Stereotactic radiosurgery to the resection bed for intracranial metastases and risk of leptomeningeal carcinomatosis

Clinical article

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Object. Following resection of a brain metastasis, stereotactic radiosurgery (SRS) to the cavity is an emerging alternative to postoperative whole-brain radiation therapy (WBRT). This approach attempts to achieve local control without the neurocognitive risks associated with WBRT. The authors aimed to report the outcomes of a large patient cohort treated with this strategy.

Methods. A retrospective review identified 91 patients without a history of WBRT who received Gamma Knife (GK) SRS to 96 metastasis resection cavities between 2007 and 2013. Patterns of intracranial control were examined in the 86 cases with post-GK imaging. Survival, local failure, and distant failure were estimated by the Kaplan-Meier method. Prognostic factors were tested by univariate (log-rank test) and multivariate (Cox proportional hazards model) analyses.

Results. Common primary tumors were non-small cell lung (43%), melanoma (14%), and breast (13%). The cases were predominantly recursive partitioning analysis Class I (25%) or II (70%). Median preoperative metastasis diameter was 2.8 cm, and 82% of patients underwent gross-total resection. A median dose of 16 Gy was delivered to the 50% isodose line, encompassing a median treatment volume of 9.2 cm³. Synchronous intact metastases were treated in addition to the resection bed in 43% of cases. Patients survived a median of 22.3 months from the time of GK. Local failure developed in 16 cavities, for a crude rate of 18% and 1-year actuarial local control of 81%. Preoperative metastasis diameter $\geq$ 3 cm and residual or recurrent tumor at the time of GK were associated with local failure ($p = 0.04$ and 0.008 , respectively). Distant intracranial failure occurred in 55 cases (64%) at a median of 7.3 months from GK. Salvage therapies included WBRT and additional SRS in 33% and 31% of patients, respectively. Leptomeningeal carcinomatosis developed in 12 cases (14%) and was associated with breast histology and infratentorial cavities ($p = 0.024$ and 0.012 , respectively).

Conclusions. This study bolsters the existing evidence for SRS to the resection bed. Local control rates are high, but patients with larger preoperative metastases or residual/recurrent tumor at the time of SRS are more likely to fail at the cavity. While most patients develop distant intracranial failure, an SRS approach spared or delayed WBRT in the majority of cases. The risk of leptomeningeal carcinomatosis does not appear to be elevated with this strategy.

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KEY WORDS • stereotactic radiosurgery • Gamma Knife • resection bed •
resection cavity • leptomeningeal

BRAIN metastases are the most frequent intracranial tumors in adults, with an incidence approaching 20% in some oncological populations.⁵ Management options include surgery, whole-brain radiation therapy (WBRT), and stereotactic radiosurgery (SRS). For patients who undergo resection, the standard of care is

Abbreviations used in this paper: GK = Gamma Knife; GTR = gross-total resection; LMC = leptomeningeal carcinomatosis; RPA = recursive partitioning analysis; SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

postoperative WBRT.^{32,44,49} In this setting, WBRT reduces tumor recurrences at the resection cavity and at distant brain sites.^{25,35} There are concerns, however, about the effect of WBRT on neurocognition and quality of life.^{7,11,31,42,47} Over the past several years an alternative strategy of SRS to the surgical resection bed has emerged. The goal of this approach is to maintain local control at the cavity while delaying or avoiding the need for WBRT. The patient best suited for this technique and the prognostic factors associated with tumor control continue to be defined. In this article, we report the outcomes

of a large cohort of patients treated with SRS to the resection bed. We quantify the risk of leptomeningeal carcinomatosis, data that have been rarely reported in previous studies. We end by summarizing the existing literature and discussing future directions for this strategy.

