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# Cavity-directed radiosurgery as adjuvant therapy after resection of a brain metastasis

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## Abstract

**Object—**As a strategy to delay or avoid whole-brain radiotherapy (WBRT) after resection of a brain metastasis, the authors used high-resolution MR imaging and cavity-directed radiosurgery for the detection and treatment of further metastases.

**Methods—**Between April 2001 and October 2009, 112 resection cavities in 106 patients with no prior WBRT were treated using radiosurgery directed to the tumor cavity and for any synchronous brain metastases detected on high-resolution MR imaging at the time of radiosurgical planning. A median dose of 17 Gy to the 50% isodose line as the rim of enhancement around was prescribed to the gross tumor volume, defined the resection cavity. Patients were followed up via serial imaging, and new brain metastases were generally treated using additional radiosurgery, with salvage WBRT typically reserved for local treatment failure at a resection cavity, numerous failures, or failures occurring at short time intervals. Local and distant treatment failures were determined based on imaging results. Kaplan-Meier curves were generated to estimate local and distant treatment failure rates, overall survival, neurological cause–specific survival, and time delay to salvage WBRT.

**Results—**Radiosurgery was delivered to the resection cavity alone in 57.5% of patients, whereas 24.5% of patients also received treatment for 1 synchronous metastasis, 11.3% also received treatment for 2 synchronous metastases, and 6.6% also received treatment for 3–10 additional lesions. The median overall survival was 10.9 months. Overall survival at 1 year was 46.8%. The local tumor control rate at 1 year was 80.3%. The disease control rate in distant regions of the brain at 1 year was 35.4%, with a median time of 6.9 months to distant failure. Thirty-nine of 106 patients eventually received salvage WBRT, and the median time to salvage WBRT was 12.6

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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. Author contributions to the study and manuscript preparation include the following. Conception and design: Chan, Jensen, Ellis, Shaw, Tatter. Acquisition of data: Chan, Jensen. Analysis and interpretation of data: Chan, Jensen, McCoy, Ellis, Tatter. Drafting the article: Chan, Jensen, McCoy, Tatter. Critically revising the article: Chan, Jensen, Bourland, Ellis, Urbanic, Tatter. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Jensen, McCoy. Administrative/technical/material support: Chan, Jensen, McCoy, Bourland, deGuzman, Ellis, Ekstrand, Munley. Study supervision: Chan, Jensen.

months. Kaplan-Meier estimates showed that the rate of requisite WBRT at 1 year was 45.9%. Neurological cause–specific survival at 1 year was 50.1%. Leptomeningeal failure occurred in 8 patients. One patient had treatment failure within the resection tract. Seven patients required reoperation: 2 for resection cavity recurrence, 3 for radiation necrosis, 1 for hydrocephalus, and 1 for a CSF cutaneous fistula. On multivariate analysis, a preoperative tumor diameter > 3 cm was predictive of local treatment failure.

**Conclusions—**Cavity-directed radiosurgery combined with high-resolution MR imaging detection and radiosurgical treatment of synchronous brain metastases is an effective strategy for delaying and even foregoing WBRT in most patients. This technique provides acceptable local disease control, although distant treatment failure remains significant.

### Keywords

resection cavity; stereotactic radiosurgery; brain metastasis

The role of WBRT in the management of a resected brain metastasis has been a point of controversy. minority While a randomized trial by Patchell et al.[14] described a local and distant disease control advantage for WBRT after resection of a solitary metastasis, the trial was not statistically powered to and did not show an overall survival benefit. Moreover, the neurocognitive toxicities associated with WBRT can cause morbidity and have been shown to increase in incidence and severity, with the time after WBRT,[13] potentially limiting the quality of life in a significant Minority of patients with good systemic cancer control. In addition, WBRT has been shown to cause fatigue, worsen Karnofsky performance status, and induce a delay in the delivery of systemic therapy. But observation alone is also a potentially suboptimal approach, as the likelihood of neurological death is significantly higher in patients who receive no adjuvant therapy after resection of a brain metastasis.[14]

At our institution, we have practiced a strategy of cavity-directed radiosurgery following resection of a brain metastasis as a means of potentially delaying or avoiding altogether the toxicities of WBRT. Additional metastases detected either before resection or during radiosurgery are treated at the same time that radiosurgical treatment is delivered to the cavity. With this therapeutic strategy, we aim to postpone the use of WBRT until the occurrence of multiple failures in distant regions of the brain, local failure at the resection cavity, or failures occurring at short time intervals, with the intention of withholding WBRT completely in patients whose brain disease does not mandate its use.

