 SRS + WBRT vs. WBRT $39,117
Lal et al. [21]	Brain	USA/multiple	Decision tree	1. SRS 2. SRS + WBRT	SRS vs. SRS + WBRT $41,783
Lester-Coll et al. [22••]	Brain	USA / Medicare	Markov model	1. SRS 2. SRS + WBRT 3. WBRT	SRS vs. SRS + WBRT: $51,438 SRS vs. WBRT: $117,418 SRS + WBRT vs. WBRT: $746,997
Savitz et al. [23]	Brain	USA/Medicare	Markov model	1. WBRT 2. HA-WBRT 3. SRS + WBRT 4. SRS + HA-WBRT	6-month LE: SRS $92,478 12-month LE: HA-WBRT, $42,872 24-month LE: SRS + HA-WBRT, $80,253
Wernicke et al. [24]	Brain	USA/multiple	Retrospective	1. S + Cs-131 2. S + SRS	S + Cs-131 dominant
Haley et al. [25]	Bone	USA/Medicare	Retrospective	1. SBRT 2. 3DCRT	3DCRT associated with 29–71% of SBRT cost and more acute toxicity
Kim et al. [26••]	Bone	USA/Medicare	Markov model	1. SBRT 2. 3DCRT	SBRT $124,552
Papatheofanis et al. [27]	Bone	USA/Medicare	Markov model	1. SRS 2. 3DCRT	SRS $41,500
Leung et al. [28]	Liver	Taiwan/National Health Insurance	Markov model	1. Sorafenib 2. SBRT	Sorafenib NT$3,788,238
Lanni et al. [29]	Lung	USA/Medicare	Retrospective	1. SBRT 2. 3DCRT	SBRT dominant
Lester-Coll et al. [30]	Lung (oligomets)	USA/Medicare	Markov model	1. SBRT 2. Surgery 3. Systemic therapy	NSCLC (adenocarcinoma): SBRT dominant NSCLC (EGFR mutated): SBRT $126,303 NSCLC (squamous): SBRT $902,849 vs. paclitaxel/-carboplatin Melanoma: surgery $3,494,568 vs. SBRT Colon: surgery dominant
Mitera et al. [31]	Lung	Canada/Ontario Ministry of Health and	Retrospective	1. SBRT 2. 3DCRT	SBRT $1120

Table 2 (continued)

Reference	Site	Country/payer	Type of study	Arms	Result/ICER
		Long-Term Care			
Puri et al. [32]	Lung	USA/Medicare	Markov model	1. SBRT 2. Surgery	Surgery $7753
Shah et al. [33••]	Lung	USA/Medicare	Markov model	1. SBRT 2. Surgery	Clearly operable: surgery $13,216 Marginally operable: SBRT dominant
Smith et al. [34••]	Lung	USA/Medicare	Retrospective	1. SBRT 2. Sublobar resection 3. Lobectomy	Sublobar resection vs. SBRT: $45,683 Lobectomy vs. SBRT: $28,645
Sher et al. [35]	Lung	USA/Medicare	Markov model	1. SBRT 2. 3DCRT 3. RFA	SBRT vs. 3DCRT: $6000 SBRT vs. RFA: $14,100
Leung et al. [36]	Pancreas	Taiwan/National Health Insurance	Markov model	1. Gem-IMRT 2. Gem-SBRT 3. Gem	Gem-IMRT vs. Gem: NT$27,120,168 Gem-SBRT vs. Gem: NT$2,145,683
Murphy et al. [37]	Pancreas	USA/Medicare	Markov model	1. Gem-3DC-RT 2. Gem-IMRT 3. Gem-SBRT 4. Gem	Gem-SBRT vs. Gem: $69,500 Gem-SBRT vs. Gem-IMRT: SBRT dominant Gem-SBRT vs. Gem-3DCRT: SBRT dominant
Hodges et al. [38]	Prostate	USA/Medicare	Markov model	1. SBRT 2. IMRT	SBRT dominant
Halpern et al. [39]	Prostate	USA/Medicare	Retrospective	1. SBRT 2. IMRT 3. Proton therapy 4. Brachytherapy	SBRT associated with $9945 and $27,561 savings in cost compared to IMRT and proton therapy but higher toxicity
Parthan et al. [40]	Prostate	USA/Medicare	Markov model	1. SBRT 2. IMRT 3. PT	SBRT dominant
Sher et al. [41••]	Prostate	USA/Medicare	Markov model	1. Robotic SBRT 2. Non-robotic SBRT 3. IMRT	IMRT vs. robotic SBRT: $285,000 IMRT vs. non-robotic SBRT: $591,100
Yu et al. [42••]	Prostate	USA/Medicare	Retrospective	1. SBRT 2. IMRT	SBRT associated with $7378 savings in cost but higher toxicity

