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CLINICAL STUDY

The cost-effectiveness of surgical resection and cesium-131 intraoperative brachytherapy versus surgical resection and stereotactic radiosurgery in the treatment of metastatic brain tumors

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Abstract This study aims to evaluate the cost-effectiveness of surgical resection (S) and Cesium-131 (Cs-131) [S + Cs-131] intraoperative brachytherapy versus S and stereotactic radiosurgery (SRS) [S + SRS] for the treatment of brain metastases. Treatment records as well as hospital and outpatient charts of 49 patients with brain metastases between 2008 and 2012 who underwent S + Cs-131 (n = 24) and S + SRS (n = 25) were retrospectively reviewed. Hospital charges were compared for the single treatment in question. Means and curves of survival time were defined by the Kaplan–Meier estimator, with the cost analysis focusing on the time period of the relevant treatment. Quality adjusted life years (QALY) and Incremental cost-effectiveness ratios (ICER) were calculated for each treatment option as a measure of cost-effectiveness. The direct hospital costs of treatments per patient were: S + Cs131 = $19,271 and S + SRS = $44,219. The median survival times of S + Cs-131 and S + SRS were 15.5 and 11.3 months, and the 12 month survival rates were 61 % and 49 % (P = 0.137). The QALY for S + SRS when compared to S + Cs-131 yielded a $p < 0.0001$, making it significantly more cost-effective. The ICER also revealed that when compared to S + Cs-131, S + SRS was significantly inferior ($p < 0.0001$). S + Cs-131 is more cost-effective compared with S + SRS based on hospital charges as well as QALYs and ICER. Cost effectiveness, in addition to efficacy and risk, should factor into the comparison between these two treatment modalities for patients with surgically resectable brain metastases.

Keywords Brain metastases · Cesium-131 brachytherapy · Stereotactic radiosurgery (SRS) · Cost-effectiveness analysis · Economic evaluation · Incremental cost-effectiveness ratio (ICER) · Quality adjusted life year (QALY)

Abbreviations

Cs-13	Cesium-131
I-125	Iodine-125
ICER	Incremental cost-effectiveness ratio
KPS	Karnofsky performance status
LINAC	Linear accelerators
QALY	Quality adjusted life year
SRS	Stereotactic radiosurgery
S	Surgical resection
WBRT	Whole brain radiotherapy

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Introduction

Brain metastases are the most common form of intracranial neoplasm [1, 2], occurring in 20–40 % of patients with cancer and with an increasing incidence [3–5]. Brain metastases are often associated with poor prognosis and the natural history and survival of treatment with steroids alone has been shown to be 1–2 months [6]. Whole brain radiotherapy (WBRT) treatment techniques increase survival to 3–6 months [7–9]. Surgical resection (S) of brain metastases in addition to WBRT has been shown to extend survival to 11 months [10, 11]. However, due to the increased risk of neurocognitive decline associated with WBRT [12–15] attention has shifted to focal post-operative treatment options.

Recent innovations in radiotherapy have introduced partial and focused forms of radiation techniques such as stereotactic radiosurgery (SRS) as another treatment option to a patient with a limited number of lesions [12, 16–21] or as a boost to WBRT [22–25]. The reported mean survival following SRS alone varies depending on RPA class [19] but frequently ranges between 8 and 10 months [16, 18]. The local control of the resection cavity is reported to be similar to post-operative WBRT, ranging from 70 to 100 % [26]. However, SRS in the post-operative setting has certain limitations in its application for the treatment of brain metastases. A delay of several weeks between surgery and irradiation can lead to repopulation of cancer cells during the waiting period [27]. Moreover, SRS is not an optimal treatment option for large (>3 cm) or non-round (irregularly shaped) surgical cavities, which have been shown to be associated with inferior local control compared with smaller lesions [28–30]. Therefore, other treatment modalities such as intraoperative brachytherapy have been investigated, which offers immediate therapy before cellular repopulation begins and targets large, irregular cavities as well as small round ones [31]. Initial studies using iodine-125 (I-125) brachytherapy reported favorable local control and median survival rates [32, 33]. However, the use of I-125 has also been associated with high rates of radiation necrosis (up to 26 %) [32, 33].