While such a strategy has been reported in the literature, in the current study we aimed to describe the natural history of brain disease and recurrence following cavity-directed radiosurgery by using metrics similar to those used in the seminal trial by Patchell and colleagues.[14] Specifically, we attempted to investigate the patterns of treatment failure with regard to local disease control, distant disease control, the need for WBRT, and the likelihood of neurological death. We also attempted to elucidate any possible risk factors for treatment failure. Our study represents the largest analysis of the use of adjuvant radiosurgery following resection of a brain metastasis.

## Methods

### Data Acquisition

This retrospective study was approved by the Wake Forest University Institutional Review Board. The Wake Forest University Medical Center Department of Radiation Oncology Gamma Knife Tumor Registry was searched for all patients who received radiosurgical treatment to a brain metastasis resection cavity any time this strategy was used between

April 19, 2001, and October 31, 2009. Patients who had received prior WBRT were excluded from the analysis. One hundred six patients with 112 treated resection cavities were identified. Patient outcomes were determined using the patients' electronic medical records. Dosimetric data were obtained using plans archived from the GammaPlan treatment planning system.

## Radiosurgery Technique

After evaluations by a radiation oncologist and neurosurgeon, informed consent for GKS was obtained. Patients underwent radiosurgery on a Leksell Model C unit. Prior to GKS, each patient underwent a high-resolution, contrast-enhanced, stereotactic MR imaging study of the brain. Treatment planning was performed using Leksell GammaPlan (Elekta AB). After resection, each patient received Gamma Knife treatment to at least 1 resection cavity as well as any other synchronous brain metastases indentified during the treatment planning MR imaging. The radiosurgical dose was prescribed to the gross tumor volume, defined as the rim of enhancement around the resection cavity (Fig. 1). A margin around the gross tumor volume was not applied in this study. As evidence emerged that a lower conformality index value predicted for a greater likelihood of local recurrence,[17] the treating physicians became more likely to create plans with higher conformality index values.

## Patient Follow-Up and Use of WBRT

On follow-up, patients were generally evaluated clinically and with brain MR imaging 6–8 weeks after the GKS procedure and every 3 months thereafter. Prior to October 4, 2005, treatment and surveillance MR imaging studies were generally performed using 1.5-T MR units; after that date, studies were generally performed using 3.0-T units. Further brain metastases were usually treated via GKS, with WBRT generally reserved to salvage local failure at a previously treated resection cavity, to treat 4 or more total brain metastases over time, or for short-interval distant failures. For each patient, we attempted to determine the cause of death. Neurological deaths were defined as in the randomized trial by Patchell et al. [14] In short, patients were considered to have died of a neurological cause if they had neurological deterioration in the presence of stable systemic disease, if they had severe neurological disability and died of intercurrent illness, or if they had progressive neurological dysfunction and progressive systemic disease.

## Statistical Analysis

Overall survival was calculated from the time of GKS to death due to any cause or was censored at the date of the last follow-up. The time to neurological death was calculated from the time of GKS to death due to a neurological cause or was censored at the date of the last follow-up or nonneurological death. The time to LTF was calculated from the time of GKS to LTF or was censored at the time of the last imaging study if there was no local failure. The time to DTF was calculated from the time of GKS to DTF or was censored at the time of the last imaging study if there was no distant failure. The time to WBRT was calculated from the time of GKS to WBRT or was censored at the date of the last follow-up if the patient did not receive WBRT. Survival curves were generated using the Kaplan-Meier method. Log-rank tests were performed on univariate analysis, and a Cox proportional hazards regression was performed on multivariable analysis. Multivariable models were built by a priori consideration of the factors for which data were gathered. Resection type (gross or subtotal) was not modeled for LTF because of the low number of events within resection types. A 2-sided p value $< 0.05$ was considered to be statistically significant. All analyses were performed in SAS, version 9.2 (SAS Institute, Inc.), and Stata, version 10.1 (StataCorp LP).

