Long-term outcome of gamma knife radiosurgery for metastatic brain tumors originating from lung cancer

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Abstract

Background: Gamma knife radiosurgery (GKRS) has emerged as an important treatment option for metastasis brain tumors (MBTs). However, the long-term outcome of GKRS on MBTs originating from lung carcinoma is not well understood. The treatment of MBTs derived from lung cancer with GKRS at our institution is reviewed.

Methods: We performed a retrospective review (2000-2013) of 173 patients with MBTs from lung cancer who received GKRS. Out of 173 patients, 38 patients had recurrent tumors after microsurgical resection and whole brain radiotherapy (WBT).

Results: GKRS in MBTs metastasized from lung carcinoma showed significant variations in tumor growth control (decreased in 79 [45.7%] patients, arrested growth in 54 [31.2%] patients, and increased tumor size in 40 [23.1%] patients). The median survival in the study population was 14 months. Overall survival after 3 years was 25%, whereas progression-free survival after 3 years was 45%. The predictive factors for improving survival in the patients with MBTs were recursive partitioning analysis (RPA) class I ($P = 0.005$), absence of hydrocephalus ($P = 0.001$), Karnofsky performance scale (KPS) >70 ($P = 0.007$), age ≤ 65 ($P = 0.041$), tumor size ≤ 3 cm ($P = 0.023$), controlled primary tumor ($P = 0.049$), and single number of MBTS ($P = 0.044$).

Conclusion: Long-term follow-up revealed that GKRS offers a high rate of tumor control and good overall survival period in both new and recurrent patients with MBTs originating from lung carcinoma. Thus, GKRS is an effective treatment option for new patients with MBTs from lung cancer, as well as an adjuvant therapy in patients with recurrent MBTs derived from lung cancer.

Key Words: Gamma knife radiosurgery, lung cancer, long-term outcome, metastatic brain tumors, predictive factors

INTRODUCTION

Lung cancer is the leading cause of death from all malignant tumors worldwide and the most common source of metastasis brain tumors (MBTs). Literature-based evidence suggested that about 40-50% of patients have single or multiple MBTs that originated from lung cancer.[38] Metastatic brain tumors are the most common intracranial neoplasms with an incidence of nearly 200,000 new cases diagnosed each

year in the USA.[15,38] The incidence of MBTs derived from lung carcinoma is increasing as the survival of patients with brain metastases is increasing with significant advance in cancer therapy. Conventionally, resection and whole brain radiation were widely practiced for the treatment of MBTs.[10,12,16,29] Recently, gamma knife radiosurgery (GKRS) has emerged as an important treatment option for the management of brain metastases.[3,4,34,41-43] GKRS has been used as an adjunct therapy with whole brain radiotherapy (WBT) to irradiate the distant micrometastases.[13,16] Numerous studies including retrospective and prospective series reported the safety and efficacy of GKRS alone on MBTs.[4,6,42] In addition, literature review also suggested that GKRS is more beneficial than other treatment options including WBT and resection in terms of excellent local rate of control, shorter hospital stay, lower cost, lower mortality and morbidity, minimum invasiveness, and wide access to GKRS for repeated treatments.[6,14,29,38] However, little information is available in literature regarding long-term outcomes of GKRS on brain metastases derived from lung cancer. In this retrospective study, we evaluated our experience in the management and long-term outcomes of GKRS on MBTs derived from lung carcinoma, focused particularly on tumor control, survival, and predictive factors of survival.

MATERIALS AND METHODS

This study was done after approval by the Institutional Review Board at our institution. Information related to clinical history, surgery, neuroimaging, and outcomes of the patients with MBTs originated from lung cancer between 2000 and 2013 were collected retrospectively by review of the patient's case notes, follow-up chart, and radiology reports. We had information on outcome in all the patients.

Patients and tumor characteristics

The median age of the patients in this study was 58 years (range 32-82 years). Out of 173 patients, 94 (54.3%) were males and 79 (45.7%) were females; 121 (69.9%) were Caucasians, 52 (30.1%) were African Americans. Thirty-eight (22%) patients had recurrence brain metastases. According to recursive partitioning analysis (RPA classification), 107 (61.8%) had class I MBTs, 60 (34.7%) had class II MBTs, and 6 (3.5%) had class III MBTs. Fifty-eight (33.5%) patients had single MBTs and 115 (66.5%) had multiple MBTs. Brain metastases were located in the following order including 48 (27.8%) cases in the frontal lobe, 34 (19.6%) in the parietal lobe, 23 (13.3%) in the temporal lobe, 22 (12.7%) in the occipital lobe, and 42 (24.3%) in the cerebellum. Thirty-one (17.9%) patients had extra-cranial metastasis and eight (4.6%) cases had hydrocephalus [Tables 1 and 2].