Cs-131, an FDA cleared isotope, presents an excellent alternative. Its $t_{1/2}$ is only 9.7 days, delivering the majority of the intended dose within 1 month. Wernicke et al. recently reported excellent outcomes with low rates of radiation necrosis in a Phase II trial intraoperative Cs-131 brachytherapy [31]. However, the cost effectiveness of intraoperative brachytherapy has not yet been studied in comparison with post-resection SRS. Comprehensive comparison of these two treatment modalities requires consideration of cost as well as for efficacy and risk. In this study we focus on the cost of these two competing therapies to a single brain metastasis. The costs of additional treatments to additional synchronous or metachronous local or distant metastases were eliminated from consideration so as not to bias the results.

Materials and methods

Patients

With the IRB-approval, treatment records and the hospital and out-patient receipts of 49 patients with brain metastases were retrospectively reviewed at New York Presbyterian/Weill Cornell Medical Center between 2008 and 2012. Treatments included S + Cs-131 (n = 24) and S + SRS (n = 25). Our institution began using intracavitary Cs-131 inpatients who required surgery to a brain metastasis for diagnosis or relief of mass effect. Patients that chose not to go on the Cs-131 trial, or who needed surgery before the Cs-131 could be ordered to the hospital were treated with S + SRS. Moreover, patients treated from 2008 to 2010 before Cs-131 was utilized and who received S + SRS were also included in this study. Additional synchronous or metachronous distant metastases were treated with SRS, although the cost of this additional treatment was not included in this study since not all patients had the same number of additional metastases.

Treatment techniques

Surgery

Patients underwent resection of lesions for which surgery was clinically indicated i.e. relief of mass effect, need for tissue diagnosis, size >3 cm, single easily accessible lesion. The extent of resection was noted from post-operative MRI scans performed within 48 h of surgery and read by a neuro-radiologist.

Intraoperative Cs-131 brachytherapy

At the time of resection, Cs-131 stranded seeds (IsoRay, Richland, WA) with an activity of 3–5 mCi were implanted with a planned dose of 80 Gy to a 5 mm depth from the surface of the resection cavity. The implant was pre-calculated based on pre-operative data of tumor size and our institutional physics nomogram and adjusted real time for the resulting intracavitary volume of the resected metastasis. The 10 cm Cs-131 suture-stranded seeds (0.5 cm inter-seed spacing) were delivered in strings of 10 seeds per string and subsequently cut into smaller lengths as per the nomogram and placed as a permanent volume implant along the cavity in a tangential pattern to maintain a 7–10 mm spacing between strings. The seeds are then covered with surgicel (Ethicon) to prevent seed migration and alteration of dosimetry and tisseel (Baxter) is used to line the cavity to limit cavity shrinkage and further prevent seed dislodgement.

Stereotactic radiosurgery (SRS)

For the SRS, the planning target volume (PTV) included the GTV plus 2–3 mm margins, to account for patient setup and target motion uncertainty. Since 2010, 2 mm margins were made standard to account for uncertainty in resection cavity delineation. The prescribed dose was used to RTOG protocol 90-05 [34]. Treatment was delivered with either intensity-modulated static fields (IMRS), volumetric modulated arc therapy (VMAT) or dynamic conformal arcs (DCA). IMRS or VMAT was prescribed so that at least 95 % of the PTV received at least 100 % of the prescribed dose, and DCA therapy was prescribed at the 80 % isodose line. Patients uniformly were treated with a frameless radiosurgery technique using the Novalis TxTM linear accelerators (Varian Medical Systems, Palo Alto, CA). Cone beam CT (CBCT) scans with six of freedom registration allowed for precise positioning prior to treatment [35, 36].