# Results

## Patient Characteristics

One hundred six patients with 112 resection cavities were treated. Patient and treatment characteristics are listed in Table 1. Patients were relatively evenly divided between males (51.9%) and females (48.1%). The median age at the time of GKS was 56.1 years (range 22.6–88.0 years). The primary tumor was non–small cell lung cancer in 47.2% of patients, breast cancer in 14.2%, gastrointestinal cancer in 13.2%, melanoma in 10.4%, renal cell carcinoma in 5.7%, and other in 9.4%. Resection cavity location was infratentorial in 27.7% of cases and supratentorial in 72.3%. Preoperative tumor diameter was a median of 3.4 cm (range 0.8–7 cm). Gross-total resection, as defined by the neurosurgeon at the time of surgery, was performed in 96.4% of cases. Radiosurgical treatment was delivered to the resection cavity alone in 57.5% of cases, to the resection cavity and 1 synchronous metastasis in 24.5%, to the resection cavity and 2 synchronous metastases in 11.3%, and to the resection cavity and 3–10 additional lesions in 6.6%. The median number of days from resection to GKS was 24 days (range 5–96 days). The median maximum cavity diameter at the time of GKS was 3.2 cm (range 1.0–5.8 cm). The median cavity volume at the time of GKS was 8.0 $cm^3$ (range 0.32–33.4 $cm^3$). The median treatment volume at the time of GKS was 12.65 $cm^3$ (range 1.2–74.0 $cm^3$). The median conformality index was 1.486 (range 1.042–4.750). The median radiosurgical dose to the tumor margin was 17 Gy (range 11–23 Gy). Prescriptions were generally to the 50% isodose line. The median maximum radiosurgical dose, or maximum resection cavity dose, was 34 Gy (range 18–46 Gy).

## Patient Survival

Seventy-five patients had died at the time of the last follow-up. The median overall survival was 10.9 months. The Kaplan-Meier estimates of survival showed 93.2% of patients remaining alive at 3 months after GKS, 69.0% at 6 months, 57.6% at 9 months, and 46.8% at 1 year (Fig. 2C). On univariate analysis, male sex (HR 1.823, $p = 0.0108$) and treatment in the post–October 2005 era (HR 1.89, $p = 0.0066$; Fig. 3) were found to be predictive of death. On multivariate analysis, male sex (HR 1.90, $p = 0.017$) and a maximum resection cavity dose > 35 Gy (HR 2.04, $p = 0.043$) were found to be predictive of death.

## Patterns of Treatment Failure

Fourteen patients demonstrated LTF, and thus the median time to LTF was not reached. The Kaplan-Meier estimates of LTF showed 4.7% of patients failing by 3 months after GKS, 12.7% by 6 months, 16.9% at 9 months, and 19.7% at 1 year (Fig. 2A). No factors analyzed on univariate analysis were predictive of LTF. On multivariate analysis, a preoperative tumor diameter > 3 cm was found to be predictive of LTF. Patients with pre-operative tumor diameters > 3 cm had 13.6 times the risk of LTF as compared with patients with tumor diameters ≤ 3 cm, adjusting for other characteristics in the model (HR = 13.6, $p = 0.012$).

Fifty-seven patients experienced DTF, and the median time to DTF was 6.9 months. Kaplan-Meier estimates of DTF showed 25.1% of patients failing by 3 months after GKS, 43.9% by 6 months, 59.6% by 9 months, and 64.6% by 1 year (Fig. 2B). On univariate analysis a larger pre-operative tumor diameter, analyzed as a continuous variable (HR 1.280, $p = 0.0372$), and a maximum radiosurgical dose > 35 Gy (HR 1.740, $p = 0.0404$) were predictive of DTF. On multivariate analysis, a maximum resection cavity dose > 35 Gy was found to be predictive of DTF (HR 2.72, $p = 0.017$).