Methods

Data Collection

With the approval of the institutional review board, we retrospectively examined the medical records of all patients receiving Gamma Knife (GK) SRS to an intracranial surgical bed after resection of a brain metastasis between 2007 and 2013 at Pennsylvania Hospital. Patients were excluded if they had a history of WBRT before GK or an upfront plan for GK followed by WBRT. Patients with no clinical follow-up were excluded. We included patients who died before the first post-GK imaging study could be obtained. Because this initial surveillance scan was typically obtained 2–3 months after GK, restricting the study to only patients with follow-up imaging would have artificially inflated the survival rate of the cohort. Patient and disease characteristics were collected from the electronic medical record. The extent of surgery was determined by MRI 24 hours postoperatively, with a gross-total resection (GTR) denoting no evidence of enhancing residual tumor. Extracranial disease for patients whose primary tumor was previously treated was classified as none, stable, or progressive based on systemic imaging prior to GK. Cases in which the primary tumor was discovered at the same time as brain disease were classified as newly diagnosed, and the patients in these cases had not yet received treatment of the primary site. Recursive partitioning analysis (RPA) class was assigned according to Gaspar et al.¹⁰ Local tumor failure was defined as new or worsening nodular enhancement at the resection bed. All cases with radiological concern for local failure were additionally reviewed for consensus by 2 radiation oncologists (E.O. and M.A.B.), and advanced imaging modalities such as MRI perfusion were considered before final classification was made. Distant failure was defined as the development of new parenchymal brain metastases at sites away from the surgical cavity or the development of leptomeningeal carcinomatosis (LMC). Leptomeningeal carcinomatosis was diagnosed based on MRI, clinical symptoms, and/or cerebrospinal fluid cytology. Treatment volume for a resection cavity was defined as the volume of tissue receiving at least the prescribed marginal dose encompassing that cavity. For example, if a cavity was prescribed 15 Gy to the 50% isodose line, then the treatment volume for that cavity was the corresponding volume receiving 15 Gy or more. These values were calculated retrospectively using the GammaPlan software (Elekta AB). Dates of death were confirmed via the medical record, Social Security Death Index, or online newspaper obituaries.

Radiosurgical Technique and Follow-Up

On the day of GK, patients were fitted with a Leksell stereotactic head frame under local anesthesia and con-

scious sedation. Brain MR images were then obtained at 1-mm slices with double-dose gadolinium contrast. Treatment was delivered via a Model 4-C or Perfexion GK (Elekta AB), targeting the surgical cavity and the surrounding enhancing tissue without an additional margin. Synchronous intact metastases were treated with GK during the same session. After the procedure, patients recovered in the GK suite and frames were removed. Anti-epileptic agents were not routinely given, and steroids were administered at the treating physician's discretion. After GK, follow-up included clinical visits (typically at 1 month and then at 3-month intervals) as well as surveillance brain MRIs (typically at 2–3 months and then every 3 months).

Statistical Analysis

Overall survival was computed using the Kaplan-Meier method, and all cases were included in the analysis. Living patients or those lost to follow-up were censored at the date of last clinical encounter in the health system. Local and distant failure was examined by the Kaplan-Meier method in cases with available post-GK imaging. For these analyses, patients who received salvage WBRT were censored at last MRI before WBRT but continued to be followed for toxicity and survival. All cases were examined for the use of salvage therapies. Statistical tests were performed using Stata 12 (StataCorp). Univariate analyses were computed with the log-rank test and multivariate analyses via the Cox proportional hazards model. Hazard ratios and confidence intervals were noted. A *p* value < 0.05 was considered statistically significant, and no adjustment was performed for multiple comparisons.

Results

The study cohort consisted of 91 patients with 96 treated resection cavities. Patient and disease characteristics are shown in Table 1. The most common primary tumors were non-small cell lung (43%), melanoma (14%), and breast (13%). Brain metastases were discovered a median of 20 months after initial diagnosis of the primary tumor (range 0–204 months). Extracranial disease was newly diagnosed or progressive in 42 cases (46%), while the remaining 49 patients (54%) had either stable disease or no evidence of tumor outside the brain. The majority of cases were RPA Class II (70%). A gross-total resection was achieved in 79 cavities (82%), and a subtotal resection in 17 (18%). Stereotactic radiosurgery was performed a median of 6 weeks after resection (range 1–12 weeks). At the time of GK treatment planning, 17 patients with a GTR on 24-hour postoperative MRI had scans concerning for local recurrence in the cavity. In total, 34 cavities had concern for residual or recurrent tumor at the time of SRS. A typical prescription dose was 16 Gy to the 50% isodose line, encompassing a median treatment volume of 9.2 cm³. In addition to the resection bed, a median of 2 synchronous intact metastases (range 1–6) were treated in 39 patients (43%).