Imaging examinations and follow-up

Regular follow-up was performed in the outpatient setting. Follow-up exams consisted of MRI scans and physical evaluation every 2 months. MRI exams were performed utilizing the following sequences: T1-weighted, FLAIR, T2-weighted, GRE and diffusion weighted imaging. Also, post-contrast gadolinium enhanced T1-weighted images were obtained in axial, sagittal and coronal planes with 3 mm slice thickness. Additionally, patients were assessed clinically with physical examination every 2 months with specific attention drawn to any new neurological deficits. At the time of disease progression, new metastases were treated with SRS or WBRT, depending on the number of lesions.

Cost effective analysis endpoints and statistical methods

In this analysis, the receipts were collected and analyzed at the New York Presbyterian/Weill Cornell Medical Center. The cost consisted of the direct hospital related costs of each treatment. The costs in this study included direct patient care costs and excluded administrative overhead, facility maintenance, and other non-patient care costs. Costs did not take into consideration reimbursement as this varied widely based on the insurance plan of the individual. Moreover, length of stay was not included in this analysis since at our institution length of stay varies based on the availability of rehabilitation beds, the patient's insurance plan, the approval of transfer to rehabilitation, the availability of transportation. These socio-economic factors would bias the results and thus length of stay was not factored into cost. Survival was also analyzed in this study, rather than local control rates, since survival is critical to calculating QALYs. Local control rates, radiation necrosis, and other complications have been reported in a separate study controlling for size of tumor and pathology [31]. In this study, Wernicke et al. demonstrated local freedom from progression (FFP) was 100 %. There was 1 adjacent leptomeningeal recurrence, resulting in a 1 year regional FFP of 93.8 % (95 % CI 63.2–99.1 %). 1 year distant FFP was 48.4 % (95 % CI 26.3–67.4 %). Median OS was 9.9 months (95 % CI 4.8 months, upper limit not estimated) and 1 year OS was 50.0 % (95 % CI 29.1–67.8 %). Complications included CSF leak (1), seizure (1), and infection (1). There was no radiation necrosis.

Median and curves of survival time were defined by the Kaplan–Meier estimator; further, the cost analysis focused on the time period of the relevant treatment. Cost effectiveness was defined as cost in dollars for a particular therapy per unit clinical outcome, defined as the median survival in years.

The cost-effective analysis was based on the quality-adjusted life years (QALY). QALY are utilized as a measure to quantify the quality of the survival each treatment modality provides. In order to accurately quantify the quality QALY were defined using two different scales: QALY A was defined as normal life, 1; mild disability, 0.8; moderate disability, 0.5; severe disability, 0.3; vegetative state, 0.2, and mortality, 0 [37–39]. QALY B utilized the Karnofsky performance status (KPS) grading system [40]. Incremental cost-effectiveness ratios (ICER) were calculated as cost per incremental cost/incremental effect. The ICER measures the incremental cost of each modality and evaluates its incremental rise in cost associated with its incremental rise in benefit as determined by the QALY. ICER indicate how much extra cost is incurred to produce any extra gains in QALY owing to implementation of a particular strategy compared with an alternative strategy.

Results

Patient characteristics and survival

Demographic and clinical characteristics of the 49 patients in this study are presented in Table 1. The mean age of patients in the S + Cs-131 group was 65 years (range, 45–84 years) and in the S + SRS group it was 61 years