Leptomeningeal failure occurred in 8 patients, all of them female. Such failures were diagnosed a median of 160 days (range 3–367 days) after GKS to the resection cavity. The resection cavity had a cerebellar location in 4 of these 8 patients. Primary tumors in these patients included breast cancer in 5, non–small cell lung cancer in 1, anal cancer in 1, and melanoma in 1. Five of these patients died of neurological causes, 2 remained alive at the end of the study period, and 1 patient died of respiratory failure due to progressive lung disease with postobstructive pneumonia and lymphangitic spread of the tumor 3.6 months after the diagnosis of leptomeningeal disease. For all but 1 patient, leptomeningeal failure was at least a component of the first DTF.

One patient had treatment failure in the resection tract. He had undergone resection of a solitary dural metastasis from adenocarcinoma of the lung followed by GKS to the resection cavity. Within 3 weeks, facial swelling developed and imaging demonstrated extensive recurrence within the dura of the resection tract along with extensive skull base involvement. He was treated using WBRT with additional electron patches as needed to boost more superficial disease. He died 2 months later.

### Salvage WBRT

Fifty-two percent of patients died without requiring WBRT. Thirty-nine patients received salvage WBRT, and the median time to salvage WBRT was 12.6 months. Of the 75 patients who died during the study period, 43 (57.3%) did not receive WBRT during their treatment course. The Kaplan-Meier estimates of salvage WBRT showed 12.4% of patients being treated by 3 months after GKS, 29.0% by 6 months, 43.8% by 9 months, and 45.9% by 1 year (Fig. 2D). On univariate analysis a larger pre-operative tumor diameter, analyzed as a continuous variable, was predictive of the need for salvage WBRT (HR 1.373, $p = 0.0188$). On multivariate analysis, a preoperative tumor diameter > 3 cm (HR 3.06, $p = 0.025$), maximum radiosurgical dose > 35 Gy (HR 3.33, $p = 0.021$), and cavity volume < 8 $cm^3$ at the time of GKS (HR 3.92, $p = 0.009$) were found to be predictive of the need for salvage WBRT.

### Neurological Cause of Death

Forty-one patients died of a neurological cause, representing 50% of the causes of death in our cohort. The median time to neurological death was 12.6 months. The Kaplan-Meier estimate of neurological cause–specific survival was 95.9% at 3 months after GKS, 74.4% at 6 months, 62.0% at 9 months, and 50.1% at 1 year (Fig. 4). On univariate analysis, no factors were found to be predictive of neurological cause–specific survival. On multivariate analysis, a maximum resection cavity dose > 35 Gy was predictive of a neurological cause of death (HR 3.28, $p = 0.010$).

### Neurological Toxicity

Seven patients required reoperation for neurological toxicity potentially related to the use of this treatment approach. Two patients required reresection for recurrence at the resection cavity, 1 at 4.0 months and the other at 9.1 months after GKS. Three patients required reresection for radionecrosis at the resection cavity at 17.2, 18.8, and 41.1 months after the initial GKS. In the interim all 3 received WBRT: doses up to 45 Gy in 25 fractions of 1.8 Gy each in 2 cases and up to 37.5 Gy in 15 fractions of 2.5 Gy each in 1 case. By 16.6 months after the initial GKS to the resection cavity, 1 patient required ventriculoperitoneal shunt placement for increasing ventriculomegaly with associated gait instability, worsening memory, and urinary urgency; both the increasing ventriculomegaly and the urinary urgency were thought to be due to hydrocephalus versus ex vacuo ventriculomegaly. In the interim she had also undergone WBRT receiving a dose of 45 Gy in 25 fractions of 1.8 Gy each because of dural recurrence. One patient required the repair of a CSF cutaneous fistula 15.9 months after GKS to the resection cavity. One patient required medical management for toxicity potentially related to the use of this treatment approach; this patient was started on donepezil for dementia 32.4 months after GKS to the resection cavity.

## Discussion

Cavity-directed radiosurgery is an adjuvant treatment option following resection of a brain metastasis. Whole-brain radiotherapy has been considered the standard adjuvant therapy, given the results of a randomized trial that showed a significant reduction in LTF, DTF, and neurological death.[14] However, recent evidence has suggested that WBRT can significantly impact the neurocognitive function of patients, and this effect is particularly distressing in the significant minority of patients who become long-term survivors.[3]

Several studies have now documented excellent local control rates of cavity-directed radiosurgery (Table 2).[1,4,7–9,11,17] This approach was originally described in the setting of resection for LTF following WBRT[10] but has since been expanded for use in a population that never received WBRT. Factors that appear to affect the success rate of such a strategy include the preoperative size of the tumor, the conformality of the radiosurgery plan, and preoperative involvement of the pia mater. In our series, patients with preoperative tumors larger than 3 cm had a significantly greater rate of LTF than those with smaller tumors. In the study by Soltys et al.,[17] patients with a lower conformality index had a greater local failure rate, suggesting that the treatment of a margin of normal brain tissue around the tumor cavity may be beneficial.

