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Scientific Article

Cystic Brain Metastasis Outcomes After Gamma Knife Radiation Therapy

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Purpose: The response of cystic brain metastases (BMets) to radiation therapy is poorly understood, with conflicting results regarding local control, overall survival, and treatment-related toxicity. This study aims to examine the role of Gamma Knife (GK) in managing cystic BMets.

Methods and Materials: Volumetric analysis was conducted to measure tumor and edema volume at the time of GK and follow-up magnetic resonance imaging studies. Survival was described using the Kaplan-Meier method, and the cumulative incidence of progression was described using the Aalen-Johansen estimator. We evaluated the association of 4 variables with survival using Cox regression analysis.

Results: Between 2016 and 2021, 54 patients with 83 cystic BMets were treated with GK at our institution. Lung cancer was the most common pathology (51.9%), followed by breast cancer (13.0%). The mean target volume was 2.7 cm^3 (range, 0.1-39.0 cm^3), and the mean edema volume was 13.9 cm^3 (range, 0-165.5 cm^3). The median prescription dose of single-fraction and fractionated GK was 20 Gy (range, 14-27.5 Gy). With a median follow-up of 8.9 months, the median survival time (MST) was 11.1 months, and the 1-year local control rate was 75.9%. Gamma Knife was associated with decreased tumor and edema volumes over time, although 68.5% of patients required steroids after GK. Patients whose tumors grew beyond baseline after GK received significantly more whole-brain radiation therapy (WBRT) before GK than those whose tumors declined after GK. Higher age at diagnosis of BMets and pre-GK systemic therapy were associated with worse survival, with an MST of 7.8 months in patients who received it compared with 23.3 months in those who did not.

Conclusions: Pre-GK WBRT may select for BMets with increased radioresistance. This study highlights the ability of GK to control cystic BMets with the cost of high posttreatment steroid use.

Introduction

Brain metastases (BMets) affect a significant portion of oncologic patients and can be a cause of morbidity and mortality. Studies estimate that at least 70,000 patients are diagnosed with BMets in the United States each year,[1] increasing as survival improves and as neuroradiological screening occurs more frequently. The prognosis for this

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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patient population is poor, with median survival times of less than a year for all primary sites.[2] Treatment options include surgery and radiation, with steroids to manage peritumoral edema. More recently, immunotherapies and targeted therapies have also been shown to provide intracranial disease response.[3] Patients with a solitary BMet who are surgical candidates can undergo resection. Stereotactic radiosurgery (SRS) is generally used to treat asymptomatic, small, and/or surgically inaccessible lesions.[4] Although indications for SRS have expanded in recent years, whole-brain radiation therapy (WBRT) is still used in patients with high intracranial tumor burden and in prophylactic cranial irradiation for patients with small cell lung cancer.[5]

Brain metastases can present as cystic lesions, solid lesions, or a combination. A metastasis may become cystic from central necrosis or hemorrhage within the lesion.[6] When treating large cystic metastases, preradiation surgery or cyst drainage may be used.[7] The response of cystic metastases to radiation therapy is poorly understood, although it has been hypothesized that they may be associated with worse local control (LC), overall survival (OS), and treatment-related toxicity after treatment. Historically, cystic metastases were deemed unsuitable for radiation owing to the assumption that it was less effective against the hypoxic and noncellular centers.[6] However, the literature is conflicting. Some studies investigating OS after SRS and/or WBRT observed worse OS for cystic lesions compared with solid lesions,[8,9] whereas others observed no difference in OS in these lesions.[10] Similarly, some studies found worse LC after SRS,[7,11,12] whereas another study found no difference in LC after WBRT, despite slower tumor regression.[10] No differences in treatment-related toxicity between cystic and solid lesions have been appreciated in the literature.[7] It is also not understood whether observed differences in postradiation outcomes between patients with cystic versus solid BMets are the result of extracranial disease burden, intracranial disease burden, or radioresistance.[7] The goal of this study was to add to the existing knowledge on treatment parameters and outcomes for cystic BMets treated with Gamma Knife (GK) SRS at our institution.

