Cost-effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for up to 10 brain metastases

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OBJECTIVE The JLGK0901 study found that stereotactic radiosurgery (SRS) is a safe and effective treatment option for treating up to 10 brain metastases. The purpose of this study is to determine the cost-effectiveness of treating up to 10 brain metastases with SRS, whole-brain radiation therapy (WBRT), or SRS and immediate WBRT (SRS+WBRT).

METHODS A Markov model was developed to evaluate the cost effectiveness of SRS, WBRT, and SRS+WBRT in patients with 1 or 2–10 brain metastases. Transition probabilities were derived from the JLGK0901 study and modified according to the recurrence rates observed in the Radiation Therapy Oncology Group (RTOG) 9508 and European Organization for Research and Treatment of Cancer (EORTC) 22952–26001 studies to simulate the outcomes for patients who receive WBRT. Costs are based on 2015 Medicare reimbursements. Health state utilities were prospectively collected using the Standard Gamble method. End points included cost, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs). The willingness-to-pay (WTP) threshold was \$100,000 per QALY. One-way and probabilistic sensitivity analyses explored uncertainty with regard to the model assumptions.

RESULTS In patients with 1 brain metastasis, the ICERs for SRS versus WBRT, SRS versus SRS+WBRT, and SRS+WBRT versus WBRT were \$117,418, \$51,348, and \$746,997 per QALY gained, respectively. In patients with 2–10 brain metastases, the ICERs were \$123,256, \$58,903, and \$821,042 per QALY gained, respectively. On the sensitivity analyses, the model was sensitive to the cost of SRS and the utilities associated with stable post-SRS and post-WBRT states. In patients with 2–10 brain metastases, SRS versus WBRT becomes cost-effective if the cost of SRS is reduced by \$3512. SRS versus WBRT was also cost effective at a WTP of \$200,000 per QALY on the probabilistic sensitivity analysis.

CONCLUSIONS The most cost-effective strategy for patients with up to 10 brain metastases is SRS alone relative to SRS+WBRT. SRS alone may also be cost-effective relative to WBRT alone, but this depends on WTP, the cost of SRS, and patient preferences.

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KEY WORDS stereotactic radiosurgery; whole-brain radiation therapy; brain metastases; cost effectiveness; Markov model; oncology

Up to 40% of cancer patients will develop brain metastases during the course of their disease.⁹ Whole-brain radiation therapy (WBRT) has historically been used to treat brain metastases and is associated with high rates of intracranial control but often results in significant neurocognitive sequelae.^{3,6,20,24} Three randomized controlled trials that evaluated stereotactic radiosurgery

(SRS) versus SRS followed by WBRT for 1–4 brain metastases found that the addition of WBRT improved intracranial control and decreased the need for salvage therapies, but worsened multiple quality-of-life indices.^{2,6,14}

We previously developed a decision analytic model that compared SRS alone to SRS and immediate WBRT (SRS+WBRT) using data from the European Organiza-

ABBREVIATIONS EORTC = European Organization for Research and Treatment of Cancer; ICER = incremental cost-effectiveness ratio; IQR = interquartile range; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; RTOG = Radiation Therapy Oncology Group; SRS = stereotactic radiosurgery; SRS+WBRT = stereotactic radiosurgery and immediate whole-brain radiation therapy; WBRT = whole-brain radiation therapy; WTP = willingness to pay.

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FIG. 1. A: Abbreviated decision tree and Markov model used to compare 3 strategies for treating 1 or 2–10 brain metastases. **B:** Influence diagram shows the network of 3 disease-related health states.

tion for Research and Treatment of Cancer (EORTC) 22952–26001 randomized controlled trial. We found that SRS improved quality-adjusted life years (QALYs) and SRS+WBRT can be reserved for patients with poor performance status, regardless of which treatment they receive.¹⁸ Subsequently, the JLGK0901 prospective observational study found that the overall survival (OS) of patients with 5–10 brain metastases treated with SRS alone is noninferior to patients with 2–4 brain metastases treated with SRS alone.²⁷ However, comparative effectiveness studies evaluating SRS and WBRT for treating up to 10 brain metastases are lacking. In addition, the costs of treating up to 10 brain metastases with SRS have not been previously examined. Therefore, we sought to update our model to assess the cost-effectiveness of treating up to 10 brain metastases with SRS and WBRT.