Local Failure

Eighty-six patients with 91 treated cavities had follow-up imaging. Local failure developed in 16 cavities

TABLE 1: Patient and disease characteristics*

Characteristic	No. (%)
sex†	
men	36 (40)
women	55 (60)
age in yrs at GK†	
median	60
range	22–82
primary tumor†	
NSCLC	39 (43)
melanoma	13 (14)
breast	12 (13)
colorectal	8 (9)
renal	6 (7)
sarcoma	3 (3)
esophageal	2 (2)
ovarian	2 (2)
bladder	1 (1)
oropharynx	1 (1)
endometrial	1 (1)
thyroid	1 (1)
testicular	1 (1)
unknown adenocarcinoma	1 (1)
extracranial disease†	
newly diagnosed/progressing	42 (46)
none/stable	49 (54)
RPA class†	
I	23 (25)
II	64 (70)
III	4 (4)
preop diameter in cm‡	
median	2.8
range	0.8–6.9
tumor location‡	
supratentorial	74 (77)
infratentorial	22 (23)
surgery extent‡	
GTR	79 (82)
STR	17 (18)
wks from resection to GK†	
median	6
range	1–12
marginal cavity dose in Gy‡	
median	16
range	12–21
isodose level in %‡	
median	50
range	40–70

(continued)

TABLE 1: Patient and disease characteristics* (continued)

Characteristic	No. (%)
treatment vol in cm ³ ‡	
median	9.2
range	0.6–34.7
synchronous intact mets†	
yes	39 (43)
no	52 (57)

* Mets = metastases; NSCLC = non-small cell lung cancer; STR = subtotal resection.

† N = 91 patients.

‡ N = 96 resection cavities.

for a crude rate of 18%. According to the Kaplan-Meier method, 1-year actuarial local control was 81% (Fig. 1). On univariate analysis, factors associated with local failure were breast histology, infratentorial location, preoperative metastasis diameter ≥ 3 cm, and residual or recurrent tumor in the cavity at the time of GK (Table 2). On multivariate analysis, preoperative metastasis diameter and residual/recurrent tumor were significantly associated with local failure ($p = 0.04$, HR 3.7, 95% CI 1.04–13.3 and $p = 0.008$, HR 4.8, 95% CI 1.5–15.3, respectively).

Distant Failure

Among the 86 patients with follow-up imaging, 55 (64%) developed distant intracranial failure at a median of 7.3 months from GK (Fig. 2). On univariate analysis, treatment volume over 10 cm³ and residual/recurrent tumor at the time of GK showed some association with distant failure ($p = 0.09$ and 0.11, respectively). No other tested factor was correlated (primary histology, status of extracranial disease, presence of synchronous metastases, or time from surgery to GK). On multivariate analysis, no factor was significantly associated with distant failure.

Leptomeningeal Carcinomatosis

Among the 86 cases with follow-up imaging, 12 developed leptomeningeal carcinomatosis (LMC) for a crude rate of 14%. On univariate analysis, breast histology and

Fig. 1. Freedom from local tumor failure after GK SRS.

TABLE 2: Local failure analysis

Characteristic	p Value	
	Univariate Analysis	Multivariate Analysis
histology (breast vs other)	0.063	0.14
cavity location (infratentorial vs not)	0.056	0.15
preop tumor size (≥ 3 cm vs not)	0.078	0.04
wks from resection to GK (≥ 6 vs not)	0.64	—
prescribed dose (< 16 Gy vs not)	0.91	—
treatment vol (≥ 10 cm ³ vs not)	0.27	—
residual/recurrent tumor at GK	0.004	0.008

infratentorial cavity location were associated with LMC (Table 3). On multivariate analysis, both factors were independent, statistically significant predictors of LMC ($p = 0.024$, HR 3.8, 95% CI 1.2–12.4 and $p = 0.012$, HR 4.6, 95% CI 1.4–14.9, respectively).