Methods and Materials

Patient population and eligibility criteria

After institutional review board approval, we conducted a retrospective cohort study. A database of patients with cystic BMets treated with GK between 2016 and 2021 at Froedtert & The Medical College of Wisconsin (F&MCW) was constructed. Eligible patients were identified via a McKesson PACS workstation, mPower, which is a built-in search tool that searches keywords and filters exclusion criteria within radiology reports. An initial list of 3763 patients with radiographic evidence of cystic brain lesions was generated. This was narrowed down to 77 patients

Table 1 Baseline characteristics among patients with cystic brain metastases before Gamma Knife

Characteristic	Patients (N = 54)*
Age at diagnosis, median ± SD (range), y	
Malignancy	59.1 ± 13.0 (29-93)
Brain metastases	61.4 ± 13.1 (31-93)
Karnofsky performance scale score (N, %)	
100	2 (3.7)
90	17 (31.5)
80	21 (38.9)
70	11 (20.4)
60	2 (3.7)
40	1 (1.9)
Primary histology (N, %)	
Non-small cell lung cancer	23 (42.6)
Breast cancer	7 (13.0)
Small cell lung cancer	5 (9.3)
Other	19 (35.2)
Brain metastases at diagnosis, (N, %)	
1	24 (44.4)
2	12 (22.2)
3	5 (9.3)
4	2 (3.7)
5	2 (3.7)
>5	9 (16.7)
Pre-GK neurologic symptoms (N, %)	
Yes	37 (68.5)
No	17 (31.5)
Pre-GK or concurrent steroids (N, %)	
Yes	35 (64.8)
No	19 (35.2)
Tumor location (N, %)	
Frontal	35 (42.2)
Cerebellum	15 (18.1)
Occipital	13 (15.7)
Parietal	8 (9.6)
Temporal	6 (7.2)
Basal ganglia	2 (2.4)
Thalamus	2 (2.4)
Internal capsule	1 (1.2)
Orbital	1 (1.2)

Abbreviations: GK = Gamma Knife, SD = standard deviation.
*Data are presented as the number (percentage) of patients unless otherwise indicated.

with cystic BMets treated with GK. The final sample size was 54 patients with a total of 83 cystic BMets after addressing the exclusion criteria. Data from patients were pulled from Epic electronic health records to create a database for analysis. Patient demographic and treatment variables are listed in Table 1.

The inclusion criteria included (1) radiologic evidence of cystic BMets at diagnosis or later in the disease course, (2) age of at least 18 years at diagnosis of cystic lesion, (3) treatment of brain tumor initiated at F&MCW between 2016 and 2021, (4) receipt of GK for treatment of cystic BMets, and (5) completion of pre- and posttreatment imaging at F&MCW. The exclusion criteria included (1) no treatment for cystic BMets at F&MCW, (2) no receipt of GK, (3) treatment received outside of the 2016 to 2021 time frame, (4) no completion of pre- and posttreatment imaging at F&MCW, (5) incomplete follow-up visits or surveillance imaging at F&MCW, (6) only solid lesions at the time of GK, (7) enrollment on a clinical trial and receipt of surgical resection of BMets one day post-GK, and (8) medical records with inadequate documentation of treatment course and outcomes. Cystic lesions were defined as lesions with hypointense centers on postcontrast T1-weighted magnetic resonance imaging (MRI) with associated ring enhancement. If a lesion had both solid and cystic components, it was classified as cystic. Because the acquired data were retrospective from medical records, a waiver of consent was accepted by the institutional review board, and informed consent was not indicated for this study.