Methods

We report our methods according to the guidelines of

the Society for Medical Decision Making for good research practices, model transparency, and validation.⁸

Markov Model

Our Markov model has been previously described in detail.¹⁸ While our previous model compared SRS alone to SRS+WBRT, the current updated model contains a third arm of WBRT alone (Fig. 1). In addition, patients are stratified as having 1 or 2–10 brain metastases. Patients transition between different health states, including a posttreatment stable state, a state of intracranial progression, and a transient state of neurological death. Patients in the stable state undergo MRI of the brain every 1.5 or 3 months after SRS or WBRT, respectively. We obtain an MRI every 1.5 months after SRS because prognostic, volumetric changes in the treated lesions are identified at this time interval.²⁵ Patients with 1 and 2–10 brain metastases who underwent SRS alone received additional salvage SRS procedures 33% and 43% of the time, respectively.²⁷ While in the stable and intracranial progression states, patients can

TABLE 1. Model parameters and assumptions

Variable	Base Case & Modeled Distribution Values (IQR)	Authors & Year
β -distributed transition probabilities		
Progression from stable state		Yamamoto et al., 2014
1 brain metastasis	0.016 (0.012–0.020)	
2–10 brain metastases	0.029 (0.022–0.036)	
Death from stable state		Yamamoto et al., 2014
1 brain metastasis	0.040 (0.030–0.050)	
2–10 brain metastases	0.059 (0.044–0.073)	
Death from progression state		Yamamoto et al., 2014
1 brain metastasis	0.078 (0.059–0.098)	
2–10 brain metastases	0.045 (0.034–0.057)	
Salvage SRS		Yamamoto et al., 2014
1 brain metastasis	0.33 (0.24–0.41)	
2–10 brain metastases	0.43 (0.32–0.54)	
Neurological death		Yamamoto et al., 2014
1 brain metastasis	0.10 (0.075–0.13)	
2–10 brain metastases	0.04 (0.03–0.05)	
Probability of neurocognitive decline		Yamamoto et al., 2014
1 brain metastasis	0.004 (0.003–0.005)	
2–10 brain metastases	0.004 (0.003–0.005)	
Probability of radionecrosis	0.001 (0.00075–0.0013)	Yamamoto et al., 2014
γ -distributed HR for impact of SRS boost on local control	1.20 (0.60–1)	Andrews et al., 2004
γ -distributed HRs for impact of WBRT on outcomes		
Intracranial failure	0.61 (0.46–0.77)	Kocher et al., 2011
Salvage SRS	0.31 (0.23–0.39)	Kocher et al., 2011
Neurocognitive decline	1.55 (1.16–1.94)	Kocher et al., 2011
β -distributed utilities		
Stable after SRS	0.85 (0.75–0.90)	Lester-Coll et al., 2016 ¹⁷
Stable after WBRT	0.70 (0.50–0.80)	Lester-Coll et al., 2016 ¹⁷
Progression	0.55 (0.45–0.65)	Lester-Coll et al., 2016 ¹⁷
Neurological death	0.25 (0.15–0.30)	Lester-Coll et al., 2016 ¹⁷
Radionecrosis	0.50 (0.40–0.60)	Lester-Coll et al., 2016 ¹⁷
Neurocognitive decline	0.30 (0.20–0.40)	Lester-Coll et al., 2016 ¹⁷
γ -distributed costs		
SRS	\$13,389 (\$10,042–\$16,737)	Institutional Medicare fees
WBRT	\$4,949 (\$3,712–\$6,186)	Institutional Medicare fees
Craniotomy	\$21,828 (\$16,371–\$27,285)	Institutional Medicare fees
MRI of the brain w or w/o contrast	\$778 (\$584–\$973)	Institutional Medicare fees
Progression	\$6,055 (\$4,541–\$7,569)	Obermeyer et al., 2014
Death	\$5,389 (\$4,042–\$6,736)	Obermeyer et al., 2014

develop Grade 3–4 toxicities such as neurocognitive decline and radionecrosis. Patients who experienced Grade 3–4 radionecrosis underwent craniotomy. Toxicities, neurological death, and the use of salvage therapy were followed in the model using trackers with individual Monte Carlo simulations. The time horizon of the model was 24 months in order to correspond to the outcomes reported in the JLGK0901 study. The full structure of the model is provided in the Supplemental Appendix.

The primary end points included QALYs and cumulative

costs. Incremental cost-effectiveness ratios (ICERs)—the difference in costs divided by the difference in effectiveness between 2 treatment arms—were computed. A treatment strategy with an ICER value that is less than the societal willingness to pay (WTP) is cost-effective. In the base case, WTP was defined as \$100,000 per QALY gained, but we also explored up to \$300,000 per QALY gained.