Table 1 Patient demographics and tumor characteristics

	S+CS131 (n = 24)		S+SRS (n = 25)	
Mean age, range (years)	65	(45–84)	61	(32–84)
Gender				
Male	10	42 %	15	60 %
Female	14	58 %	10	40 %
Median dose (Gy)	80		20	
Mean RPA class	1.88		1.76	
1	5	21 %	8	32 %
2	17	71 %	15	60 %
3	2	8 %	2	8 %
Mean pre-treatment KPS	86.67		73.85	
≥70	22	92 %	23	92 %
<70	2	8 %	2	8 %
Tumor primary histology				
Lung	15	63 %	11	44 %
Breast	2	8 %	6	24 %
Kidney	2	8 %	1	4 %
Colon	1	4 %	3	12 %
Others	4	17 %	4	16 %
Number of mets				
1	15	63 %	23	92 %
2	4	17 %	2	8 %
3	3	13 %		
>3	2	8 %		
Location of mets				
Frontal	10	42 %	8	32 %
Parietal	7	29 %	5	20 %
Cerebellar	4	17 %	6	24 %
Occipital	2	8 %	4	16 %
Temporal	1	4 %	2	8 %
Extent resection				
GTR	24	100 %	23	92 %
STR	0	0 %	2	8 %
Tumor volume (cc)				
Median	7.75	(1.05–62.01)	4.45	(0.03–46.8)

(range, 32–84 years). The most common site of the metastatic tumors to the brain originated in the lungs, breast, and colon. All patients received surgery via a single craniotomy. The median radiation dose was 80 Gy for the S + Cs-131 group and 20 Gy for the S + SRS group. The median survival of S + Cs-131 and S + SRS were 15.5 and 11.3 months, and the 12 month survival rates were 61 and 49 %, respectively.

Cost-effective analysis

Table 2 summarizes the cost-effective analysis. The direct hospital costs of treatment per patient were: S + Cs131 = $19,271 and S + SRS = $44,219. Utilizing the two methods to quantify the QALY yielded similar results between each method using the median survivals for each group as reported above ($p < 0.0001$). The total costs divided by the QALY yields the cost-effectiveness for each treatment option. S + Cs-131 was significantly the more cost-effective method ($p < 0.0001$) when comparing the cost-effectiveness to S + SRS.

Additionally, evaluation of the cost-effectiveness using an ICER further shows the benefit of S + Cs-131. In the ICER analysis, summarized in Table 3, when compared to S + SRS, S + Cs-131, is viewed as being strongly dominant. A negative ICER value means that there is a less

Table 2 Cost-effective analysis by quality-adjusted life years (QALY) comparing two treatment modalities

Treatment	Total cost ($)	QALY A	QALY B	Cost effectiveness A	Cost effectiveness B	P value comparing cost effectiveness to S+Cs-131
S+Cs-131	19271	0.78	0.67	24706	28763	–
S+SRS	44219	0.47	0.45	93916	98859	<0.0001

Table 3 Incremental cost effectiveness ratios (ICERs) based on treatment method

Treatment	Total cost ($)	QALY A	QALY B	Incremental cost ($)	Incremental effect A (relative to S+Cs-131)	Incremental effect B (relative to S+Cs-131)	ICER (relative to S+Cs-131)
S+Cs-131	19271	0.78	0.67	0	0	0	–
S+SRS	44219	0.47	0.45	13758	−0.31	−0.22	Negative

expensive and more effective treatment option, which in this case is S + Cs-131. Figure 1 compares the relative median survival times, 12 month survival rate, and hospital related costs between groups.

Discussion

There are several treatment options for patients with brain metastases and the cost effectiveness of each should be taken into account when the options are being weighed. Historically, WBRT has been the standard of care therapy for most patients with brain metastases [7–9, 41]. Although WBRT is effective at preventing local recurrence and controlling distant disease, it is associated with detriments in quality-of-life (QoL) measures [42, 43] and deterioration in neurocognitive abilities [12–15]. Additionally, WBRT offers no overall survival benefit compared with local therapy [16, 21, 44].

Surgical resection has been utilized for several reasons such as providing rapid relief of symptoms resulting from the mass effect of a large tumor, improving local control of brain metastases, and establishing a histological diagnosis when a brain metastasis is suspected [45]. Unfortunately, tumor recurrence with surgery alone is relatively high, around 46 % [44]. Rates of recurrence correlate with factors such as tumor size, location, histology, and en bloc resection. Therefore, adjuvant WBRT has been employed in the post-operative setting and has been shown to reduce local recurrences by 29 % [10]. However, such reduction in local recurrence comes at the expense of neurocognitive complications [10, 12, 46]. For this reason, attention has been turned to the addition of focal radiation to the resection bed in an effort to reduce the incidence of local failure while preserving neurocognitive abilities.

