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CLINICAL ARTICLE

Clinical Experience of Postoperative Gamma Knife Radiosurgery to the Surgical Bed at the 7 Day-Interval from Resection of Brain Metastasis

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Objective: To evaluate a properness about the median 7 day-interval of postoperative Gamma knife radiosurgery (GKRS), the authors compared the differences between outcomes of ours delivering postoperative GKRS with the median 7 day-interval and other researches delivering GKRS 2−6 weeks after surgical resection.

Methods: From December 2008 to November 2011, 45 patients with brain metastases due to variable causes were treated with surgical bed GKRS after the median 7 day-interval from surgical resection. We retrospectively analyzed the results of surgical bed Gamma knife radiosurgery (GKRS) performed in our institute, and compared the local control rate with other researches through a literature review.

Results: There were 33 men and 12 women whose mean age was 59 years (range 32−78 years). The most common primary lesion of brain metastases was in the lung in both genders. The operated tumors involved 38 supratentorial, and 7 infratentorial locations. At the start of treatment, 31 patients' systemic disease was active and 14 patients' was controlled. Nineteen patients had only one metastatic lesion, nine had two to three lesions, and 17 had more than four lesions. Forty-two cases of lesions were grossly total resected, and three were subtotal resected. The median interval from resection to GKRS was 7 days (range 3−19). Only 6 of 45 cases (13%) failed local control after surgical bed radiosurgery. The primary lesions of local failure were 3 esophageal cancer cases (50%), 1 lung cancer case (17%), 1 kidney cancer case (17%), and 1 colon cancer case (17%). All 6 cases were supratentorial lesions and grossly total resected. The median time to local control failure was 6 months (range 2−14 months). After GKRS, leptomeningeal carcinomatosis (LMC) were developed in one case (2%), positioned in supratentorial area, and the time to LMC was 2.4 months.

Conclusion: We conclude that GKRS only after the surgical resection of brain metastases seems to be an effective treatment strategy and identified that postoperative GKRS with the median 7 day-interval, earlier than previous studies, gave an acceptable local control rate (87%) with a low LMC incidence as other surgical bed GKRS reports.

KEY WORDS: Metastatic brain tumor · Gamma knife radiosurgery (GKRS) · Leptomeningeal carcinomatosis (LMC) · Surgical bed.

INTRODUCTION

Brain metastases are the most common central nervous system tumors. They affect up to 40% of patients with primary extracranial tumors.[6)21)] Every year, more than 170,000 new cases are estimated to occur in the United States alone.[3)] Management plans for these patients include surgical resection, stereotactic radiosurgery (SRS), whole-brain+ fractionated radiation therapy (WBRT), and chemotherapy alone or in combination.[6)21)] Surgical resection is an effective primary treatment strategy that relieves symptoms associated with mass effect, promotes functional independence, and increases overall survival.[6)21)]

Although metastases are grossly well circumscribed, residual microscopic tumor bed invasion may lead to local tumor recurrence.[2)] Patchell, et al.[25)] found that 46% of patients who were observed after resection of brain metastases developed local recurrence, whereas 10% of patients who received adjuvant WBRT had local failure. Therefore, surgical resection followed by WBRT was chosen as a treatment paradigm for surgically indicated cases. However, the use of WBRT is controversial nowadays because of the risk of neurotoxicity and neurocognitive decline.[6)20)26)] Thus, stereotactic radiosurgery has recently been proposed as an alternative adjuvant treatment after the primary surgical resection of brain metastases to prevent negative effects of WBRT.[6)] To evaluate a properness about the 7 day-interval

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GKRS after surgical resection in the treatment of brain metastases, we retrospectively analyzed the results of surgical bed radiosurgery performed in our institute.

MATERIALS AND METHODS

Patients

From December 2008 to November 2011, 45 patients diagnosed as brain metastases from variable origins were treated with surgical bed radiosurgery after surgical resection in our institute. We reviewed and analyzed the clinical changes in these cases. The mean follow-up duration was 12.3 months (range 6−41). After postoperative GKRS, patients were routinely checked up with the 3 month-interval MRI in the outpatient clinic.

Forty-five (33 men, 12 women) patients were included in this study (Table 1). The median ages were 61 years (range, 32−78). The most common primary disease was lung cancer, affecting 21 patients (47%), followed by breast cancer, affecting seven (16%) and esophagus cancer, affecting five (11%). The other primary lesions were from the kidney, liver, skin (melanoma), rectum, colon, ovary, and hypopharynx. At the time of resection and radiosurgery, systemic disease was active in 31 patients (69%), in control 14 (31%). The locations of the resected tumors were the supratentorial area in 38 cases (84%) and the infratentorial area in 7 (16%).