One-way sensitivity analyses—in which 1 parameter was varied while all others were held constant—were conducted for all parameters to evaluate the extent to which

TABLE 2. Internal validation metrics

Internal Validation Metric	Model	JLGK0901 Clinical Data
1 brain metastasis		
Median OS	15 mos	14 mos
Median PFS	12 mos	11 mos
Neurological death	10%	10%
Neurocognitive decline	6%	6%
Radionecrosis	1%	1%
2–10 brain metastases		
Median OS	12 mos	11 mos
Median PFS	8 mos	6 mos
Neurological death	10%	9%
Neurocognitive decline	10%	10%
Radionecrosis	1%	1%

FIG. 2. Calibration of the model comparing OS to the outcomes of the JLGK0901 study.

uncertainty and variability influenced the model results. We studied ranges that corresponded to the interquartile range (IQR) around a parameter. The thresholds for which the preferred strategy (defined by the highest gain in QALYs) shifted were identified. Probabilistic sensitivity analyses—where the values are drawn randomly from a probability distribution function and repeated 100,000 times using Monte Carlo simulations—were performed to explore the impact of uncertainty with regard to the transition probabilities, costs, and utilities on the model results. All analyses were conducted in TreeAge Pro (version 2016; TreeAge).

Model Inputs

The model inputs and assumptions are summarized in Table 1. We updated our previously published model using data on OS and progression-free survival (PFS), as reported in the JLGK0901 study for patients with 1 or 2–10 brain metastases, because these end points were significantly different from one another based on the number of brain metastases.²⁷ Data were graphically extracted from the published Kaplan-Meier curves using a validated graphical digitizer (WebPlotDigitizer, version 3.4; Ankit Rohatgi). We then calibrated our cycle-specific transition probabilities to the JLGK0901 data by using an iterative, nonlinear optimizing algorithm to minimize the difference between the target data (JLGK0901) and the modeled data. For the probabilistic sensitivity analysis, uncertainty in the transition probabilities was modeled using β distributions (which are bounded by 0 and 1) based on the IQR.⁵ The rates of local control, intracranial failure, neurocognitive decline, and salvage SRS for the patients treated with SRS alone were then modified by the hazard ratios associated with WBRT that were reported in the Radiation Therapy Oncology Group (RTOG) 9508 and EORTC 22952–26001 trials in order to model outcomes with WBRT alone or SRS+WBRT, respectively.^{1,14} Uncertainty in the estimates of the hazard ratios were modeled by γ distributions, which are bounded by 0 and infinity.⁴

Costs and Utilities

This analysis was conducted from a US third-party payer perspective, and costs were inflated to 2015 US dollars using the Consumer Price Index (http://www.bls.gov/data/inflation_calculator.htm). We used institutional Medicare fees for the majority of the costs in our model (Table 1), while the costs of progressive cancer and end-of-life care were lifted from a published analysis of nationally representative Medicare beneficiaries with poor-prognosis cancer.²³ These estimates of poor-prognosis cancer included hospitalizations and palliative care; however, the costs of cancer-directed treatment including surgery and chemotherapy were excluded. The cost of SRS was based on a course of Gamma Knife radiosurgery with 10 shots, which is the maximum reimbursement that Medicare provides for this treatment at our institution. Utilities quantify patient preferences for health states on a scale from 0 to 1, where 1 represents perfect health and 0 is death. Each disease state in the model was assigned a health utility score based on a Standard Gamble assessment of 55 patients and nurses at Yale.¹⁷ These utility values incorporate minor toxicities from SRS and WBRT, and full descriptions of the health states can be found in that publication.¹⁷ Costs and utilities were discounted at 3% per year. Uncertainty in utilities and costs were modeled by the β and γ distributions, respectively.

Results

Model Validation and Base Case Results

The modeled outcomes closely mirrored the target clinical data with regard to OS, PFS, neurological death, and the rates of neurocognitive decline and radionecrosis (Table 2 and Fig. 2).