Recently, the use of post-operative SRS has been becoming more popular [47–50]. The local control of the resection cavity is reported to be similar to WBRT, ranging from 70 to 100 %, incidence of radiation necrosis is 0–33 %, and intracranial distant failure is 28–65 % [26]. The volume of irradiated tissue has been determined a predictor of symptomatic radiation necrosis in patients

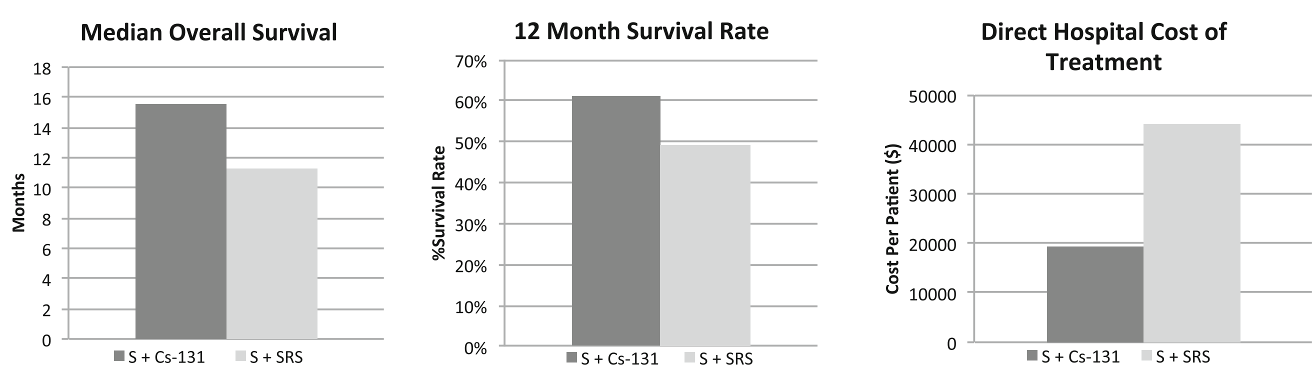

Fig. 1 Comparison between Cs-131 and S+SRS: **a** median overall survival (months). **b** 12 months survival rate (%). **c** direct hospital cost of treatment per patient ($)

irradiated with SRS. Blonigen et al. reported that symptomatic radiation necrosis was observed in 10 % and asymptomatic radiation necrosis in 4 % for patients who received SRS to a mean dose of 18 Gy. Following multivariate regression analysis showed tumor volume (V8–V16 Gy) to be most predictive of symptomatic radiation necrosis ($p < 0.0001$) [51]. However, post-operative SRS presents a challenge in producing conformal plans targeting tumor cavities of a larger size (>3 cm) or irregular shapes (a round cavity makes an ideal target for SRS). In fact, larger tumor cavities treated with this technique may render poor local control (actuarial local tumor control rate at 1 year for lesions ≤3 cc was 96 % (95 % CI: 90–100 %) and >3 cc was 59 % (95 % CI: 39–79 %) [30], resulting from less conformal treatment plans [47, 51].

Intraoperative brachytherapy is an alternative method to improve local control after resection of brain metastases. This process involves lining the resection cavity with radiation sources at the time of resection. Brain metastases are usually focal and very well-circumscribed, in contrast to intrinsic brain tumors that may infiltrate deeply into surrounding brain. Adjunctive intraoperative visualization techniques (i.e. intraoperative MRI, intraoperative ultrasound) may be employed by the surgeon to make sure that GTR or residual tumor <1 cm^3 be achieved in order for intraoperative Cs-131 to be applied. Intraoperative brachytherapy allows a high dose of radiation to be given to a localized area with a very steep dose fall-off, covering the tumor bed but sparing normal brain tissue beyond the vicinity of the tumor bed. Studies have shown local control of the resection cavity to be between 80 and 95 % [32, 33].