Gamma Knife radiosurgery

The median number of treated lesions was 2 (range, 1-12). The median number of treated cystic lesions was 1 (range, 1-5). The mean target volume was 2.7 cm^3 (range, 0.1-39.0 cm^3), and the mean edema volume was 13.9 cm^3 (range, 0-165.5 cm^3). The dose range of single-fraction and fractionated GK was 14 to 27.5 Gray (Gy), with a median dose of 20 Gy. Five patients (9.3%) received fractionated GK, with a median dose of 25 Gy (range, 24-27.5 Gy) and a median number of fractions of 5 (range, 3-5). Five patients (9.3%) received systemic therapy concurrent with GK.

Pre-GK, concurrent, and post-GK therapy

Before receiving GK, 17 patients (31.5%) completed radiation therapy (82.3% of such cases involving WBRT), whereas 12 patients (22.2%) underwent intracranial surgical resection. Systemic therapy up to 1 year before the start of GK included chemotherapy (n = 23 [42.6%]), immunotherapy (n = 11 [20.4%]), and targeted therapy (n = 10 [18.5%]). This is summarized in Table E1.

After GK, 5 patients (9.3%), including 1 of the 9 patients who had concurrent systemic therapy, underwent surgical resection of the treated lesion. Thirty-eight patients (70.4%) received systemic therapy within 1 year post-GK, with 27 (50.0%) on chemotherapy, 16 (29.6%) on immunotherapy, and 14 (25.9%) on targeted therapy. Sixteen (29.6%) patients underwent additional intracranial radiation, 10 of whom (62.5%) received additional GK. Three patients underwent a second set of intracranial radiation (2 GK and 1 WBRT), and 1 received a third GK treatment. This is summarized in Table E2.

Study approach and measures

Local control was defined as the absence of local progression. For the purposes of this study, local progression was defined as any tumor that radiographically exhibited an interval volume increase of at least 20%, and the change must have been at least 0.2 cm^3 in magnitude. Remote tumor progression was defined as the appearance of new BMets. Time to progression was defined as the period between GK and the first MRI demonstrating evidence of progression, with death before progression treated as a competing risk. Survival was measured from the date of GK.

We conducted a longitudinal volumetric analysis of 83 cystic BMets to measure tumor and peritumoral edema volume at the time of GK and follow-up MRI studies. Volumes were measured by contouring tumors and edema in MIM software (version 7.0.6, build KB13-05). Further analysis was focused on BMets at least 2.0 cm^3 in volume, because minor fluctuations in volume observed in smaller tumors (by increments of 0.1 cm^3) translated into large changes from baseline, complicating local progression data.

Statistical analysis

Patient characteristics were compared between patients with tumors that ultimately grew beyond baseline after GK and patients with tumors that decreased in volume using Fisher exact tests for categorical variables and Wilcoxon rank sum tests for continuous variables. Overall survival was described using the Kaplan-Meier estimator, and the cumulative incidences of local progression and nonprogression mortality were described using the Aalen-Johansen estimator, with progression and nonprogression mortality treated as competing risks. Cox proportional hazards regression analysis was used to simultaneously evaluate the association of age at diagnosis with BMets, pre-GK resection, pre-GK systemic therapy, and pre-GK radiation with survival. Median survival times (MSTs) were estimated using the Kaplan-Meier method, and survival time distributions were compared