Table 1. Summary of 45 patients' characteristics

Sex	
Male	33 (73%)
Female	12 (27%)
Mean age	59 (32−78)
Primary lesion	
Lung	21 (47%)
Liver	3 (7%)
Breast	7 (16%)
Rectum	1 (2%)
Colon	1 (2%)
Esophagus	5 (11%)
Kidney	3 (7%)
Ovary	1 (2%)
Melanoma	2 (4%)
Hypopharynx	1 (2%)
Systemic disease	
Active	31 (69%)
Controlled	14 (31%)
Remission	0 (0%)
Operated tumor location	
Supratentorial	38 (84%)
Infratentorial	7 (16%)

Radiosurgical technique

Gamma knife radiosurgery (GKRS) was performed on different dates from the tumor resection in each patient depending on the clinical circumstances. The median interval from resection to GKRS was 7 days (range 3−19). The target of postoperative GKRS to the tumor bed covered the resection cavity plus a few millimeters from the cavity margin. The total dose was dependent on the size of the surgical area. Irradiation was performed using the Leksell Gamma Knife Perfexion (Elekta Instruments, Norcross, GA, USA).

RESULTS

Number of metastases and operation

Nineteen patients had only one metastatic lesion, 9 had two to three lesions, and more than four lesions were found in 17 patients. Gross total resection was performed in 42 cases (93%), and subtotal in 3 (7%). According to the interpretation of the neuro-radiologist and neurosurgeon, gross total resection (GTR) was confirmed as the absence of evident residual mass on postoperative MRI and stereotactic MRI for GKRS.

Radiosurgical features

The mean target volume of postoperative GKRS was 15.6 cc (range 1.5−54.0). The median marginal doses of 50% isodose were 15Gy (range 13−18), and the median maximal doses of 50% isodose were 30Gy (range 26−36) in postoper-

Table 2. Characteristics of Gamma knife radiosurgery after resection of metastatic brain tumor

	Patients, N	Median Interval to GKS, day	GTR, %	Average cavity Vol., cc	Median margin dose, Gy	Median maximal dose, Gy
All patients	45	7	93%	15.6	15	30
Local control group	39	7	92%	15.6	15	30
Local failure group	6	6	100%	15.9	15	30

GTR : gross total resection

ative GKRS. The mean follow-up duration was 12.3 months (range 6−41).

The outcomes of follow-up

There were only 6 cases (13%) of 45 of failed local control after GKRS (Table 2). The primary origin of local failure was esophageal cancer in 3 cases (50%) and lung, kidney and colon cancer in 1(17%). All 6 cases of lesions were supratentorially located and grossly totally resected. The targeted cavity volume was a mean of 15.9cc (range 8.7−24.0) in the local failure group, but 15.6cc (range 1.5−54.0) in the local control group. The median time to local failure was 6 months. The median interval from resection to GKRS was 7 days (range 3−19) in the local control group and 6 days (range 4−14) in the local failure group. During follow-up after GKRS, leptomeningeal carcinomatosis (LMC) developed in one case (2%), which was located in supratentorial area, but none was noted in infratentorial area.

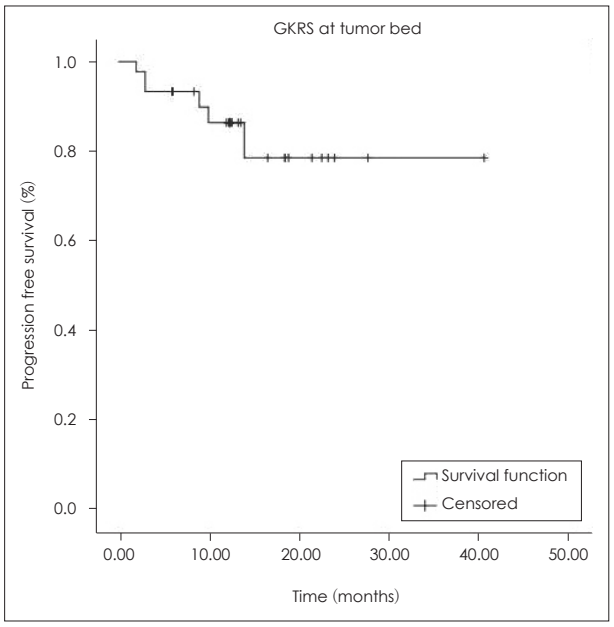

Fig. 1. Kaplan-Meier local progression free survival (PFS) of the postoperative GKRS to the surgical bed.