ICER incremental cost-effectiveness ratio, *SBRT* stereotactic body radiation therapy, *WBRT* whole brain radiation therapy, *HA* hippocampal-avoidance, *SRS* stereotactic radiosurgery, *3DCRT* three-dimensional conformal radiation therapy, *S* surgery, *Cs* cesium, *LE* life expectancy, *NT$* new Taiwan dollar, *NSCLC* non-small cell lung cancer, *EGFR* epidermal growth factor receptor, *RFA* radiofrequency ablation, *Gem* gemcitabine, *IMRT* intensity modulated radiation therapy, *PT* proton therapy

Wernicke et al. is the only study to our knowledge that compares intraoperative brachytherapy (cesium-131) to surgery and SRS for brain metastases [24]. Treatment records of 49 patients were reviewed and brachytherapy was the dominant strategy as

it was associated with lower costs and similar survival compared to SRS. However, this study only examined hospital-related costs and not patient costs, including all subsequent treatment which significantly limits its generalizability.

Finally, Savitz et al. is the only published cost-effectiveness analysis to date that compares SRS to hippocampal-sparing WBRT to SRS [23]. This is an important consideration given that the majority of studies reviewed here find improved QALYs with SRS presumably by improving cognitive outcomes. The model used four simulated cohorts of patients aged 65 years with one to three brain metastases with median survivals of 3, 6, 12, and 24 months. The authors found increasing cost-effectiveness of both SRS and hippocampal-sparing WBRT compared to WBRT with increasing life expectancy. For example, assuming 3-month median survival, SRS and hippocampal-sparing WBRT were associated with ICERs of $131,245 and $3,339,718, respectively. However, assuming 24-month median survival yielded ICERs of $24,701 and $80,253, respectively. Thus, we can conclude that both treatments are clearly or probably cost-effective versus whole-brain radiotherapy for best-prognosis patients. The primary limitation of this study is the lack of data on longer term neurocognitive outcomes associated with hippocampal-sparing WBRT.

Bone

There are three published cost-effectiveness analyses comparing spine SBRT to fractionated external beam radiation therapy (EBRT). Papatheofanis et al. used a Markov model to compare CyberKnife™ SBRT to EBRT and found that SBRT was associated with $1933 less than EBRT for a marginal gain of 0.08 QALYs, with a clearly cost-effective ICER of $41,500 per QALY [27]. In contrast, Kim et al. found that SBRT was associated with a similar gain in QALYs (0.08), but at an additional cost of $7380, resulting in an ICER of $124,552 per QALY [26••]. On sensitivity analysis, SBRT became cost-effective at $100,000 per QALY if median survival was greater than 11 months. There are significant differences in the design of these models and parameters used that likely explain the discrepancy. While both models estimated a higher treatment cost associated with SBRT, the study by Papatheofanis et al. did not incorporate re-treatment costs. Rather, patients whose tumors relapsed went on to receive palliative care. Relapsed spinal tumors in Kim et al. were re-treated, but palliative care and/or end-of-life costs were not captured. Papatheofanis et al. also assumed a 10-fold reduction in tumor relapse after SBRT while Kim et al. assumed a 3-fold reduction: neither figure are supported by robust data. The comparatively higher relapse rate with EBRT and higher costs associated with relapses are likely to explain why net SBRT costs were lower than EBRT in the study by Papatheofanis et al. Similar to Kim et al., a retrospective matched-pair analysis found higher costs associated with SBRT, but lower rates of acute toxicity and re-treatment. ICERs were not calculated for this study [25].

