Early Gamma Knife stereotactic radiosurgery to the tumor bed of resected brain metastasis for improved local control

Clinical article

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Object. Optimal case management after surgical removal of brain metastasis remains controversial. Although postoperative whole-brain radiation therapy (WBRT) has been shown to prevent local recurrence and decrease deaths, this modality can substantially decrease neurocognitive function and quality of life. Stereotactic radiosurgery (SRS) can theoretically achieve the same level of local control with fewer side effects, although studies conclusively demonstrating such outcomes are lacking. To assess the effectiveness and safety profile of tumor bed SRS after resection of brain metastasis, the authors performed a retrospective analysis of 110 patients who had received such treatment at the Centre Hospitalier Universitaire de Sherbrooke. They designed the study to identify risk factors for local recurrence and placed special emphasis on factors that could potentially be addressed.

Methods. Patients who had received treatment from 2004 through 2013 were included if they had undergone surgical removal of 1 or more brain metastases and if the tumor bed was treated by SRS regardless of the extent of resection or prior WBRT. All cases were retrospectively analyzed for patient and tumor-specific factors, treatment protocol, adverse outcomes, cavity outcomes, and survival for as long as follow-up was available. Univariate and multivariate Cox regression analyses were performed to identify risk factors for local recurrence and predictors of increased survival times.

Results. Median patient age at first SRS treatment was 58 years (range 37–84 years). The most frequently diagnosed primary tumor was non–small cell lung cancer. The rate of gross-total resection was 81%. The median Karnofsky Performance Scale score was 90%. Tumor bed SRS was performed at a median of 3 weeks after surgery. Median follow-up and survival times were 10 and 11 months, respectively. Actuarial local control of the cavity at 12 months was 73%; median time to recurrence was 6 months. According to multivariate analysis, risk factors for recurrence were a longer surgery-to-SRS delay (HR 1.625, $p = 0.003$) and a lower maximum radiation dose delivered to the cavity (HR 0.817, $p = 0.006$). Factors not associated with increased recurrence were subtotal or piecemeal resections, prior WBRT, histology of the primary tumor, and larger cavity volume. No factors predictive of survival were identified. Symptomatic radiation-induced enhancement occurred in 6% of patients and leptomeningeal dissemination in 11%. Pathologically confirmed radiation-induced necrosis occurred in 1 (0.9%) patient.

Conclusions. Adjuvant tumor bed SRS after the resection of brain metastasis is a valuable alternative to adjuvant WBRT. Risk factors for local recurrence are lower maximum radiation dose and a surgery-to-SRS delay longer than 3 weeks. Outcomes were not worse for patients who had undergone prior WBRT and subtotal or piecemeal resections. Pending the results of prospective randomized controlled trials, the authors' study supports the safety and efficacy of adjuvant SRS after resection of brain metastasis. SRS should be performed as early as possible, ideally within 3 weeks of the surgery.

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KEY WORDS • Gamma Knife • tumor bed • brain metastasis • stereotactic radiosurgery

BRAIN metastases are a significant source of illness and death among cancer patients⁸ and will eventually develop in about 20%–40% of patients with

a primary extracranial neoplasm.⁹ The intent of current optimal case management remains mostly palliative. Resection has been shown to improve neurological symptoms, improve functional independence, and increase survival times.¹⁹ However, surgery alone is associated with a 46%–59% rate of local recurrence, presumably because

Abbreviations used in this paper: SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

any residual microscopic disease is left unaddressed.⁴ Adjuvant whole-brain radiation therapy (WBRT) can treat both local and distant microscopic disease and has been shown to decrease local recurrence in the first year by 10%–28%. WBRT also decreases the incidence of new distant brain metastasis from 37% to 14% and decreases neurological deaths without, however, increasing overall survival times.^{13,18} Yet WBRT is not without consequences. A recent study has shown that in addition to physical symptoms such as hair loss and skin reactions, WBRT induces neurocognitive decline; symptoms are evident as early as 4 months after treatment.⁵ Because neurocognitive function is known to be correlated with quality of life,¹⁴ this finding is highly relevant clinically. In theory, the same level of local control—with fewer side effects—could be achieved by performing stereotactic radiosurgery (SRS) to the tumor bed after resection.