The estimated local progression free survival (PFS) rates of the postoperative GKRS to the surgical bed were 93.3% at 6 months, 86.4% at 12 months, and 78.6% at 24 months (Fig. 1). We showed a shorter interval from surgery to GKRS than other researches[11)13)15)17)21)] and an allowable crude local control rate (87%) (Table 3).

Targeting errors at Gamma knife radiosurgery plan

In our 3 of 6 local failure cases, we found targeting errors that the target volume didn't cover the whole enhancing cavity (Fig. 2). We considered that misinterpretation of postoperative surgical change in MRI was one of the reasons why

Table 3. Local control and median interval from resection to SRS

Author, Year	Patients, N	Crude local control, %	Median interval from resection to SRS, day	GTR, %	Median margin dose, Gy
Iwai et al.,[11)] 2008	21	76	21	86	NR
Mathieu et al.,[21)] 2008	40	73	28	80	16
Jensen et al.,[13)] 2010	106	80	24	96.4	17
Kalani et al.,[15)] 2010	68	80	15.5	NR	15
Kelly et al.,[17)] 2012	17	89	NR median interval, 3−6 week-interval	94	18
Our institute, 2015	45	87	7	93	15

GTR : gross total resection, NR : not reported, SRS : stereotactic radiosurgery

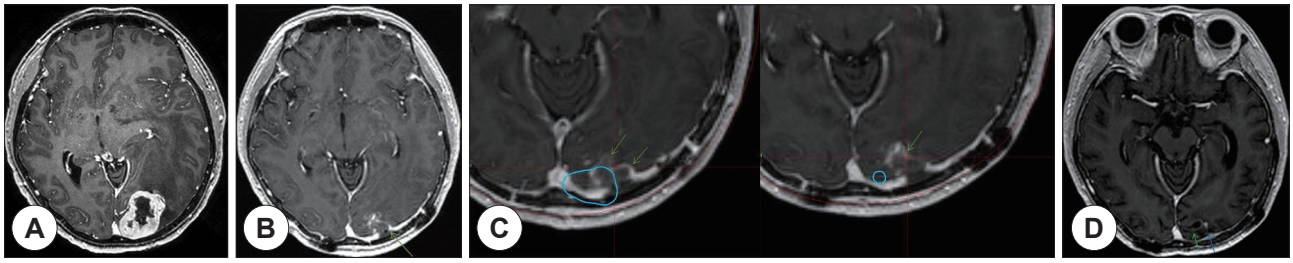

Fig. 2. CASE F/56 lung cancer. A 56-year-old woman with known lung cancer. Gross total resection was performed, and she underwent radiosurgery. At Post-resection T1Gd Gamma Knife MRI (B), there was remnant tumor in the left occipital region (green arrow). We didn't cover the whole tumor cavity (green arrow) at the time of radiosurgery (C). After 14 months, she failed local control. The follow up contrast enhanced T1-weighted magnetic resonance imaging scans showed tumor recurrences (green and blue arrow) (D). After all, she received the repeat GKRS. Axial contrast enhanced T1-weighted magnetic resonance imaging scans before resection (A), Post-resection T1Gd Gamma Knife MRI (B), Gamma Plan snapshot at the time of radiosurgery (C), the follow-up MRI (after 14 months) (D).

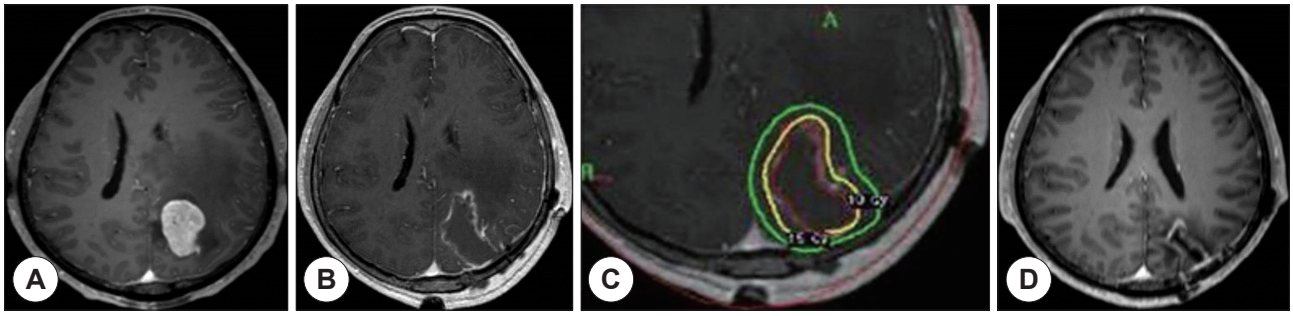

Fig. 3. CASE M/50 lung cancer. A 50-year-old man with known lung cancer. Complete resection was performed, and he underwent radiosurgery. At the follow-up MRI (1.5 years), he had no local recurrence. Axial contrast enhanced T1-weighted magnetic resonance imaging scans before resection (A), Post-resection T1Gd Gamma Knife MRI (B), Gamma Plan snapshot at the time of radiosurgery (C), and 18 months after radiosurgery (D).

targeting errors occurred.

