Effectiveness of Postoperative Gamma Knife Radiosurgery to the Tumor Bed After Resection of Brain Metastases

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OBJECTIVE: **The role of Gamma knife radiosurgery (GKS) after the resection of brain metastases remains undefined. We evaluated the outcomes of postoperative GKS to the tumor bed after the resection of brain metastasis compared with GKS alone without resection in the same patients.**

METHODS: **We performed a retrospective review of 24 patients who underwent GKS to the tumor bed after the resection of brain metastases. In this cohort, 25 metastatic lesions were treated with postoperative GKS, and 37 brain metastatic lesions were simultaneously managed with GKS alone without resection.**

RESULTS: **The median target volume and marginal dose of GKS to the surgical bed were 10.5 cm^3 and 15.0 Gy, respectively. The median target volume and marginal dose of GKS alone for the metastatic lesions were 0.5 cm^3 and 21.0 Gy, respectively. The actuarial 1-year and 2-year overall survival of the patients were 43.1% and 28.7%, respectively. The median overall survival of all patients was 11 months. The actuarial 6-month and 12-month local progression-free survival of GKS alone for metastatic lesions without resection were 92.6% and 84.9%; however, the actuarial 6-month and 12-month local progression-free survival of GKS to the surgical bed were 82% and 71%, respectively.**

CONCLUSIONS: **For patients with brain metastases treated with surgical resection, postoperative GKS to the resection area is an effective and safe treatment option. Particularly, concurrent postoperative GKS to the surgical cavity with GKS alone for multiple small metastatic lesions is a feasible treatment strategy for multiple brain metastases.**

INTRODUCTION

Metastatic brain tumors are the most common central nervous tumors in adults (2) and occur in 20%–40% of all patients with a diagnosis of cancer (8). Unfortunately, brain metastases have a poor prognosis, which was reported as the median survival time ranging from 2.3 to 7.1 months in the 1990s (7). Recently, although their median survival time is somewhat increasing because of the advancement of treatment strategy, brain metastases still show dismal outcomes.

There are various types of treatment modalities for brain metastases, including surgery, chemotherapy, whole-brain radiation therapy (WBRT), and Gamma knife radiosurgery (GKS). Among them, surgical resection is one of the most important elements in the treatment of brain metastases. Particularly for a large metastatic tumor with a significant mass effect, surgical removal is advocated. Contrary to the uncontroversial issue that symptomatic large brain metastases should be removed surgically, considerable controversy exists concerning optimal management after surgical resection. Traditionally, WBRT after surgical resection has been the main treatment modality for brain metastases since 2 monumental prospective randomized trials were reported (17, 18).

Diverse strategies for brain metastases are being tried, however, and they also have shown good clinical outcomes. One of the

Key words
- Gamma knife surgery
- Metastasis
- Postoperative
- Radiosurgery
- Surgical bed
- Tumor bed

Abbreviations and Acronyms
GKS: Gamma knife radiosurgery
MRI: Magnetic resonance imaging
OS: Overall survival
PFS: Progression-free survival
WBRT: Whole-brain radiation therapy

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strategies is postoperative GKS to the tumor bed after the resection of metastases (19). Here, we investigated our clinical data of postoperative GKS in patients who underwent surgical resection of intracranial metastases followed by GKS to the resection area. Characteristically, in this study, we evaluated the outcomes of postoperative GKS to the tumor bed compared with those of distant metastatic lesions of the same patients who were concurrently treated with GKS alone.

MATERIAL AND METHODS

Patients

This study included the patients who underwent postoperative GKS to the tumor bed after the resection of metastases between December 2006 and December 2014 at Samsung Medical Center. The patients who had residual tumor after surgery were excluded. Twenty-four patients with 25 lesions were treated with postoperative GKS to the tumor bed during the study period. Concurrently with postoperative GKS to the tumor bed, 37 distant brain metastatic lesions were treated simultaneously with GKS alone without resection in the same patients. We analyzed the clinical data of these 2 groups of lesions between postoperative GKS to the surgical bed and GKS alone. This retrospective study was approved by the institutional review board of our institute.