Patients were treated with GKS a median of 24 days after resection, although the range spanned from 5 to 96 days after surgery. While the increased time delay between resection and adjuvant radiosurgery was not predictive of LTF, only 7 of 106 patients underwent radiosurgery more than 6 weeks after surgery. Authors of previous studies have also performed adjuvant radiosurgery in this approximate time interval.[11] Thus, we recommend applying radiosurgery, if it is selected, to the resection cavity within 6 weeks of craniotomy.

Potential disadvantages of cavity-directed radiosurgery include the withholding of WBRT and the subsequent likelihood of DTF. In a randomized trial, Patchell et al.[14] described a DTF rate of 37% in the absence of WBRT. However, while contrast-enhanced MR imaging was used in the study by Patchell and colleagues, significant advances in the detection of occult metastases have occurred since then. Authors of recent studies have reported on methods for improving the detection of occult brain metastases such as a higher-dose contrast agent,[5] high-relaxivity contrast agents,[2] spoiled gradient recalled acquisition in steady state (GRASS) sequences,[6] and 3.0-T magnet strength.[16] With the optimized detection of further metastases at the time of radiosurgical planning, cavity-directed radiosurgery for these additional metastases can be thought of as a more focal adjuvant therapy for the brain after metastasectomy. In multiple randomized trials in patients who have intact metastases, withholding WBRT in favor of radiosurgery alone has not been found to affect overall survival.[1,3,12] While a proportion of patients who undergo cavity-directed radiosurgery may later receive WBRT, we found that the median time delay to WBRT was 12.6 months in our series. As much as 57.3% of patients undergoing adjuvant radiosurgery after resection never required WBRT as part of the management of their cancer. Previous studies have suggested that DTF leads to an increased likelihood of neurocognitive decline.[15] In the current study, however, DTF did not predict for neurological death ($p = 0.23$).

Therapies for patients with metastatic cancer in general and metastatic brain disease in particular have improved over the past several years. Novel targeted agents have demonstrated improved overall survival when added to some of the traditional systemic treatments for meta-static disease. Some of these systemic therapies, such as lapatinib for breast cancer and bevacizumab for breast, lung, and colorectal cancers, may affect the natural history of patients with brain metastases. Our data have shown a statistically significant improvement in overall survival of the population treated in the 3.0-T MR imaging era at our institution, which corresponds to the post–October 2005 treatment period, as compared with patients treated prior to this time period. This improvement is likely related to the enhancements in systemic therapies rather than the use of higher-resolution MR imaging, as the use of 3-T MR imaging did not significantly change the in-brain failure pattern. Given that patients with metastatic brain disease are probably living longer than before, it is becoming increasingly important to consider the neurocognitive toxicities of WBRT, which do not appear to plateau over time.[13]

There are several limitations to this study. First, patients were treated over an 8-year period by 6 different radiation oncologists and 3 neurosurgeons. Treatment techniques changed over time, including improved imaging methods after the advent of 3-T MR imaging, and there was a trend toward decreasing conformality after evidence emerged that improved conformality led to a higher failure rate.[17] Additionally, the retrospective nature of the series limits the usefulness of the statistical analysis primarily to hypothesis generation. A randomized control trial is necessary to unequivocally determine if a cavity-directed radiosurgical approach is equivalent, superior, or inferior to WBRT as an adjuvant treatment option following resection of a brain metastasis. Important end points to evaluate in such a trial include local and distant brain disease control, neurocognitive outcomes, and the likelihood of neurological death.