To assess the effectiveness and safety of this approach, we performed a retrospective analysis of 110 patients who had received such treatment at our center. We designed the study to identify risk factors for local recurrence and placed special emphasis on factors that could potentially be addressed to improve treatment parameters and, ultimately, patient outcomes. Our institutional review board approved this study.

Methods

All patients treated at our center (Centre Hospitalier Universitaire de Sherbrooke Gamma Knife center) during 2004–2013 were screened for eligibility. Patients were included in the series if they had undergone Gamma Knife SRS to the tumor bed of pathologically confirmed and surgically removed brain metastasis. The initial database query yielded 133 eligible patients. After patient chart reviews, 23 patients were excluded: 4 did not meet the inclusion criteria, 11 had no available follow-up information, and 8 had received treatment more than 2 months after the surgery, having been referred to our center for already ongoing local recurrence. The final series therefore included 110 patients and 113 cavities.

For each patient, study variables were collected by using Excel for Mac 2011, version 14.4.2 (Microsoft Corp.). Statistical analyses were performed by using SPSS Statistics, version 22.0.0.0 (IBM). Statistical significance was defined as $p < 0.05$. A primary analysis involved the complete series. Secondary subgroup analyses involved only patients who had undergone gross-total resection and/or without prior WBRT and yielded identical results to the analysis of the full series (data not shown). Analyzed outcomes were local control (defined as the absence of confirmed tumor growth within or adjacent to the post-operative cavity on follow-up MR images) and survival times. Conditional forward stepwise Cox regression analyses were performed to identify risk factors for outcomes in univariate and multivariate models. The multivariate analysis was initially performed by using only the variables for which p was < 0.15 in the univariate analysis (data not shown). Additional variables were then added to the regression until all the variables of the univariate model were included with no effect on the statistical

significance of identified risk factors. Further actuarial analyses were performed by using the Kaplan-Meier estimator. For local control analysis, cases were censored at the last available imaging study. Different Kaplan-Meier distributions were compared by using the log-rank (Mantel-Cox) test. Continuous variables were compared by using the Pearson correlation coefficient. All times reported are relative to the date of the SRS. Final figures were produced by using IBM SPSS Statistics and Prism 6.0 (GraphPad Software Inc.).

Patient Population

Patient characteristics are presented in Table 1. The female/male ratio was 1.33:1, and median patient age was 58 years. For most patients, functional status was good at the time of SRS; the median Karnofsky Performance Scale score was 90%, median Radiation Therapy Oncology Group RPA (recursive partitioning analysis) class was II, and 62% had no focal neurological deficit. The most frequent primary pathology was non-small cell lung cancer, followed by breast and colorectal cancers. For 40% of patients, the brain metastasis was diagnosed at the same time as the primary cancer. For the other patients, brain metastasis was diagnosed a median of 24 months after diagnosis of the primary cancer.

Surgical resection of the metastasis was performed at our center for 78 (71%) patients; the others were referred specifically for SRS after having undergone surgery at other institutions. Metastases were removed en bloc for 42% of patients at a median of 9 days after the diagnosis of brain involvement. MR image-confirmed gross-total resection was achieved for 81% of cases.

Radiosurgery Procedures

All SRS procedures were performed by using the parameters detailed in Table 2. In brief, after induction of conscious sedation and local anesthesia, a stereotactic Leksell G frame (Elekta AB) was attached to the patient's head. Volumetric T1-weighted images with and without contrast enhancement were obtained and used to define the target. The neurosurgeon, radiation oncologist, and medical physicist devised a treatment plan by using Leksell GammaPlan software (Elekta AB). The 50% isodose line was used for prescription in most cases, and the median margin and maximum doses delivered to the tumor bed were 18 and 36 Gy, respectively. The prescription isodose line included an approximate margin of 1 mm of brain tissue around the resection edge and covered any residual enhancement or tumor in cases of partial resection. Any unresected remote brain metastasis was also irradiated during the procedure. After treatment, patients were briefly observed and discharged to home the same day.

Clinical and radiological follow-up examinations were performed 2 months after SRS and then every 3 months.