Liver

There is a single cost-effectiveness study of SBRT for liver hepatocellular carcinoma that compares SBRT to sorafenib. Eligible patients had advanced hepatocellular carcinoma unsuitable for surgery, transcatheter arterial chemoembolization, or radiofrequency ablation (RFA) [28]. The ICER for sorafenib compared to SBRT was NT$3,788,238 per QALY, which is higher than the WTP of threshold of Taiwan, which is NT$2,213,145 (US$67,065). Assuming this WTP, the probability of SBRT being cost-effective was 100% on probabilistic sensitivity analyses. This model is limited by the use of phase I/II studies as outcome data.

Lung

There are several cost-effectiveness studies on SBRT for treating early stage lung cancer. SBRT was initially compared with fractioned EBRT in a single-institution retrospective study from a US payer perspective by Lanni et al. [29]. SBRT was associated with lower cost ($13,639/QALY EBRT vs. $10,616/QALY SBRT, $P < 0.01$) and improved overall survival (71 vs. 42%, $P < 0.05$), although only initial treatment costs were captured in this study. A study from the Canadian public payer perspective found SBRT to cost more than EBRT ($8042 vs. $6886), although both were substantially less expensive than the costs reported by Lanni et al. SBRT was still cost-effective in the Canadian study, with an ICER of $1120 per life-year. Differences in costs observed can be attributed to differences in reimbursement between US and Canadian health care systems. In Canada, activity-related reimbursements based on the total course of treatment are used to calculate the direct costs of radiation rather than the number of fractions received [31].

The first Markov model published on lung cancer SBRT was published by Sher et al. and compared 3DCRT, SBRT, and RFA for medically inoperable, early stage non-small cell lung cancer [35]. SBRT was clearly cost-effective over both 3DCRT and RFA with ICERs of $6000 and $14,000 per QALY, respectively. The primary limitation of this study was the use of primarily single-arm phase II and retrospective data; however, SBRT remained cost-effective under nearly every scenario studied on sensitivity analysis.

Puri et al. compared SBRT to surgical resection and found that surgery was clearly cost-effective with an ICER of $7753 per QALY [32]. However, this model used data from a single institution where surgery patients were propensity-score matched with SBRT patients. Notably, even after matching, SBRT patients had statistically significant lower FEV1 (0.50 vs. 0.77, $P < 0.001$) and DLCO values (0.50 vs. 0.81, $P = 0.01$). In this study, overall survival at 5 years was

11.5% higher for patients who underwent surgery while cause-specific survival was equivalent, suggesting that the observed inferior survival associated with SBRT was a function of selection bias rather than a treatment-related effect. In contrast, a pooled analysis of two randomized trials comparing lobectomy to SBRT actually suggested improved survival with SBRT [7]. Shah et al. examined the cost-effectiveness of lobectomy and SBRT in both clearly operable and medically inoperable lung cancer patients [33••]. In patients with medically operable lung cancer, SBRT was the dominant cost-effective strategy, even up to a WTP of $500,000 per QALY on sensitivity analyses. However, for patients with clearly operable lung cancer, lobectomy was cost-effective with an ICER of $13,216 per QALY and in nearly every sensitivity analysis.

Smith and colleagues used the SEER-Medicare database to examine the cost-effectiveness of SBRT relative to surgery [34••]. The ICERs for sublobar resection and lobectomy relative to SBRT were clearly cost-effective: $45,683 and $28,645 per life-year gained, respectively. Interestingly, the direct costs of SBRT in this study were $15,000 higher than estimated by Shah et al. Similarly, costs of sublobar resection and lobectomy were $27,000 and $34,000 higher than estimated by Shah et al., respectively [33••, 34••]. Despite no statistically significant differences in outcomes, surgery was nonetheless cost-effective in Smith et al. primarily due to marginal improvements in survival with surgery (e.g., 3.8 years with SBRT vs. 4.7 years with lobectomy). Similar to Puri et al., despite the authors' best attempts to control for covariates, there remains potential for unmeasured confounding, which would likely bias the results in favor of surgery given the health requirements for operability. Moreover, life-years were used rather than QALYs, which underestimates the potential adverse quality-of-life outcomes following surgery. Overall, similar to the findings of Shah et al., the cost-effective data are consistently in favor of surgery for surgical candidates and of SBRT for inoperable lung cancer.