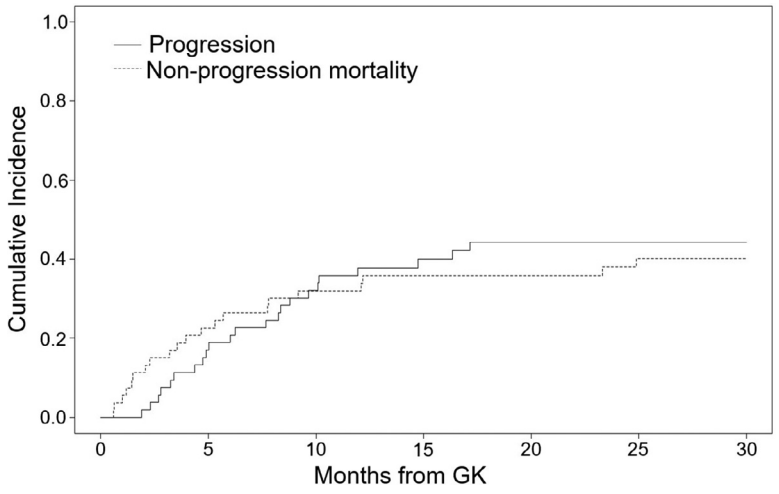

Figure 1 Cumulative incidence of local progression and nonprogression mortality versus time since Gamma Knife (months). Mortality was treated as a competing risk factor for local progression using the Aalen-Johansen estimator. *Abbreviation:* GK = Gamma Knife.

between groups using the log-rank test. For each covariate of interest, the power for the Cox proportional hazards analysis is 86% to detect a hazard ratio (HR) of mortality of 1.6 in a sample size of 54 patients, with a significance level (alpha) of .05. Statistical analysis was done using RStudio software, version 2022.07.1+554. A P value < .05 was considered statistically significant.

Results

Local and remote tumor progression

The median time to complete an initial post-GK MRI of the brain was 35 days (range, 2-131 days). Of 83 total lesions, the overall LC rate was 72.3%, and the 1-year LC rate was 75.9%. At 6 months after GK, the progression-free survival estimate was 52.9%, and the estimated cumulative incidences of progression and nonprogression mortality were 20.8% and 26.4%, respectively. At 12 months, these values were 30.2%, 37.8%, and 32.0%, respectively, and at 18 months, they were 19.8%, 44.4%, and 35.8%, respectively (Fig. 1). Seven lesions were treated for local progression: 4 were resected and 3 received WBRT. Three of the 4 resected lesions were found to have residual tumor on postoperative MRI, and 1 resected lesion received post-GK fractionated SRS. Twenty-nine patients (53.7%) experienced remote intracranial tumor progression after GK.

Treated tumor or edema volume change over time

Of the 83 total tumors, 27 (32.5%), seen across 24 patients, were at least 2.0 cm^3 in volume. At the time of GK, the mean volume of these lesions was 7.2 cm^3(range, 2.1-39.0 cm^3), and the mean volume of their surrounding vasogenic edema was 31.4 cm^3 (range, 4.01-165.5 cm^3). The median tumor volume change from the time of GK to final MRI was −70.6% (range, −99.0 to 221.4%) (Fig. 2), and the median edema volume change from the time of GK to final MRI was −38.3% (range, −97.9 to 1240.7%) (Fig. 3).

Eight of these tumors (29.6%) ultimately grew beyond baseline volumes, and peritumoral edema grew from baseline in 9 tumors (33.3%). Five of the 8 tumors with persistent growth (62.5%) were associated with persistent edema enlargement. The 3 that experienced edema decline received either pre-GK or post-GK steroids (n = 2) or post-GK steroids with bevacizumab (n = 1). The patients whose tumors ultimately grew beyond baseline were comparable with those whose tumors regressed following GK in age at BMet diagnosis, Karnofsky performance scale score, and pre-GK and post-GK neurologic symptoms, but they received pre-GK radiation significantly more (85.7% vs 18.8%; P = .0104), as summarized in Table E3. All patients with tumor growth beyond baseline who received pre-GK radiation underwent WBRT, whereas WBRT only represented 27.8% of pre-GK radiation in the total sample.