Results

The median follow-up time was 10 months (range 1.4–84.2 months). At the time of analysis, 75% of cavi-

TABLE 1: Patient characteristics

Characteristic	Value
no. of patients	110
no. of cavities	113
sex, no. (%) of patients	
F	63 (57)
M	47 (43)
median age in yrs at SRS (range)	58 (37–84)
neurological status at SRS, no. (%) of cavities	
no deficit	70 (62)
focal deficit	43 (38)
median (range) KPS score at SRS	90 (50–100)
RTOG RPA class at SRS, no. (%) of cavities	
I	34 (30)
II	70 (62)
III	9 (8)
primary pathology, no. (%) of cavities	
NSCLC	57 (50)
breast	15 (13)
colorectal	14 (12)
melanoma	11 (10)
renal	5 (5)
others	11 (10)
time of 1st brain metastasis after primary diagnosis	
synchronous diagnosis, no. (%) of patients	44 (40)
median time (range) for nonsynchronous diagnosis, mos	24 (0.1–188)
prior WBRT, no. (%) of cavities	17 (15)
median (range) delay btwn WBRT & SRS, mos	7 (0–96)
median (range) delay btwn brain metastasis & surgery, days	9 (0–2908)
resection, no. (%) of cavities	
en bloc	33 (42)
piecemeal	45 (58)
extent of resection, no. (%) of cavities	
gross total	92 (81)
subtotal	21 (19)
median (range) delay btwn brain surgery & SRS, wks	3 (0.3–7.6)
median (range) no. of treated metastases (including cavity) at 1st SRS	1 (1–9)

* KPS = Karnofsky Performance Scale; NSCLC = non-small cell lung cancer; RTOG RPA = Radiation Therapy Oncology Group recursive partitioning analysis.

ties were free of recurrence. Actuarial analysis (Table 3) estimated local control at 6, 12, 24, and 36 months to be 84%, 73%, 64%, and 58%, respectively. Recurrence was observed at a median of 6 months (range 1–57 months) after SRS. According to univariate and multivariate analyses, risk factors for recurrence were a longer surgery-to-SRS delay (HR 1.625, 95% CI 1.183–2.231, $p = 0.003$) and a lower maximum radiation dose delivered to the cavity (HR 0.817, 95% CI 0.708–0.943, $p = 0.006$) (Table 4). When stratified by the surgery-to-SRS delay, increased delays were associated with decreased rates of 12-month actuarial local control (Fig. 1). According to Kaplan-Mei-

TABLE 2: SRS treatment parameters

Parameter	Mean	Median	Range
margin dose (Gy)	17.1	18	10–20
maximum dose (Gy)	35	36	20–53
isodose line (%)	49.1	50	30–80
isocenters (no.)	16.7	15	1–49
treatment vol (cm ³)	13	12	0.6–43

er analyses, the cutoff (maximum delay) most predictive of local control was 3 weeks or sooner (Fig. 2) ($p = 0.003$), although using a 4-week cutoff still identified statistically different distributions ($p = 0.016$, data not shown). The surgery-to-SRS delay was inversely proportional to the size of the cavity ($p = 0.019$) and directly proportional to the margin dose ($p = 0.025$). With regard to treatment parameters, maximum dose directly correlated with margin dose ($p < 0.01$) and was inversely proportional to the cavity volume ($p < 0.01$), although the effect of the 2 latter factors on recurrence was not statistically significant. All other tested factors were also not significantly associated with increased risk for recurrence and included subtotal or piecemeal resections, prior WBRT, and primary tumor pathology. For primary tumor pathology, the effect of radioresistant (melanoma, renal cell carcinoma) versus non-radioresistant (all others) tumors was specifically tested and yielded no difference in outcomes.

The median survival time was 11 months (range 1.4–84 months); 44% of patients were still alive at the time of analysis. Actuarial survival rate data are presented in Table 3. The cause of death was known to be neurological (i.e., related to the progression of the cerebral disease, including systemic complications of neurological symptoms) in only 23% of patients; most others died of a systemic condition. No risk factor shown in Table 4 was significantly associated with decreased survival time according to the multivariate model, although progression of the primary tumor during the follow-up period showed a statistically significant trend toward decreased survival time according to the univariate analysis ($p = 0.045$, data not shown).