Radiosurgical Technique

GKS was performed on the different dates from surgery in each patient depending on the clinical circumstances. The median interval from surgery to GKS was 14.5 days (range, 2–118 days). Magnetic resonance imaging (MRI) was performed for all patients at the day of GKS after application of a stereotactic frame. Thus, we could know whether there was a residual mass or recurrence in the resection area. The target of postoperative GKS to the tumor bed covered the resection cavity plus a few millimeters from the cavity margin. In addition to postoperative GKS to the surgical bed, the distant metastatic lesions also were treated with GKS alone at the same time. The total dose was dependent on the size of the surgical area and distant metastatic lesions. Irradiation was performed using Leksell Gamma Knife type B, C, or Perfexion (Elekta Co., Stockholm, Sweden). In addition, the Leksell GammaPlan of the same company was used for planning.

Interpretation of Clinical Data

According to the interpretation of the neuroradiologist, gross total resection was confirmed as the absence of evident residual mass on immediate postoperative MRI or stereotactic MRI for GKS. Local progression of GKS to the tumor bed was defined as the appearance of new nodular enhancement around the resection cavity on follow-up MRI, and local progression of GKS alone was defined as growth greater than 25% in volume. The Mann-Whitney U test was used for 2-group comparisons, and the overall survival (OS) of patients and local progression-free survival (PFS) were estimated by the Kaplan-Meier method and Log-rank test using a commercial software program (SPSS, version 22.0; IBM Co., Armonk, New York, USA). *P* values of <0.05 were considered to be statistically significant.

RESULTS

Demographics of the Patients

The study group was composed of 9 men and 15 women, and their median age at the time of GKS was 57.0 years (range, 36–84 years). The most common primary malignancy of the patients was nonsmall cell lung cancer in 10 patients, followed by breast cancer in 5 patients and colon cancer in 2 patients. The other primary malignancies were melanoma, hepatocellular carcinoma, renal cell carcinoma, gastric cancer, thymic cancer, ovarian cancer, and uterine cancer in one patient each. One patient with renal cell carcinoma received 2 postoperative GKS applications to the surgical bed at a different site of the brain on different days. Patients' Karnofsky performance statuses were 100 in 1 patient, 90 in 4 patients, 80 in 11 patients, 70 in 5 patients, and 60 in 3 patients. According to recursive partitioning analysis, 4, 17, and 3 patients were assessed as classes I, II, and III, respectively.

Radiosurgical Features and the Outcomes of Follow-up

There were significant differences in target volume and marginal dose between 2 groups ($P < 0.01$). The median target volumes of the postoperative GKS to the tumor bed group and GKS alone group were 10.5 cm^3 (range, 1.2–26.9 cm^3) and 0.5 cm^3 (range 0.1–6.7 cm^3), respectively. The median marginal doses of the 50% isodose were 15 Gy (range, 10–25 Gy) in the postoperative GKS to the tumor bed group and 21 Gy (range, 14–25 Gy) in the GKS alone group (Table 1). At a time of one GKS, an average of 2.5 lesions (range, 1–7) was treated. The mean follow-up period was 16.5 months (range, 6–66 months). As a result, the actuarial 1-year and 2-year OS of the patients were 43.1% and 28.7%, respectively. The median OS of all patients was 11 months. Fourteen patients had during the study period—11 patients died from systemic progression of the primary cancer and 1 patient each died as the result of side effects from chemotherapy, leptomeningeal seeding, and intracranial hemorrhage from a new metastasis.

The estimated local PFS rates of the GKS alone group were 92.6% at 6 months and 84.9% at 12 months, whereas the local PFS rates of the postoperative GKS to the tumor bed group at 6 and 12

Table 1. Characteristics of the Postoperative GKS to the Tumor Bed Group and GKS Alone Group

	Postoperative GKS Group to the Tumor Bed	GKS Alone Group	Significance
Number	25	37	
Median target volume, cm^3	10.5	0.5	$P < 0.01$*
Median marginal dose, Gy	15	21	$P < 0.01$*
6-month local PFS	82%	92.6%	$P > 0.20$†
12-month local PFS	71%	84.9%	$P > 0.20$†

GKS, Gamma knife radiosurgery; PFS, progression-free survival.
*Mann-Whitney *U* test.
†Log-rank test.