An analysis by Lester-Coll is the only cost-effectiveness study to date to examine the cost-effectiveness of SBRT for treating lung oligometastases. The authors examined a variety of cancers—melanoma, NSCLC adenocarcinoma without an EGFR mutation, NSCLC adenocarcinoma with an EGFR mutation, NSCLC squamous cell carcinoma, and colon cancer [30]. They found that where systemic therapy options are more expensive (e.g., colon cancer, melanoma), local therapy is preferred if it can delay systemic therapy without negatively impacting survival. Where systemic therapy options are relatively less expensive (e.g., erlotinib), systemic therapy remains preferable. For example, while SBRT was dominant for NSCLC adenocarcinoma without an EGFR mutation, the ICER for NSCLC with an EGFR mutation was possibly cost-effective at $126,303 per QALY. In order for SBRT to be cost-effective at treating lung oligometases from squamous cell lung carcinoma, the cost of SBRT had to be less than $9459. These data are limited by the lack of comparative effectiveness data for managing oligometastases that informed the model.

Pancreas

Two cost-effectiveness studies have examined the role of SBRT in the management of localized cancer of the pancreas. From a US perspective, Murphy et al. compared the cost-effectiveness gemcitabine alone, gemcitabine/3DCRT gemcitabine/IMRT, and gemcitabine/SBRT [37]. Gemcitabine/SBRT was probably cost-effective at $69,500 per QALY compared to gemcitabine alone and was dominant over both 3DCRT and IMRT. A probabilistic sensitivity analysis found that gemcitabine/SBRT was cost-effective in 21% of simulations compared to 79% for gemcitabine alone, assuming a WTP of $50,000 per QALY. The main limitation of the trial is the use of data from a trial that closed early due to poor accrual. Nonetheless, gemcitabine/SBRT appears to be cost-effective over conventional radiation therapy for patients in whom radiation is indicated [45]. From the Taiwanese payer perspective, Leung et al. performed a similar study comparing gemcitabine alone, gemcitabine/IMRT, and gemcitabine/SBRT [36]. The study assumed a WTP of NT$2,021,760 (US$67,392). While gemcitabine/IMRT was not cost-effective (ICER of NT$27,120,268 per QALY), SBRT was probably cost-effective with an ICER of NT$2,145,683 per QALY. On probabilistic sensitivity analyses, gemcitabine/IMRT was cost-effective in 0% of simulations while gemcitabine/SBRT was cost-effective in 50%. Despite the differences in health care systems, the results of the two studies are very similar, probably because they used the same trial as primary model input [45].

Prostate

There is an increasing use of prostate SBRT in the USA [39]. Prathan et al. were the first to assess the cost-effectiveness of prostate SBRT and used a Markov model using primarily retrospective data to inform their model [40]. SBRT was dominant over both IMRT and proton therapy and remained cost-effective in 75 and 94% of probabilistic simulations compared to IMRT and proton therapy assuming a WTP of $50,000 per QALY. The study by Prathan et al. was published at the time where there was very limited data to inform their mode. Sher et al. compared IMRT to robotic and non-robotic prostate SBRT assuming worse toxicity with SBRT in the base case [41••]. The ICERs for IMRT over robotic and non-robotic SBRT were $285,000 and $591,100 per QALY, respectively. SBRT remained most likely to be cost-effective at a WTP of $100,000 per QALY on probabilistic sensitivity analyses. Similar to

Prathan et al., the study is limited by the use of non-randomized data to inform the model, although this study did include a larger variety of sources.

Yu et al. performed a SEER-Medicare analysis comparing costs and outcomes of prostate SBRT to IMRT and found that SBRT was associated with $7378 savings in cost but higher rates of urethritis, urinary incontinence, and/ or obstruction [42••]. Another recently published SEER-Medicare analysis included patients who also received proton therapy and brachytherapy and excluded men with baseline genitourinary and gastrointestinal comorbidities [39]. Similar to Yu et al., they found that SBRT was associated with $9945 savings compared to IMRT and $27,561 savings compared to proton therapy, but higher rates of urinary incontinence.