## Conclusions

Cavity-directed radiosurgery together with the radiosurgical treatment of additional intact metastases provides acceptable local control within the tumor cavity and may postpone or eliminate the need for WBRT in a significant proportion of patients. Patients with preoperative tumor diameters > 3 cm have a higher risk of treatment failure within the tumor cavity following radiosurgery. Close follow-up monitoring with serial neuroimaging is necessary to provide timely salvage treatment to the high percentage of patients with DTF.

## Abbreviations used in this paper

| | |
|---|---|
| **DTF** | distant treatment failure |
| **GKS** | Gamma Knife surgery |
| **LTF** | local treatment failure |
| **WBRT** | whole-brain radiotherapy |

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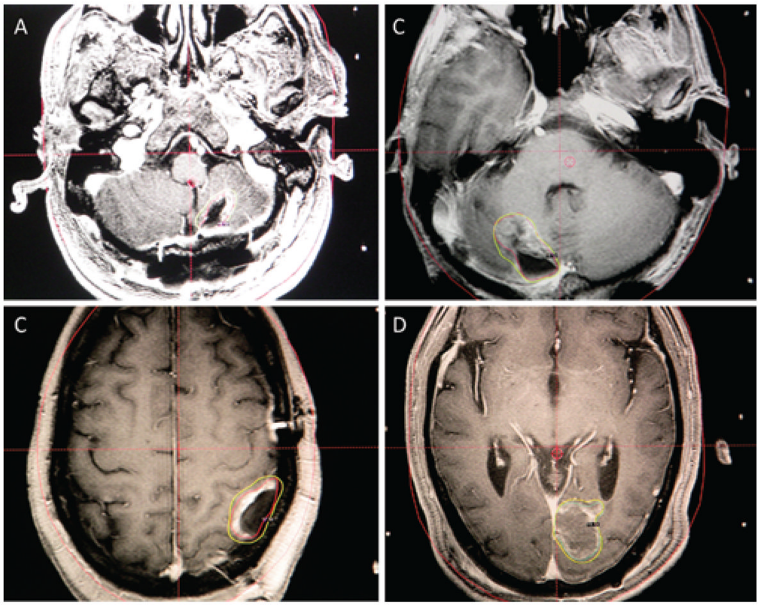

**Fig. 1.**

Targeting of the resection cavity. Four examples of resection cavities treated with radiosurgery are depicted. Axial spoiled gradient MR images showing radiosurgical dose targeting the rim of enhancement at the edge of the resection cavity. The *outer line* represents the prescription isodose (16 Gy in **A** and **C**, and 17 Gy in **B** and **D**). The *inner line* represents delineation of the cavity.