There were 9 tumors (at least 2.0 cm^3 in volume) with at least 1 year of follow-up. Comparing volume change from the time of GK to the time of final MRI in these lesions, 2 lesions (22.2%) grew, and 3 (33.3%) exhibited growth in peritumoral edema in 4 unique patients. Three patients (12.5%) with cystic lesions at least 2.0 cm^3 in volume required bevacizumab after GK owing to edema, with a median time from GK to start of bevacizumab of 414 days (range, 203-421 days), or 13.6 months. The median duration of bevacizumab use was 42 days (range, 1-381 days), or 1.4 months. Two of the 4 patients whose lesions exhibited persistent growth in tumor volume and/

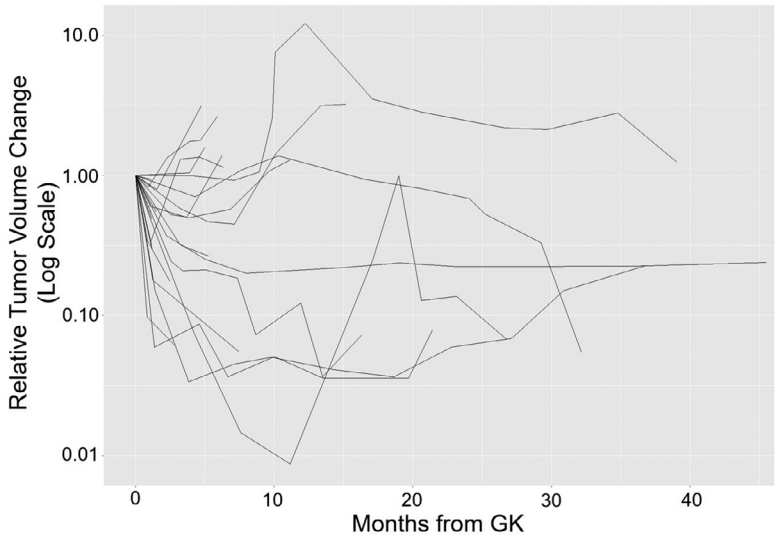

Figure 2 Relative tumor volume change from baseline versus time since Gamma Knife (months) for tumors >2.0 cm^3. Only 1 tumor per patient was included in this graph. In the 3 cases where a patient had 2 tumors >2.0 cm^3, the largest was included (for a total of 24 tumors included). *Abbreviation:* GK = Gamma Knife.

or edema volume and who had at least 1 year of follow-up imaging received bevacizumab after GK.

Toxicity

Twenty-nine patients (53.7%) reported new neurologic symptoms after GK. Thirty-five (64.8%) received steroids within 1 year of starting GK or concurrently with GK, and 37 received steroids within 1 year after GK (68.5%). This is summarized in Table E4. Four of the 9 patients (57.1%) with lesions exhibiting persistent peritumoral edema enlargement and 13 of the 22 patients (59.1%) who experienced local progression reported new neurologic symptoms after GK.

Treatment-related toxicity was further reviewed in the 24 patients with treated cystic lesions of at least 2.0 cm^3 in volume. Ten patients (41.7%) reported new neurologic symptoms after GK. Steroid use was examined as well, with 17 patients (70.8%) receiving steroids within 1 year of starting GK or concurrently with GK and 16 (66.7%) requiring steroids within 1 year after treatment. The median time from GK to the start of steroids was 25 days (range, 0-357 days), with a median duration of 162 days (range, 19-607 days), or 5.3 months. This is summarized in Table E5.

Survival

The median post-GK follow-up period was 270 days (range, 18-2099 days). The MST was 11.1 months (Fig. 4).

A multivariable Cox proportional hazards model evaluated the effects of age at diagnosis of BMets, pre-GK resection, pre-GK systemic therapy, and pre-GK radiation on mortality risk. Age at diagnosis of BMets, pre-GK systemic therapy, and pre-GK non-WBRT radiation were found to be associated with survival, with HRs of 1.45 (P = .040), 2.07 (P = .047), and 15.6 (P = .005), respectively. The Cox proportional hazards model provided a concordance statistic of 0.634, a standard error of 0.051, and a Wald test value of 13.54 (P = .02) (Table 2).