Radiation-induced T2 anomaly and enhancement occurred in 19% and 32% of cavities, respectively. Enhancement resolved spontaneously during the follow-up period for 8 cavities, suggesting that the real incidence of permanent radiation-induced changes in our series was 22% at most. Necrosis was pathologically proven for only 1 patient, who underwent surgery because symptomatic recurrence was considered the most likely diagnosis before pathological analysis had confirmed the necrosis. Radiation-induced enhancement of the cavity was symptomatic in only 7 (6%) patients. Leptomeningeal dissemination was seen in 11% of patients and was not associated with any particular primary pathology. Subsequent distant brain metastasis occurred in 54% of patients. Subsequent WBRT, SRS, and surgery were eventually performed in 28%, 38%, and 12% of patients, respectively, and mostly for the management of other metastases not associated with the cavity. Subsequent WBRT, SRS, and surgery

TABLE 3: Actuarial control and survival

Variable	% Control			
	6 Mos	12 Mos	24 Mos	36 Mos
actuarial local control (cavity)				
all patients	84	73	64	58
surgery-SRS delay ≤ 3 wks	94	87	87	72
surgery-SRS delay > 3 wks	77	61	46	46
actuarial survival	83	63	38	26

were performed at a median of 5, 6, and 11 months, respectively, after the initial SRS.

Discussion

During the past few years, tumor bed SRS has been increasingly used as an alternative to WBRT after brain metastasis resection. Several other retrospective studies have supported the safety and efficacy of adjuvant SRS in this setting.^{3,7,16} Our rate of crude local control (75%) is within the reported range of 70%–100% and near the 79% average,²⁰ as are our other outcomes of an 11-month median survival time (reported range 10–20 months),⁷ 1% rate of operated radiation-induced necrosis (published rate of 3%),¹² and 11% rate of meningeal dissemination (published rate of 13%).² However, our series is larger and provides

longer follow-up times than do most published reports of other studies,⁷ thereby reducing the positive control and survival biases associated with short-term or nonreported follow-ups. These coherent results suggest that our study population is probably similar to the cohorts in other published studies and that conclusions from our risk factor analysis might be applicable to those patients as well.

Previously identified risk factors for local recurrence include subtotal resection, larger treatment volume, and lower margin dose.^{7,16} In our series, 2 factors were significantly associated with higher rates of treatment failure: a lower maximum dose of radiation and a longer delay between resection and SRS.

Radiation Dose

Multiple authors have identified use of a low margin dose as a risk factor for local recurrence.^{10,16,22} In our series, we found a trend toward better local control when higher margin doses were used, but the trend did not meet statistical significance in any analysis (we tested the effect of both the continuous variable and a binary variable with a cutoff of ≤ 16 Gy in both the univariate and multivariate models). There was, however, in both models a significant association between higher maximum dose and better local control. Furthermore, maximum dose correlated with margin dose and was inversely proportional to the cavity volume. It might be that the wider range of possible maxi-

TABLE 4: Risk factors for local recurrence*

Risk Factor	p Value	
	Univariate Analysis	Multivariate Analysis
patient characteristic		
female sex	0.775	0.722
age	0.648	0.908
subtotal resection	0.578	0.823
piecemeal resection	0.912	0.803
prior WBRT	0.596	0.745
focal neurological deficit at SRS	0.260	0.809
KPS score at SRS	0.240	0.392
RTOG RPA class at SRS	0.240	0.141
tumor characteristic		
primary pathology	0.504	0.187
prior extracranial radiotherapy	0.884	0.544
progression of primary	0.094	0.551
cavity vol	0.544	0.770
cavity location	0.585	0.618
SRS characteristic		
surgery-to-SRS delay	0.024	0.003
margin dose ≤ 16 Gy	0.106	0.152
isodose line	0.397	0.555
maximum dose	0.035	0.006
no. of isocenters	0.968	0.447

* Boldface indicates significance ($p < 0.05$).