Illustrative local control case

A 50-year-old man underwent left lower lobe lobectomy for lung cancer, followed by adjuvant chemotherapy. The histopathology of his lung cancer was classified as moderately differentiated adenocarcinoma, stage T1N2M0.

Three years after lobectomy for the lung, he had an aggravating headache. His brain MRI showed a single metastatic lesion with edema in the left parietal lobe (Fig. 3A). Surgical resection was performed, and GTR was identified by post-operative and Gamma Knife MRI (Fig. 3B). After 8 days, GKRS was performed at the tumor bed (target volume : 12.4cc ; marginal dose : 15Gy) (Fig. 3C). He did not have any complications. At the follow-up MRI (18 months), he had no local recurrence (Fig. 3D).

DISCUSSION

Brain metastases are the most common central nervous system tumors, affecting up to 40% of patients with primary extracranial tumors.[6] Surgical resection is an effective treatment for large tumors causing symptoms of mass effect.[6] Surgery alone is not adequate for providing long-term local control for brain metastases, with close to 50% of patients at risk of local recurrence if adjuvant radiation therapy is withheld.[25] Even if a brain metastasis is considered a focal disease, it is well-demonstrated that neoplastic cells can locally invade the brain parenchyma over a short distance, which vary depending on tumor histology.[2] These residual infiltrating cells explain why local failure can occur despite gross-total resection of the tumor.[22] Therefore, after surgery, residual microscopic tumor bed invasion should be treated to prevent local tumor recurrence.

Management options for local recurrence include whole-brain fractionated radiation therapy (WBRT) and stereotactic radiosurgery. For many years, palliative WBRT was considered the primary management technique for brain metastases patients.[22] Several studies have demonstrated that WBRT after surgical resection of brain metastases decreases death resulting from neurologic causes by preventing recurrence both locally and elsewhere in the brain.[6] However, WBRT may be associated with delayed neurocognitive deterioration, inhibiting verbal memory and learning in patients.[6] For patients with the potential for long-term survival, because WBRT may be associated with delayed neurocognitive deterioration, other management options are required in order to spare normal brain functioning.[4][14][22][23] GKRS alone provides local control rates similar to those of radiosurgery plus WBRT or WBRT.[8][9][22]

GKRS has recently been proposed as an alternative adjuvant treatment after the primary surgical resection of brain metastases.[21] In theory, GKRS avoids potential neurotoxicity by providing focused radiation to the tumor bed without affecting surrounding tissue. There is increasing evidence (mostly class II) that GKRS provides equivalent functional and survival outcomes compared with surgical resection followed by WBRT for patients with small-to-moderate-sized single brain metastases.[19][24] Mathieu[22] showed that prolonged local control at the resection cavity occurred in 73% of treated patients (74% progression-free survival at 12 months). Soltys, et al.[28] performed tumor bed GKRS in 72 patients (76 cavities). At 12 months, local control was obtained in 79% of cases. Karlovits, et al.[16] reported a cohort of 52 patients who underwent tumor bed GKRS. Four cases of local recurrence (7.7%) were seen after a median follow-up of 13 months. Hwang, et al.[10] published a retrospective study comparing the outcomes of patients who underwent tumor bed GKRS (25 patients) and adjuvant WBRT (18 patients) after resection of a single brain metastasis. No local

failure was seen after GKRS, while three patients had local recurrence after WBRT. In all available series, 1-year local control varied between 73.3 and 100%, which is comparable to results published after GKRS alone without WBRT.[9)19)27)]

Our study was undertaken to assess the local control rates when radiosurgery was performed instead of WBRT for adjuvant irradiation after the surgical resection of brain metastases.

In particular, our institute treatment showed a short interval (median 7 days) compared with other researches that delivered postoperative GKRS 2−6 weeks after surgical resection. We identified that our results showed gave the acceptable local control rate (87%) and LMC control compared with previous studies.