Assessment of Model Calibration and Transparency

Of the 16 modeling studies,15 conformed to transparency best practice (Table 3), meaning the model was displayed and made clear to the reader. The cost-effectiveness analysis of various treatment options for brain metastases by Kimmel et al. did not include a figure of the decision tree used in their model [20]. It is thus more difficult to interpret their findings, and ultimately the study is not reproducible unless the authors release their model. Only 6 of the 16 modeling studies performed rigorous calibration as described by the ISPOR guidelines [18, 22••, 23, 30, 33••, 35, 41••]. These studies all describe some sort of model calibration in which the outcomes of the model are compared and modified such that they mirror the outcomes of the studies that inform the model. If authors do not report how model data fit published data, the interpretation of model results is limited, as it is impossible to be certain that the model is accurately representing known clinical outcomes. Of note, there was no published study that fully conformed to the third criteria, "to the greatest extent possible, evaluation of face validity should be made by people who have expertise in the problem area, but are impartial, and preferably blinded to the results of the

Table 3 Modeling studies that conformed to transparency best practice

Reference	Best practice criteria					
	1: Non-technical documentation	2: Technical documentation	3: Face validation	4: Rigorous verification	5: Model comparisons	6: External validation
Kimmel et al. [20]	No	No	No	No	Yes	No
Lal et al. [21]	Yes	Yes	No	No	No	No
Lester-Coll et al. [22••]	Yes	Yes	No	Yes	Yes	Yes
Savitz et al. [23]	Yes	Yes	No	Yes	Yes	Yes
Kim et al. [26••]	Yes	Yes	No	Yes	Yes	No
Papatheofanis et al. [27]	Yes	Yes	No	No	Yes	No
Leung et al. [28]	Yes	Yes	No	No	Yes	No
Lester-Coll et al. [30]	Yes	Yes	No	Yes	Yes	Yes
Puri et al. [32]	Yes	Yes	No	No	Yes	No
Shah et al. [33••]	Yes	Yes	No	Yes	Yes	Yes
Sher et al. [35]	Yes	Yes	No	Yes	Yes	Yes
Leung et al. [36]	Yes	Yes	No	No	Yes	No
Murphy et al. [37]	Yes	Yes	No	No	Yes	No
Hodges et al. [38]	Yes	Yes	No	No	Yes	No
Parthan et al. [40]	Yes	Yes	No	No	Yes	No
Sher et al. [41••]	Yes	Yes	No	Yes	Yes	Yes

analysis." To this end, we hope that a pragmatic conclusion of this review is the increased awareness and ultimately practice of model calibration in future modeling studies. Investigators should clearly report the results of their calibration testing, focusing on the endpoints that are particularly relevant for the model (e.g., overall survival, locoregional control, toxicity, etc.), and editors should insist on such information prior to manuscript acceptance.

Conclusions

Cost-effectiveness analyses of SRS and SBRT are well represented across many disease sites and employ a variety of methodological techniques. Stereotactic radiosurgery and SBRT are likely to be cost-effective management strategies, which appear to be driven by absolute cost savings from fewer radiation fractions billed to payers, while still providing similar or better cancer control compared to other techniques. However, rigorous model calibration is lacking in a majority of studies which unfortunately limits the validity and generalizability of these studies. We urge modelers to conform to the ISPOR guideline for model transparency and validation [18]. In addition, we observed that the largest limitation of most of these modeling studies is the use of retrospective and non-randomized data to inform the model. While this also limits the conclusions drawn from these models, cost-effectiveness studies can be very useful in the early stages of implementation of new technology when extensive data regarding clinical effectiveness may not yet be available. Indeed, well-performed cost-effectiveness analyses can illuminate the many areas where radiation is cost-effective and where investment in new technology is needed. Equally important is the ability of CEA to highlight the key areas of research that are necessary to properly perform technology assessment, which may range from costing studies to efficacy and toxicity analyses to utility assessment.

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Compliance with Ethical Standards

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