Fig. 1. Actuarial local control rates at 12 months after SRS, stratified by the surgery-to-SRS delay. Error bars represent standard deviations. The numbers above the histogram represent the number of cavities in each group (total = 113 cavities).

imum doses (20–53 Gy) in our treatment plans compared with margin doses (10–20 Gy) made statistical significance easier to reach for the former variable. Although it is possible that the effect of the maximum dose on local control might be a statistical error in itself, an error is unlikely given the internal consistency of our data (between maximum dose, margin dose, and cavity volume) and their agreement with that of other authors.^{10,16,22} Until future studies further clarify this issue, our data support the notion that a higher dose of radiation, marginal or maximal, improves local control.

Surgery-to-SRS Delay

Our study demonstrated an effect of the surgery-to-SRS delay on local recurrence. Current practice at multiple institutions, including ours, is to perform SRS within 6 weeks after the resection.^{12,17} The rationale for such a delay is 3-fold: 1) time enables the patient to recover from the surgery before the SRS; 2) few metastases have already recurred after 6 weeks if gross-total resection has been achieved; and 3) time allows for cavity shrinkage, thereby reducing the treatment volume and enabling use of a higher margin dose. Although the latter assumption has recently been challenged,¹¹ in our series, the surgery-to-SRS delay was indeed inversely proportional to the size of the cavity and directly proportional to the margin dose. However, regardless of the benefits on treatment parameters, a longer surgery-to-SRS delay clearly correlated with increased local recurrence (Fig. 1). A cutoff of 3 weeks or sooner (Fig. 2) best stratified patients in Kaplan-Meier analyses. The delay substantially affected actuarial local control rates; estimated 6-month control rates dropped from 94% to 77% if SRS was performed more than 3 weeks after resection (Table 3). A longer surgery-to-SRS delay might lead to an increased spread of microscopic disease that is harder to target because it is not yet enhancing. To the best of our knowledge, only 2 other studies reported their surgery-to-SRS delay,^{7,12,17} and ours is the first to demonstrate the effect. Perhaps the most useful aspect of this finding is that, unlike most other treatment parameters, this delay can actually be addressed quite safely and easily.

Prior Radiation Exposure

In our series, prior exposure of the neoplastic cells to radiation—either through irradiation of the primary cancer or through prior WBRT—was not associated with increased local recurrence. This finding suggests that any acquired radioresistance might not be clinically relevant with regard to tumor bed SRS sensitivity. Prior WBRT was also not associated with increased SRS-induced T2 anomalies or enhancement (data not shown); it is noteworthy that in our series, the only patient who underwent surgery for radiation-induced necrosis had not undergone WBRT before SRS. Together, these observations support both the safety and relevance of tumor bed SRS for patients previously treated with WBRT.

Extent of Resection

Subtotal resections are often excluded from cavity-

Fig. 2. Actuarial analysis of local control stratified by the surgery-to-SRS delay (log-rank, $p = 0.003$).

SRS series^{16,21} and in a recent meta-analysis of 629 patients were found to be associated with decreased local control.⁷ However, in the largest cohort in which these patients were included, subtotal resection was not associated with increased local recurrence.¹² Likewise, in our series, neither subtotal nor piecemeal resection was associated with increased recurrence. Indeed, the effectiveness of SRS as the primary treatment for brain metastasis is well established.^{1,6,15} Our results further suggest that treatment parameters used for tumor bed SRS can control macroscopic residual disease as well as local microscopic contaminations, as long as these are included in the treatment plan. This observation is of particular relevance with regard to metastases located near eloquent areas, where pushing the resection too far might compromise function. Although our data do not enable us to specify up to which residual volume this observation holds true, they support the idea that when gross-total resection is impossible, an effective strategy might be staged surgical debulking followed by cavity plus residual SRS.

Conclusions

Adjuvant tumor bed SRS after resection of brain metastasis is a valuable alternative to adjuvant WBRT. In our series, local control rates provided by SRS compared favorably with those published for WBRT. Lower maximum radiation dose and a surgery-to-SRS delay longer than 3 weeks were risk factors for local recurrence. Outcomes were not worse for patients who had previously undergone WBRT and subtotal or piecemeal resections. Pending the results of prospective randomized controlled trials, our study supports the safety and efficacy of adjuvant SRS after resection of brain metastasis. We encourage clinicians to perform the SRS procedure as early as possible, ideally within 3 weeks of the surgery.

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Disclosure

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