An MST of 7.8 months was observed in patients who received pre-GK systemic therapy, compared with 23.3 months in those who did not (P = .041) (Fig. E1). This was driven by patients receiving pre-GK chemotherapy, with identical MST values (P = .011). An MST of 7.9 months was observed in patients who received pre-GK WBRT, compared with 13.4 months in those who did not receive pre-GK radiation (P = .008) (Fig. E2). The 2 patients who received pre-GK non-WBRT radiation were unique in their primary tumors (testicular and parotid).

Discussion

Tumor progression

Studies have observed different proportions of tumors exhibiting local progression. Some reviewed LC rates in patients treated with different radiation modalities. In 2 studies, patients with cystic BMets treated with SRS were observed to have 1-year LC rates of 75% and 97%, compared with 88% and 96% in patients with solid BMets.[7,10] Many studies using SRS for BMets did not specify the cystic versus solid nature of lesions. Maldaun et al observed LC rates ranging from 60% to 95% in the literature.[13] Peterson et al observed LC rates of 90% at 20 weeks post-GK and 61% at 2 years post-GK.[11] Minniti et al reported

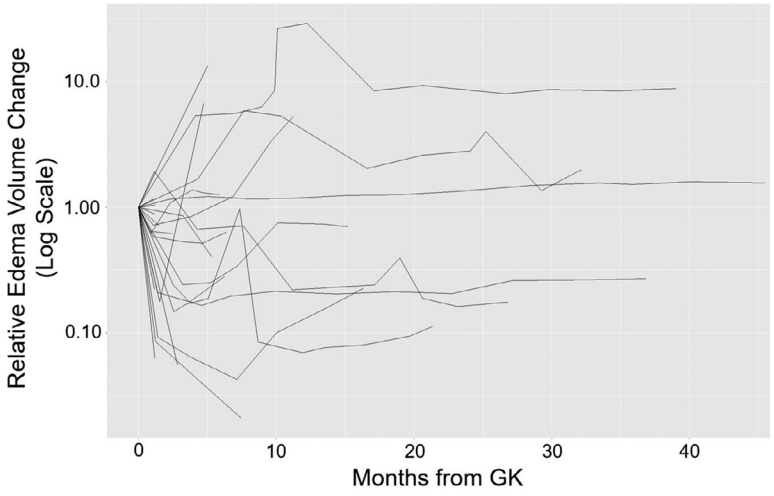

Figure 3 Relative peritumoral edema volume change from baseline versus time since Gamma Knife (months) for tumors >2.0 cm^3. Only 1 tumor per patient was included in this graph. In the 3 cases where a patient had 2 tumors >2.0 cm^3, the largest was included (for a total of 24 tumors included). *Abbreviation:* GK = Gamma Knife.

a 1-year LC rate of 43% in a prospective study.[14] Shiau et al observed a 1-year LC rate of 77% and found improved LC to be associated with a homogeneous pattern of contrast enhancement, as opposed to ring-enhancing patterns, which were associated with worse LC.[12]

One study involving GK without aspiration for cystic BMets reported a 1-year LC rate of 63% after GK, with worse LC associated with prior WBRT.[15] Flickinger et al observed a 2-year LC rate of 67%, although the cystic or solid nature of the lesions was unspecified.[16] Studies using GK with aspiration of cystic BMets reported LC rates ranging from 54% to 76%.[17-21] Franzin et al observed the greatest LC rate at 91.3% and a remote tumor progression rate of 39.1% of patients, with a median time interval of 6 months.[6]

In our study, 72.3% of cystic BMets remained locally controlled post-GK by the time of their last follow-up, and the 1-year LC rate was 75.9%. As with the other study reviewing cystic BMet response to GK without aspiration,[15] prior WBRT was associated with worse control. This suggests that prior WBRT may select for a more radioresistant form of disease. Remote tumor progression was observed in 53.7% of patients after GK. The LC observed in our study was similar to that of other studies investigating cystic BMet progression post-radiation with or without aspiration and was lower than in studies