In patients with 1 brain metastasis, the ICERs for SRS versus WBRT, SRS versus SRS+WBRT, and SRS+WBRT versus WBRT were \$117,418, \$51,348, and \$746,997 per QALY gained, respectively (Table 3). In patients with 2–10 brain metastases, while the cumulative costs were

TABLE 3. Base case results

Treatment	Cost	QALYs	ICER
1 brain metastasis			
SRS	\$34,340	0.94	\$117,418 vs WBRT
WBRT	\$14,502	0.77	\$51,348 vs SRS+WBRT
SRS+WBRT	\$26,489	0.79	\$746,997 vs WBRT
2–10 brain metastases			
SRS	\$41,494	0.78	\$123,256 vs WBRT
WBRT	\$22,060	0.63	\$58,903 vs SRS+WBRT
SRS+WBRT	\$32,460	0.64	\$821,042 vs WBRT

higher and QALYs were lower, the ICERs were similar: \$123,256, \$58,903, and \$821,042 per QALY gained, respectively. Therefore, while SRS is a very cost-effective option compared with SRS+WBRT—and SRS+WBRT is the least cost-effective option relative to WBRT—the cost-effectiveness of SRS alone compared with WBRT alone just exceeds our predetermined threshold of \$100,000 per QALY and warrants further investigation.

Sensitivity Analysis

The following sensitivity analyses concern the case of SRS versus WBRT for 2–10 brain metastases, which was found to have an ICER of \$123,256 in the base case. One-way sensitivity analyses revealed 3 important threshold values where the base case results changed. If the cost of SRS is $\leq$ \$9877 (base case value \$13,389), SRS alone becomes cost-effective at the \$100,000 per QALY threshold. If the utility of WBRT is $\leq$ 0.65 (base case value 0.70), WBRT is no longer cost effective at \$100,000 per QALY. Finally, if the utility of SRS is $\geq$ 0.90, SRS alone becomes cost effective at \$100,000 per QALY. The model was not sensitive to other parameters such as the rate of salvage therapy, disease transition probabilities (i.e., OS and PFS), and the other costs of care shown in Table 1. The impact of varying these costs and utilities are summarized in

Table 4. For instance, if perfect health is assumed for the stable state after SRS, or if 50% health is assumed for the stable state after WBRT, then the cost of SRS alone decreases to \$70,730 and \$61,472 per QALY gained, respectively. If the price of SRS decreases by 50% and 90%, the costs decreases to \$78,403 and \$38,773 per QALY gained, respectively.

Probabilistic sensitivity analysis showed the increasing probability of cost-effectiveness from 38% to 67% as WTP increased from \$100,000 to \$300,000 per QALY (Table 4 and Fig. 3). The probability of cost effectiveness also increased from 55% to 68% as the cost of SRS decreased from 50% to 90% of the base case value of \$13,389. SRS alone was preferred in 67% of simulations if the utility for the stable state after SRS was 1.0 (perfect health), assuming a WTP value of \$100,000 per QALY. However, SRS was only preferred in 1% of simulations if this utility value was lowered to 0.5, indicating that strong patient preferences for SRS are a requisite for this modality to be effective.

Discussion

We found that SRS alone is more cost-effective than SRS+WBRT for patients with up to 10 brain metastases, demonstrating ICERs of \$51,348 to \$58,903 per QALY gained. Conversely, SRS+WBRT was not a cost-effective option compared with WBRT alone, demonstrating ICERs of \$746,997 to \$821,042. SRS alone compared with WBRT alone yielded ICERs of \$117,418 to \$123,256. While this strategy was not considered cost-effective in the base case that assumed a WTP of \$100,000 per QALY, the sensitivity analysis revealed that a price reduction in the cost of SRS by \$3512 (26%) would be needed to make this a cost-effective treatment. The sensitivity analysis also revealed that patient preferences for treatments play an integral role in their perceived effectiveness.

As expected, the likelihood that SRS alone versus WBRT alone was cost-effective depended on the cost that we assume society is willing to pay. In the base case, we

TABLE 4. Summary of 1-way and probabilistic sensitivity analyses in 2–10 brain metastases

Variable	Incremental Cost	Incremental QALYs	ICER	Probability of Cost-Effectiveness
WTP				
\$100,000/QALY	\$19,434	0.15	\$123,256	38%
\$200,000/QALY	\$19,434	0.15	\$123,256	60%
\$300,000/QALY	\$19,434	0.15	\$123,256	67%
Utilities				
Stable after SRS at 1.0 health utility	\$19,434	0.27	\$70,730	67%
Stable after SRS at 0.5 health utility	\$19,434	−0.12	Dominated	1%
Stable after WBRT at 1.0 health utility	\$19,434	−0.9	Dominated	100%
Stable after WBRT at 0.5 health utility	\$19,434	0.32	\$61,472	86%
Cost				
SRS at 50% cost	\$12,059	0.15	\$78,403	55%
SRS at 10% cost	\$6,034	0.15	\$38,773	68%
SRS at 0% cost	\$4,765	0.15	\$30,658	71%