Overall Survival

At the time of analysis, 38 patients (42%) had died. The median clinical follow-up for the 53 living patients was 15.3 months (range 2.2–50.8 months) and for the entire cohort was 9.8 months (range 0.4–64.5 months). Based on the Kaplan-Meier method, the median overall survival was 22.3 months from SRS. On univariate analysis, the only factor associated with survival was active extracranial disease ($p = 0.05$). Specifically, patients with progressive systemic disease or those with newly diagnosed, untreated primary lesions had worse survival compared to patients with stable extracranial disease or those with no evidence of tumor outside the brain. As only a single factor was associated on univariate analysis, no multivariate analysis was performed.

Survival With Intracranial Control

Some patients survived and maintained intracranial tumor control for a considerable time after SRS (Fig. 3). Kaplan-Meier analysis revealed 23 patients alive and without local or distant brain failure at 12 months, 9 at 20 months, and 4 at 30 months following GK.

FIG. 2. Freedom from distant intracranial failure after GK SRS.

TABLE 3: Association with LMC

Characteristic	p Value	
	Univariate Analysis	Multivariate Analysis
histology (breast vs other)	0.0027	0.024
extent of resection (STR vs GTR)	0.44	—
cavity location (infratentorial vs not)	0.0014	0.012
synchronous mets (yes vs no)	0.88	—
intracranial progression (yes vs no)	0.92	—
treatment vol (≥ 10 cm ³ vs not)	0.96	—

Salvage Therapies

Thirty of 91 patients (33%) were salvaged with WBRT at a median of 6.1 months after GK. Salvage SRS (either GK or CyberKnife) was performed in 28 cases (31%). See Fig. 4 for details of salvage radiation therapy. Seventeen patients underwent additional neurosurgical procedures after initial GK.

Adverse Events

Six of 91 patients developed symptomatic radionecrosis requiring administration of steroids. Neurosurgical resection of radionecrosis was performed in 2 cases. Three patients had new seizures within 3 months of GK requiring initiation of antiepileptic treatment or hospitalization.

Discussion

The Rationale for SRS to the Resection Bed

Patients with brain metastases may undergo surgery for pathological diagnosis or to relieve mass effect. Post-operative WBRT is the established standard of care.^{32,44,49} Randomized trials show that WBRT improves tumor control at both the resection cavity and at distant brain sites without extending overall survival or functional independence.^{25,35} However, potential detrimental side effects of WBRT have played an important role in spurring

FIG. 3. Survival without intracranial tumor progression (local or distant) after GK SRS.

FIG. 4. Salvage radiation treatments following initial SRS to the surgical bed. pts = patients.

the investigation of SRS alone.⁴⁴ Several randomized trials have bolstered these concerns, demonstrating declines in cognitive function and health-related quality of life in patients receiving WBRT.^{7,11,31,42,47} However, none of these studies specifically compared WBRT to SRS alone in the postoperative setting. Other data suggest that an increase in intracranial tumor burden, rather than WBRT, is the principal driver of neurocognitive decline.^{1,26,38} Significant rates of distant brain relapse are a recognized downside to the SRS-only approach,²⁸ and whether this offsets the potential benefit of avoiding WBRT remains to be answered. Indeed, neurocognition is a primary end point of the ongoing Phase III trial of WBRT versus SRS following resection (NCCTG-N107C). Apart from the side effects of WBRT, SRS has the advantage of single-session delivery. This may be particularly important to avoiding delays in chemotherapy for patients with newly diagnosed primary tumors or progressing systemic disease, a group comprising 46% of our cohort.