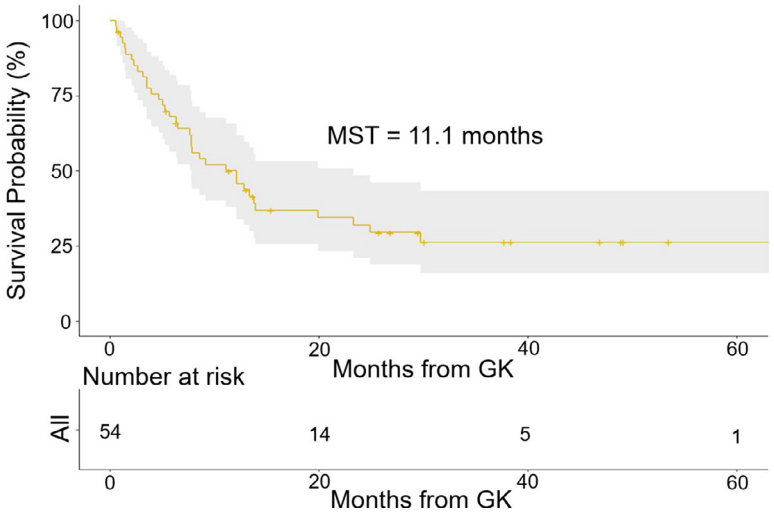

Figure 4 Kaplan-Meier survival curve for the entire patient cohort. The shaded area represents the confidence interval at each time point. *Abbreviations:* GK = Gamma Kinfe; MST = median survival time.

Table 2 Cox regression analysis of the effect of 4 demographic and treatment variables on survival

Characteristic	Hazard ratio (95% CI)	P value
Age at diagnosis of brain metastases, per decade	1.45 (1.02-2.08)	.040
Pre-GK resection		
No	1.00	-
Yes	0.67 (0.27-1.69)	.40
Pre-GK systemic therapy		
No	1.00	-
Yes	2.07 (1.01-4.26)	.047
Pre-GK cranial radiation		
None	1.00	-
WBRT	2.10 (0.80-5.49)	.13
Other radiation	15.6 (2.34-105)	.005

Abbreviations: GK = Gamma Knife; WBRT = whole-brain radiation therapy.

specifically examining solid tumor progression post-radiation, suggesting radioresistance in cystic BMets.

Treated tumor or edema volume change over time

The average tumor volume reduction observed in our study (70.6%) was comparable with that reported by Park et al (77.9%) when cystic BMets were aspirated after GK.[18] Ebinu et al reported an average reduction in tumor diameter of 27% in cystic BMets treated with GK.[15] In a study involving BMets of unspecified solid versus cystic nature treated with GK, 4% of tumors grew beyond baseline volume.[11] This is much less than observed in our study, where 29.6% of tumors beyond 2.0 cm^3 ultimately grew beyond baseline postGK.

Toxicity

In studies using SRS that did not specify the cystic versus solid nature of BMets, toxicity rates varied. Kondziolka et al observed that 34% of patients who received SRS reported side effects, in contrast to 63% who received SRS and WBRT and reported side effects.[22] Skeie et al observed acute toxicity in 2.3% of patients and late toxicity in 16.3% post-GK.[23] They also reported 73% of patients receiving steroids pre-GK, with 44% continuing steroids post-GK.[23] Minniti et al observed neurologic complications in 13.5% of patients post-SRS and steroid dependency in 16.5%.[14] Shaw et al observed 27% of patients receiving steroids after SRS.[24] Simonová et al observed 10% of patients to experience acute toxicity post-GK and require steroids (median duration of 1.5 months), with late toxicity observed in 5.5% post-GK, although this study only involved patients with solitary BMets.[25]

In our study, 41.7% of the patients with cystic BMets at least 2.0 cm^3 in volume reported new neurologic symptoms, and 66.7% required steroids within 1 year post-GK. It is unknown whether the neurologic symptoms were related to local or distant intracranial tumor or edema progression. The median time from GK to the start of steroids was 25 days, with a median duration of 5.3 months. The proportion of patients reporting new neurologic symptoms was similar to the proportion reporting adverse effects in the study from Kondziolka et al[22] but greater than the proportion in other studies.[14,23,25] The new neurologic symptoms reported by the patients in our study were not all necessarily directly from GK, and the other treatments the patients received varied, overestimating the symptoms that would be expected from GK alone. The proportion of patients in our study using steroids post-GK (66.7%) was also higher than in other studies.