The coordination of intraoperative brachytherapy requires a team effort from a number of participants outside the operating room as well as inside: dosimetrists, physicists, radiation oncologists, neurosurgeon and radiation safety work together to carry out this procedure. All parties involved must be aware of the implant, carry out pre-implant planning (this involves our institutional monogram calculation which approximates the number of seeds to be ordered), informing radiation safety and preparing them and our dosimetrists and physics team for post-operative measurements of exposure and dose delivered. Such coordination ensures not only proper execution of an implant but also safety precarious to the personnel and family.

There have been several cost-effectiveness analyses regarding the treatment of brain metastases. Vuong et al. [52, 53], Rutigliano et al. [39] and Mehta et al. [54] have reported that SRS is more cost-effective than resection alone. Lee et al. [38] reported that SRS is more cost-effective than WBRT. Lal et al. [55] reported that SRS and observation is more cost effective than SRS and WBRT. Although, these studies did show SRS to be the more cost-effective treatment option, none of them compared them to Cs-131 brachytherapy.

In this study, we were able to compare S + SRS to S + Cs-131 brachytherapy. We have demonstrated that S + Cs-131 is a cost effective alternative to S + SRS. This was determined utilizing the median overall survival and various measures to calculate QALY and ICER. In our study the QALY that were determined utilizing both measures consistently showed that S + Cs-131 was better when compared to S + SRS ($p < 0.0001$). The ICER value for S + Cs-131 falls within the range of what is considered reasonable and acceptable in the literature for the cost per QALY ($50,000) while the QALY of modalities S + SRS fell outside this range [56].

Although not statistically significant, survival was higher with S + Cs-131 compared with S + SRS, which is consistent I-125 brachytherapy data [32]. However, survival is more a function of systemic disease control and is only useful in the calculation of QALYs. In addition, the median OS for patients receiving S + SRS was consistent with those reported in the literature [16, 18, 57, 58]. In order for the costs of S + SRS to compete with those of S + Cs-131, even assuming an equal quality of life for both arms, the overall survival from the S + SRS arm would need to be more than double the S + Cs-131 group. If one assumes an equal OS between the arms, the quality of life from the S + SRS arm would need to be more than double that as from the S + Cs-131 group. Therefore, even given the possible bias regarding patient allocation to the treatment arms, this analysis confirmed S + Cs-131 as the more cost-effective treatment arm when considering the direct hospital related costs of treatment.

It is important to discuss some of the limitations of this study. Our study is a single-center study that is characterized by small sample size yet has the advantage of being able to more accurately record the costs, both professional and technical. Criticisms of this study relate to its retrospective nature. Patient selection factors may have influenced the decision to perform one treatment modality over another. This study examines cost-effectiveness as they relate to hospital related costs and not patient costs. Follow-up costs and possible subsequent treatment was not part of this current analysis. We have assumed a similar distribution of such costs across the multiple treatment modalities. Although necrosis requiring re-operation would sharply raise the costs associated with that treatment, our results yielded no cases of radiation necrosis with S + Cs-131.

Conclusions

S + Cs-131 is a more cost effective alternative to S + SRS of brain metastases. Median survival was greater for this treatment arm and resulted in a greater QALY. Relative to

S + Cs-131, S + SRS resulted in a negative ICER as it was more expensive yet provided a lower QALY. Therefore, from a resource allocation perspective, S + Cs-131 for brain metastases is the more cost-effective treatment option. There were lower costs directly charged by the hospital for S + Cs-131. Therefore, the overall cost-effectiveness of each treatment option should be taken into careful consideration when deciding the appropriate treatment for patients with brain metastases.

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Compliance with ethical standards

Conflict of interest None.

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