Jarvis, et al.[12)] showed that most tumor bed cavities do not collapse after the surgical resection of brain metastases, and nearly one-third are larger at the time of GKRS. These surgical cavity dynamics have an important role in optimizing GKRS timing. They suggest that delaying GKRS after surgery does not offer the benefit of cavity collapse in most cases.[12)] In addition, in the approximate 4-week interval before GKRS, they observed cases of radiographic tumor progression, both locally at the cavity bed and elsewhere in the brain, suggesting that there is a potential risk of treatment delays.[12)] These studies lend weight to the theory that a proper GKRS interval without delay can reduce a local control failure.

There are no obvious guidelines about the proper interval from surgical resection to GKRS in patients with brain metastases yet. The duration between resection and GKRS is an unexplored topic.[6)] In the initial published experiences of radiosurgery of the resection cavity, GKRS was typically delivered 2−4 weeks after surgery, but the optimal time after surgery for radiosurgical treatment is unknown.[12)] Delaying GKRS allows the healing of acute surgical trauma before radiation delivery, but this must be balanced against the risk of tumor regrowth.[12)] Mathieu, et al.[21)] recommended a period of no longer than 6 weeks on the basis of their institutional experience and review of previously reported durations to radiosurgery. They suggested that a longer delay before the initiation of irradiation after resection might accelerate local recurrence.[21)]

Six studies,[11)13)15)17)21)] including our institute, were reviewed to identify crude local control rate with the interval from surgical resection to GKRS. We showed a shorter interval from surgery to GKRS than others and an allowable crude local control rate (87%) (Table 3).

Our institute showed a short interval from tumor resection to SRS compared with previousstudies.[11)13)15)17)21)] We identified that our results with the 7 day-interval gave an acceptable local control rate. Surely, there are various factors affecting local control, such as the selection of patients, radiation dose, and GKRS planning algorithms. Nevertheless, if patients have a similar condition, the 7 day-interval could be a positive factor of local control by reducing the chance of tumor regrowth, post-surgical cavity dynamics, and other causes.

Moreover, our institute revealed that there was no LMC at the infratentorial tumor and 3% (1/ 38 patients) LMC at the supratentorial tumor (the time to LMC : 2.4 months), but Suki, et al.[29)] showed that there is an increased risk of LMC after GKRS of the metastatic posterior fossa tumor.

In patients with brain tumor, the poor prognosis is affected by the extent of tumor removed. The resection of an enhancing tumor (gross total resection) is known to prolong progression-free of patients.[18)] By allowing a comparison with the preoperative MRI findings, postoperative MRI has become the method of choice for determining the presence of any residual tumor.[18)] Early postoperative MRI (within 72 hours) is commonly used to determine if a complete tumor resection has been achieved or to show how much enhancing tumor remains in situ.[1)] This postoperative MRI study is the basis for making postsurgical decisions. However, early postoperative enhancement due to surgical manipulation and tumor-induced contrast enhancement can look very much alike.[5)] Therefore, benign postoperative enhancement can be difficult to distinguish from that caused by residual tumor. This benign enhancement has been explained by postsurgical repair mechanisms at the resection site that result from hypervascularization and disruption of blood-brain barrier. Postoperative benign linear enhancement can be observed for up to 3 months after treatment, and meningeal enhancement often persists even longer.[1)] Thus, misinterpretation of residual tumor and benign postoperative reactive enhancement should be avoided.

We underwent gadolinium-enhanced MRI of the brain within 48 hours of surgery to assess the extent of resection. This post-op MRI and post-resection Gamma Knife MRI were the basis for the clinical target volume and margins. In our 3 of 6 local failure cases, we found targeting errors that the target volume didn't cover the whole enhancing cavity. We considered that misinterpretation of postoperative surgical change in MRI was one of the reasons why targeting errors occurred. These targeting errors were thought to con-

tribute to local failure. These experience provided a good lesson that Gamma Knife radiosurgery targeting should be done precisely through careful interpretation of remnant tumor and postoperative reactive change.

Limitations

A number of factors may have contributed to the observed results reported in this analysis. The studies included in this review were all case series, mostly retrospective, and thus are subject to reporting, cohort, and selection biases. A further large and controlled trial will be required to support our postulation.

CONCLUSION

Although it is well known that the WBRT after surgical resection for brain metastases is a recommended adjuvant management modality by National Comprehensive Cancer Network guideline (Version 2.2014), our surgical bed GKRS results showed its effectiveness of the high incidence of local control and satisfactory clinical outcomes. Additionally, we identified that postoperative GKRS with the median 7 day-interval, earlier than previous studies, gave an acceptable local control rate (87%) with a low LMC incidence as other surgical bed GKRS reports.

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