The Current Evidence for SRS

As we await Level I evidence on the strategy of SRS to the resection bed, what tentative conclusions can clinicians glean from over 1100 total cases (Table 4) now reported in the literature?^{6,8,9,12,14–16,18,21–24,27–29,33,36,39} The typical patient is RPA Class II and status post GTR of a single non-small cell lung cancer metastasis. The 5 largest cohorts, including the present study, demonstrate crude recurrence rates at the resection cavity of 11%–19%, with a 1-year actuarial local control ranging from 81% to 91%.^{8,18,28,39} Series of

postoperative WBRT have reported local recurrence rates between 10% and 27%.^{30,35,40} It is important to note that direct comparisons across different published cohorts are limited by multiples biases. With this caveat, it appears that SRS may achieve similar control rates at the resection cavity as WBRT. The available evidence (Table 4) in aggregate demonstrates that about 53% of patients will develop new distant brain metastases and about 32% will be salvaged with WBRT. The substantial rate of distant failure highlights the importance of close clinical and imaging follow-up for patients treated with this technique.

Survival and Intracranial Tumor Control

Factors that correlate with survival and intracranial tumor control are varied and conflicting in the existing literature. Our finding that patients with active extracranial disease have worse survival supports similar conclusions by prior authors,^{8,16,33,43} although other studies have explicitly reported no correlation.^{6,21} Prognostic factors for local control are also in dispute, particularly relating to size and volume. Multiple studies, including ours, have demonstrated no correlation between treatment volume and local failure.^{6,8,12,22,29,33,43} Other series have reached the opposite conclusion.^{16,28,36,39,40} Our data echo the findings of Jensen et al. and Brennan et al. that preoperative tumors ≥ 3 cm are at higher risk for local failure despite treatment volume being unrelated.^{6,18} Perhaps, as suggested by Brennan et al., larger tumors reflect a more aggressive biology and make for a more technically difficult resection.⁶ We also found that residual or recurrent tumor

TABLE 4: Selected literature of single-session SRS to the resection bed*

Authors & Year	No. of Patients/ Cavities	Treatment Modality	Common Primary Sites (%)	GTR (%)	Median Dose (Gy)	Crude LF (%)	1-Yr Actuarial LC (%)	Distant Failure (%)	Salvage WBRT (%)	Median Survival (mos)	LMC (%)
Iwai et al., 2008	21/21	GK	NSCLC (24), colon (24)	86	17†	24	82	48	NR	20	24
Mathieu et al., 2008	40/40	GK	NSCLC (40), melanoma (20)	80	16	27	74	54	16	13	NR
Karlovits et al., 2009‡	52/52	LINAC	NSCLC (46), breast (17)	92	15	8	NR	44	31	15	NR
Limbrick et al., 2009	15/16	GK	NSCLC (40), breast (27)	81	20	27	NR	60	40	20	NR
Do et al., 2009	30/33	LINAC§	NSCLC (47), breast (20)	NR	15	12	82	63	47	12	NR
Jagannathan et al., 2009	47/47	GK	NSCLC (40), melanoma (20)	100	19†	7	95	87	28	11	NR
Hwang et al., 2010	25/25	GK	NSCLC (60), breast (16)	95	15–20¶	0	100	33	NR	15	NR
Kalani et al., 2010	68/68	GK	NSCLC (44), breast (15)	100	15	21	NR	NR	NR	13.2	NR
Rwigama et al., 2011	77/77	CyberKnife§	NSCLC (43), breast (14)	100	18	26	76	47	26	14.5	NR
Jensen et al., 2011	106/112	GK	NSCLC (47), breast (14)	96	17	13	87	54	37	10.9	7.5
Ogiwara et al., 2012	56/56	GK	NSCLC (45), breast (18)	100	16	9	NR	38	14	21	NR
Prabhu et al., 2012	62/64	LINAC§	NSCLC (41), melanoma (23)	81	18	17	78	NR	NR	13	NR
Kelly et al., 2012	17/18	LINAC§	NSCLC (35), melanoma (35)	94	18	11	NR	35	24	N/A	NR
Choi et al., 2012**	112/120	CyberKnife§	NSCLC (43), melanoma (16)	90	20	11	91	59	28	17	NR
Robbins et al., 2012	85/85	LINAC	NSCLC (59), melanoma (13)	68	16	19	81	55	35	12	8.2
Hartford et al., 2013	47/49	LINAC	NSCLC (49), melanoma (15)	76	10	16	86	63	45	NR	NR
Kellogg et al., 2013	59/59	LINAC§	NSCLC (64), melanoma (15)	NR	16†	2	98	NR	42	15.3	NR
Luther et al., 2013	120/120	GK	NSCLC (40), breast (21)	100	16	14	NR	40	NR	NR	NR
Brennan et al., 2014	39/40	LINAC	NSCLC (57), breast (18)	92	18	30	78	47	NR	14.7	NR
Present study	91/96	GK	NSCLC (43), melanoma (14)	82	16	18	81	64	33	22.3	14

* LC = local control; LF = local failure; N/A = not reached; NR = not reported.