Survival

One study involving SRS without aspiration for cystic BMets reported an MST of 17 months.[10] Wang et al found no significant difference in survival between patients with cystic and solid BMets treated with SRS, although the volume of cystic BMets exhibited slower shrinkage than of solid BMets.[10] Studies involving GK with aspiration for cystic BMets observed MST ranging from 7 to 17.8 months.[6,18-20,26] In patients treated with WBRT, Sun et al observed an MST of 10.2 months in patients with cystic BMets, which was significantly lower than that observed in patients with solid BMets, with an MST of 17.0 months.[9] In studies using SRS for BMets that did not specify the cystic versus solid nature of lesions, MST

ranged from 6.8 to 14.7 months[11,13,14,17,27]. The MST in our study (11.1 months) was comparable to much of the literature involving patients with cystic BMets but lower than in studies specifically examining MST in patients with solid BMets.

Cox regression analysis demonstrated that pre-GK resection (n = 12) was associated with a good prognosis, whereas age at diagnosis of BMets, pre-GK systemic therapy (n = 28), and pre-GK non-WBRT radiation (n = 2) were associated with poor prognosis. The sample size of patients who received pre-GK non-WBRT radiation in our data set was noticeably low. Although statistical significance was reached, conclusions cannot be appropriately drawn due to this limitation. Of the variables included in the Cox proportional hazards model, the Kaplan-Meier method demonstrated statistical significance in pre-GK systemic therapy and pre-GK radiation.

Limitations

Retrospective medical record reviews involve distinct disadvantages and biases including limiting results to demonstrating association rather than causation. We did not distinguish between neurologic symptoms being the result of GK, local or distal tumor progression, or other unrelated causes. Conclusions cannot be made regarding toxicity based on the reporting of neurologic symptoms in this study. Steroid administration post-GK was not distinguished between being a result of treatment or tumor-related toxicity. Radiation-induced necrosis can complicate local progression analysis. The Cox proportional hazards model did not consider all variables that may have influenced survival in our data set owing to sample size limitations.

Conclusions

Gamma Knife for cystic BMets was associated with a 1-year LC rate of 75.9% and an overall decrease in tumor and peritumoral edema volumes over time. After GK, 66.7% and 12.5% of patients with tumors at least 2.0 cm^3 in volume required steroids (median duration, 41 days) and bevacizumab (median duration, 42 days), respectively, to manage symptomatic edema and/or aggressive disease. Patients whose tumors grew beyond baseline after GK received significantly more pre-GK WBRT than those whose tumors declined following GK, suggesting that cystic BMets may become more resistant to GK after prior WBRT. The results of this study highlight the ability of GK to control cystic BMets with the added cost of higher symptom development and posttreatment steroid use. The presence of cystic BMets should not deter radiation oncologists from using GK but may indicate decreased potential benefit from upfront WBRT.

Disclosures

Joseph A. Bovi reports a relationship with Imaging Biometrics that includes consulting or advising. Christopher J. Schultz reports a relationship with Elekta AB that includes funding grants and travel reimbursement; a relationship with Siemens Healthineers that includes board membership and funding grants; and relationships with Accuray Inc and Mantia Medical Imaging that include funding grants. Lindsay Puckett reports a relationship with Accuray Inc that includes speaking and lecture fees. The other authors declare no personal, financial, or institutional interests in any of the drugs, materials, or devices described in this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.adro.2023.101304.

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