FIG. 3. Probabilistic sensitivity analysis comparing SRS to WBRT for 2–10 brain metastases. **A:** Incremental cost-effectiveness scatterplot of 10,000 Monte Carlo simulations shows the increasing likelihood of the cost effectiveness of SRS with higher WTP thresholds. **B:** Cost-effectiveness acceptability curve shows the probability of cost effectiveness as a function of WTP.

conservatively assumed a WTP threshold of \$100,000 per QALY. However, economists, as well as the WHO, have argued that based on our society's attitudes a threshold of 2× to 3× the per capita annual income should be used, or roughly \$110,000 to \$160,000 per QALY in the United States. Furthermore, others have deduced a threshold as high as \$200,000 to \$300,000 per QALY on the basis of

increased health care spending and survey data.²² To place these numbers into context, the ICER for human papilloma vaccination in high-risk populations is \$87,240 per QALY, and for end-stage renal disease dialysis the ICER is \$130,000 per QALY.^{16,22} Recent cost-effectiveness studies of cancer-targeted therapies have found ICERs in the \$400,000 to \$500,000 per QALY range.^{7,11} Therefore, while

SRS alone versus WBRT alone was not cost-effective at the \$100,000 per QALY WTP threshold, it may nonetheless be considered to be cost-effective by some health care providers and policy makers in the United States.

Previous cost-effectiveness studies have found SRS alone to be the preferred management strategy, but these studies are generally limited to patients with fewer brain metastases. A modeling study that used a decision tree with data from the MD Anderson Cancer Center randomized trial on SRS or SRS+WBRT for 1 to 3 brain metastases determined the ICER for SRS versus SRS+WBRT to be \$41,783 per QALY gained.¹⁵ A retrospective by Hall et al. reviewed the records of 289 patients treated with SRS or SRS+WBRT to determine both survival outcomes and Medicare reimbursement for all treatments incurred and found that SRS was the most cost-effective option.¹³ However, only 14% of patients in this study treated with SRS alone had more than 4 brain metastases.

Our study has limitations. While our model was primarily informed by data from the JLGK0901 study, we modified parameters based on data from RTOG 9508 and EORTC 22952–26001 to simulate outcomes with WBRT. These 3 studies have different patient populations, so outcomes may not be applicable to every individual patient with brain metastases. Furthermore, costs will inevitably vary across different health care systems. Our model is only applicable to patients with up to 10 metastases because patients with more than 10 metastases were excluded from the JLGK090 study. Our estimated costs of having progressive disease were based on a large heterogeneous sample of poor-prognosis cancer patients, which excluded the costs of cancer-directed therapies such as surgery and chemotherapy.²³ The individual costs of patients with brain metastases will vary depending on the site of disease and treatments received. We did not explicitly model the costs of minor toxicities incurred while in the stable disease state. It is possible that there are other serious toxicities and potentially costly complications from treatment that we have not accounted for in our model. We did not model newer strategies to preserve neurocognitive function, such as hippocampal-sparing intensity-modulated radiation therapy, which could impact both costs and effectiveness.^{12,26} Examining prospectively collected patient costs in a randomized trial or a registry should be the subject of a future study. Finally, our study does not incorporate other strategies for controlling intracranial metastases such as immunotherapy, which was recently shown to have activity in brain metastases from melanoma and non-small cell lung cancer with an acceptable safety profile.¹⁰ Stereotactic body radiation therapy has been shown to be cost-effective compared with pembrolizumab for pulmonary metastases.¹⁹ As Phase III data emerge for using pembrolizumab in the treatment of brain metastases, comparative and cost-effectiveness analyses of pembrolizumab, SRS, and WBRT are warranted.

Despite these limitations, we believe our conclusions are justified because our model was informed by high-quality data. Patient utilities were prospectively elicited using the Standard Gamble method,^{17,21} and the costs of the primary treatments were directly measured. Many of the limitations discussed above are equally applicable to

all 3 treatment arms, and therefore would not be expected to significantly change the results of the model.

Conclusions

For patients with up to 10 brain metastases, SRS alone is more cost effective than SRS+WBRT. SRS alone may also be more cost-effective than WBRT alone, but depends on the amount society is willing to pay for health care, the cost of SRS, and patient preferences.

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Author Contributions

Conception and design: all authors. Acquisition of data: Lester-Coll. Analysis and interpretation of data: Lester-Coll, Dosoretz, Magnuson, Chiang, Yu. Drafting the article: Lester-Coll. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Lester-Coll. Statistical analysis: Lester-Coll. Administrative/technical/material support: Yu. Study supervision: Yu.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

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