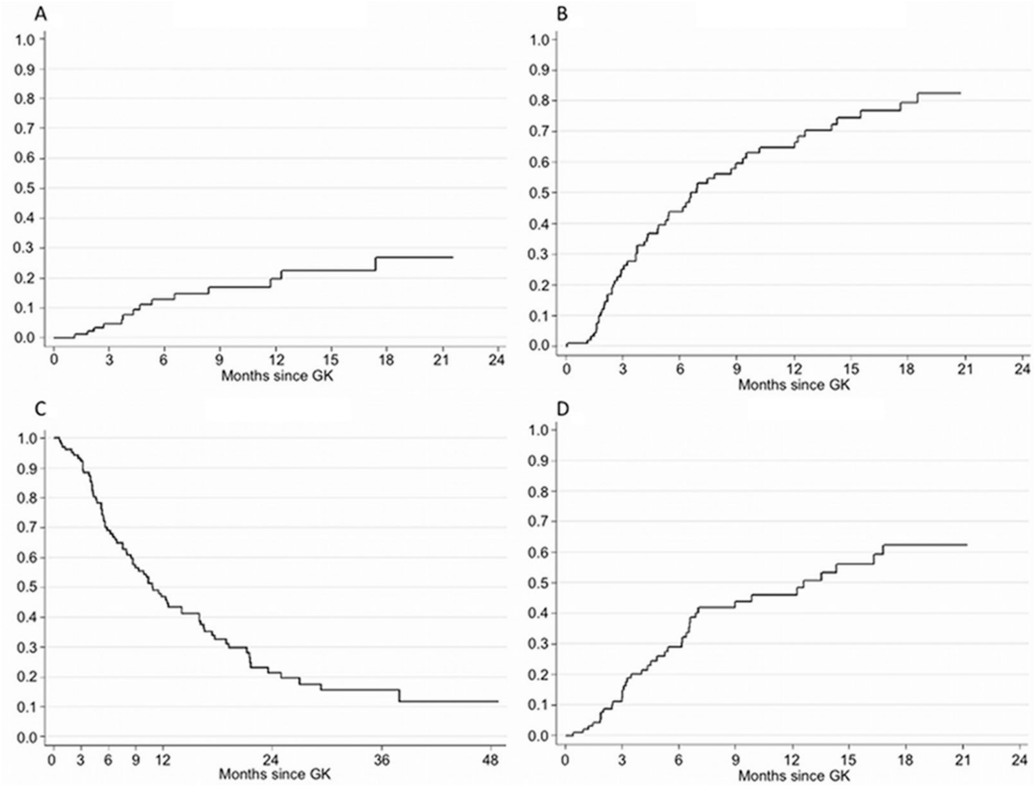

**Fig. 2.**

**A**: Kaplan-Meier plot of time to LTF. **B:** Kaplan-Meier plot of time to DTF. **C:** Kaplan-Meier plot of overall survival. **D:** Kaplan-Meier plot of time to WBRT. GK = Gamma Knife. The y axis in each graph represents the percentage of patients.

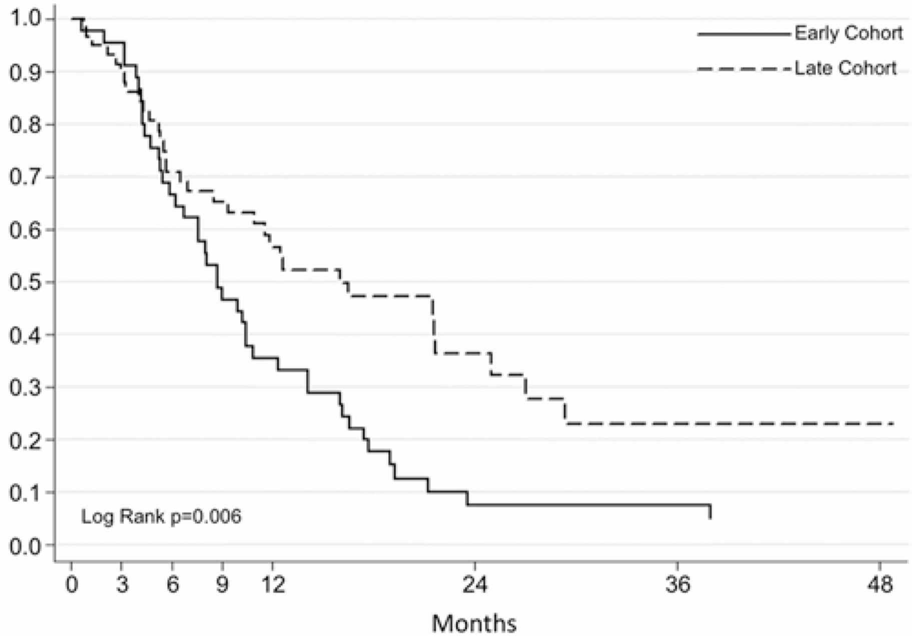

**Fig. 3.**

Kaplan-Meier plot depicting overall survival based on the treatment era. The cutoff date between treatment eras was October 4, 2005, which represented the date after which radiosurgical planning was performed on a 3-T MR unit. The y axis represents the percentage of patients.