† Value reported as the mean.

‡ Update of prior report by Quigley et al.

§ Majority of patients treated with single fraction but some treated with multiple fractions.

¶ Values presented as the range.

** Update of prior report by Soltyis et al.

in the resection cavity was predictive of local failure. It is unclear whether earlier treatment would have been advantageous for patients who initially had a GTR and recurred by the GK planning scan, and time to radiosurgery was not significant in our models. However, 2 recent studies revealed that most resection cavities do not shrink over time after surgery, suggesting that GK should be performed shortly thereafter.^{3,17}

Leptomeningeal Carcinomatosis

In theory, resection of a metastasis may seed cerebrospinal fluid and elevate the risk of leptomeningeal carcinomatosis (LMC).^{20,41} Adjuvant WBRT holds a hypothetical advantage over focal SRS for sterilizing the meninges. However, LMC is not well reported in prior SRS series. The rate was 24% in a small early experience¹⁵ but about 8% in 2 larger studies.^{18,39} Only the first series analyzed factors associated with LMC, finding infratentorial lesions at higher risk.¹⁵ More recently, Atalar and colleagues updated a previous SRS cohort⁸ with a focus on LMC.⁴ They reported a rate of 13% and found breast histology to be the only associated factor.⁴ Our rate of 14% confirms this prior study, and we demonstrated a significant independent association for both breast histology and infratentorial cavity location. Are patients who undergo SRS to the resection bed at elevated risk for LMC? In general, the overall incidence of LMC in solid malignancies ranges from 5% to 15%.⁴⁸ The rates were 5% and 10% following resection (mostly without adjuvant radiation) for supratentorial and infratentorial lesions in 2 large surgical series.^{45,46} In a cohort of 66 patients treated with resection followed by WBRT, 11% developed LMC.¹³ The incidence was 13% in a recent study of SRS alone to multiple intact metastases.³⁴ Additionally, data on whether WBRT reduces the risk of LMC are conflicting.^{19,46} Differences in patient populations and definitions of LMC make comparisons between these studies challenging. However, the available evidence suggests that patients treated with SRS to the resection cavity have similar rates of LMC as patients in other settings. Prospective trials are needed to fully answer this question.

Future Directions for SRS

A major anticipated advance will be the reporting of the North Central Cancer Treatment Group N107C study. This multi-institutional trial randomizes patients to WBRT or cavity-directed SRS following resection of a single metastasis. The primary end points are overall survival and neurocognition at 6 months following radiotherapy. Future studies will also help identify which patients benefit most from this strategy. In our cohort, some patients fared poorly and required salvage WBRT within weeks of GK, while others lived years without any intracranial progression (Fig. 3). More data will aid in appropriately tailoring postoperative radiotherapy, whether WBRT or SRS. Another area of future investigation is neoadjuvant SRS. Asher and colleagues recently reported results of SRS delivered before planned resection.² Theoretical advantages to this approach include clearer target delineation, higher delivered dose, and treatment while the tumor has an intact blood supply.

Limitations

Our study is limited by the biases of a retrospective analysis. Additionally, we lacked data on neurocognitive function after GK and did not record whether deaths were from neurological progression. These limitations will be addressed by the NCCTG-N107C randomized trial.

Conclusions

This large retrospective cohort bolsters the existing evidence for SRS to the surgical resection bed. Local control rates are high, but patients with larger preoperative metastases or residual/recurrent tumor at the time of SRS are more likely to fail at the cavity. While most patients develop distant intracranial failure, an SRS approach spared or delayed WBRT for a majority of cases. The risk of leptomeningeal carcinomatosis does not appear to be elevated with this strategy.

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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