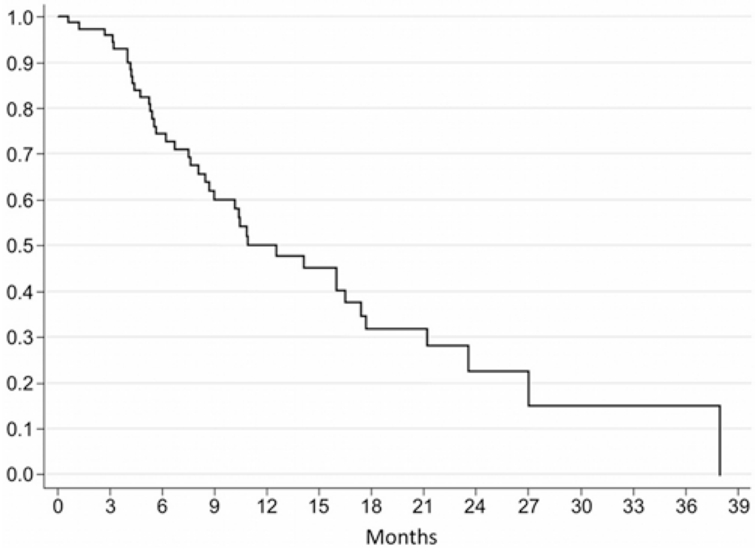

**Fig. 4.**

Kaplan-Meier plot of time to neurological death. The y axis represents the percentage of patients; the x axis, the number of months post-GKS.

## TABLE 1

Summary of patient and tumor characteristics*

| Characteristic | No. |
|---|---|
| sex (%) | |
| M | 55 (51.9) |
| F | 51 (48.1) |
| age at time of GKS in yrs (range) | 56.1 (22.6–88.0) |
| primary tumor type (no. of patients [%]) | |
| breast cancer | 15 (14.2) |
| NSCL cancer | 50 (47.2) |
| GI cancer | 14 (13.2) |
| renal cell carcinoma | 6 (5.7) |
| melanoma | 11 (10.4) |
| other | 10 (9.4) |
| patients w/ multiple resection cavities (%) | 6 (5.7) |
| location of brain metastases (%) | |
| infratentorial | 31 (27.7) |
| supratentorial | 81 (72.3) |
| median preop tumor diameter in cm (range) | 3.4 (0.8–7.0) |
| patients w/ preop tumor diameter >3 cm (%) | 63 (59.4) |
| no. of synchronous metastases in patients (%) | |
| 0 | 61 (57.5) |
| 1 | 26 (24.5) |
| 2 | 12 (11.3) |
| 3–10 | 7 (6.6) |
| resection type (%) | |
| GTR | 108 (96.4) |
| STR | 4 (3.6) |
| time from craniotomy to GKS in days (range) | 24 (5–96) |
| patients w/ >24 days from surgery to GKS (%) | 52 (49.1) |
| median max cavity diameter at GKS in cm (range) | 3.2 (1.0–5.8) |
| patients w/ cavity diameter >3 cm at GKS (%) | 64 (60.4) |
| median cavity vol at GKS in $cm^3$ (range) | 8.0 (0.32–33.4) |
| patients w/ cavity vol >8 $cm^3$ at GKS (%) | 54 (50.9) |
| median treatment vol at GKS in $cm^3$ (range) | 12.65 (1.2–74) |
| CI (range) | 1.486 (1.042–4.750) |
| patients w/ CI >1.5 (%) | 49 (46.2) |
| median radiosurgical dose to tumor margin in Gy (range) | 17 (11–23) |
| patients w/ tumor margin radiosurgical dose >17.5 Gy (%) | 40 (37.7) |
| median max radiosurgical dose in Gy (range) | 34 (18–46) |
| patients w/ max radiosurgical dose >35 Gy (%) | 47 (44.3) |

*CI = conformality index; GI = gastrointestinal; GTR = gross-total resection; NSCL = non–small cell lung; STR = subtotal resection.

## TABLE 2

Literature review of contemporary studies of adjuvant therapy following resection of a brain metastasis[*]

| Authors & Year | No. of Patients | Adjuvant Therapy | Local Disease Control Rate |
|---|---|---|---|
| Patchell et al., 1998 | 49 | 50.4 Gy WBRT | 90 |
|  | 46 | observation | 54 |
| Soltys et al., 2008 | 72 | cavity-directed SRS | 79 |
| Mathieu et al., 2008 | 40 | cavity-directed SRS | 73 |
| Hwang et al., 2010 | 25 | cavity-directed SRS | 100 |
| Jagannathan et al., 2009 | 47 | cavity-directed SRS | 94 |
| Aoyama et al., 2006 | 44 | cavity-directed SRS | 84 |
| Do et al., 2009 | 30 | cavity-directed SRS | 87 |
| Karlovits et al., 2009 | 52 | cavity-directed SRS | 92 |
| present study | 106 | cavity-directed SRS | 80 |

[*] SRS = stereotactic radiosurgery.