Radiosurgical technique

Gamma knife stereotactic radiosurgery was performed using the Leksell stereotactic unit; model "C" with automatic positioning system (APS). The Leksell head frame was applied to the patient's head under IV sedation and local anesthesia. The patient was then transferred to the magnetic resonance imaging (MRI) suite for imaging. High resolution contrast enhanced

Table 1: Basal characteristics of the patients

Variables	Value
Age (years)	
Median	58
Range	32-82
Gender (%)	
Male	94 (54.3)
Female	79 (45.7)
Ethnicity (%)	
Caucasians	121 (69.9)
African Americans	52 (30.1)
Age>65 years, no (%)	
Yes	38 (22)
No	135 (78)
Hydrocephalus (%)	
Yes	8 (4.6)
No	165 (96.8)
RPA class, *n* (%)	
Class 1	107 (61.8)
Class 2	60 (34.7)
Class 3	6 (3.5)
Treatment policy (%)	
Gamma knife radiosurgery (GKRs)	137 (79.2)
Recurrence (Sx+GKRS)	36 (20.8)

RPA: Recursive partitioning analysis, GKRs: Gamma knife radiosurgery

Table 2: Tumor characteristics

Variables	Value
Tumor size	
Mean size, cm	2.27
Median size, cm	2.1
Size range, cm	0.7-6.0
Presence of single or multiple MBTs (%)	
Single MBT	58 (33.5)
Multiple MBT	115 (66.5)
Tumor location (%)	
Frontal	48 (27.8)
Parietal	34 (19.6)
Temporal	23 (13.3)
Occipital	22 (12.7)
Cerebellum	42 (24.3)
Extra-cranial metastasis (%)	
Yes	31 (17.9)
No	142 (82.1)

MBTs: Metastasis brain tumors

axial pictures of the brain were taken in the 3-D spoiled gradient-recalled (SPGR) sequence. The imaging data was then transferred to the gamma knife planning computer via the Ethernet. The Leksell Gamma Plan software version 5.34 was used to perform the dose planning. A management team including neurosurgeon, radiation oncologist, and medical physicist performed dose selection and planning. The total tumor volume that received the prescribed dose varied from 0.28 to 32 cm^3 (mean, 4.6 cm^3). The mean isodose line was 50.05% (range 40-60). The 50% isodose line was used in 163 (94.21%) patients. The mean marginal dose to the tumor was 16.54 Gy (range 10-22), the mean maximum dose to the tumor was 32.80 Gy (range 20-44). Mean radiation exposure time was 35.18 min (range10-90) [Table 3]. The head frame was removed after the procedure and a single dose of intravenous methylprednisolone (40 mg) was given to the patient. Thereafter, the patient was transferred to the Neurosurgery service floor for overnight observation.

Follow-up

Preoperative and follow-up data were collected from the study population. If necessary, patients were contacted by telephone to update their outcome status. Neuroimaging studies were performed at 3-month intervals after GKRS for detailed neurological examination to demonstrate the improvement or worsening of preexisting signs and symptoms, development of any new sign or symptom, and any change in MR images. The median duration of follow-up was 8 months (1-128 months).

Statistical analysis

Commercially available software, SPSS version 21.0 (SPSS, Inc, Chicago Illinois), was used for statistical analysis. Overall and progression-free survival was analyzed using the Kaplan–Meier test. The log-rank (Mantel–Cox) test was used to analyze the survival difference in the cases. Cox regression model was used to demonstrate the predictive factors of the outcome. A $P < 0.05$ was considered as significant.

RESULTS

Tumor growth control and brain edema response after GKRS

Tumor growth control after GKRS is listed in Table 4. The average tumor size was 2.27 cm (range 0.4-6 cm). The most recent follow-up showed decreased tumor size in 79 (45.7%) patients, arrested tumor growth in 54 (31.2%) patients, and increased tumor size in 40 (23.1%) patients. Ten (5.78%) patients in progressed group developed new lesions. Thirty-eight (66%) MTBs were decreased, 10 (19%) MTBs remained stable, and 8 (15%) MTBs showed increased volume of perifocal brain edema [Table 4].

Survival outcome

The median survival in the study population was 14 months. Overall survival after 3 years was 25%, whereas progression-free survival after 3 years was 45% [Figure 1a and b].

RPA classification
The median survival time for RPA class I, II, and III were 15, 12, and 5 months, respectively. The difference in the median survival reached statistical significance (log-rank $P < 0.008$) [Figure 1c].

Karnofsky performance status
The median survival time for the patients with Karnofsky performance scale (KPS) >70 after GKRS was 18 months and median survival in patients with KPS ≤70 was 8 months. This difference in median survival time between these two groups reached statistical significance (log-rank $P = 0.005$) [Figure 1d].

Hydrocephalus
The actuarial median survival time for the patients with hydrocephalus after GKRS was 3 months and in patients without hydrocephalus was 15 months. This difference in median survival time between these two groups reached statistical significance (log-rank $P < 0.0001$) [Figure 1e].

Age >65 years and ≤65 years
The median survival time for the patients aged >65 years was 12 months and in patients aged ≤65 was 15 months. This difference in median survival time between these two groups reached statistical significance (log-rank $P = 0.035$) [Figure 2a].

Table 3: Dose used during GKRS

Parameter	Value
Mean marginal dose in Gy (range)	16.54 (10-22)
Mean maximum dose in GY (range)	32.80 (20-44)
Mean isodose line % (range)	50.05 (40-60)
Radiation time (min)	35.18 (10-90)

GKRS: Gamma knife radiosurgery

Table 4: Outcome after GKRS treatment

Follow-up	Value
Median survival (months)	14
Tumor response, *n* (%)	
Decreased	79 (45.7)
No change	54 (31.2)
Increased	40 (23.1)
Brain edema response (%)	
Decreased	38 (66)
No change	10 (19)
Increased	8 (15)
Further intervention (%)	
GKRS	22 (13)
Resection	7 (4)

GKRS: Gamma knife radiosurgery

Recurrence of MBTs

The median survival time for the patients with recurrent MBTs after GKRS was 11 months and in patients without recurrent MBTs was 14 months. This difference in median survival time between these two groups did not achieve statistical significance (log-rank $P = 0.16$) [Figure 2b].
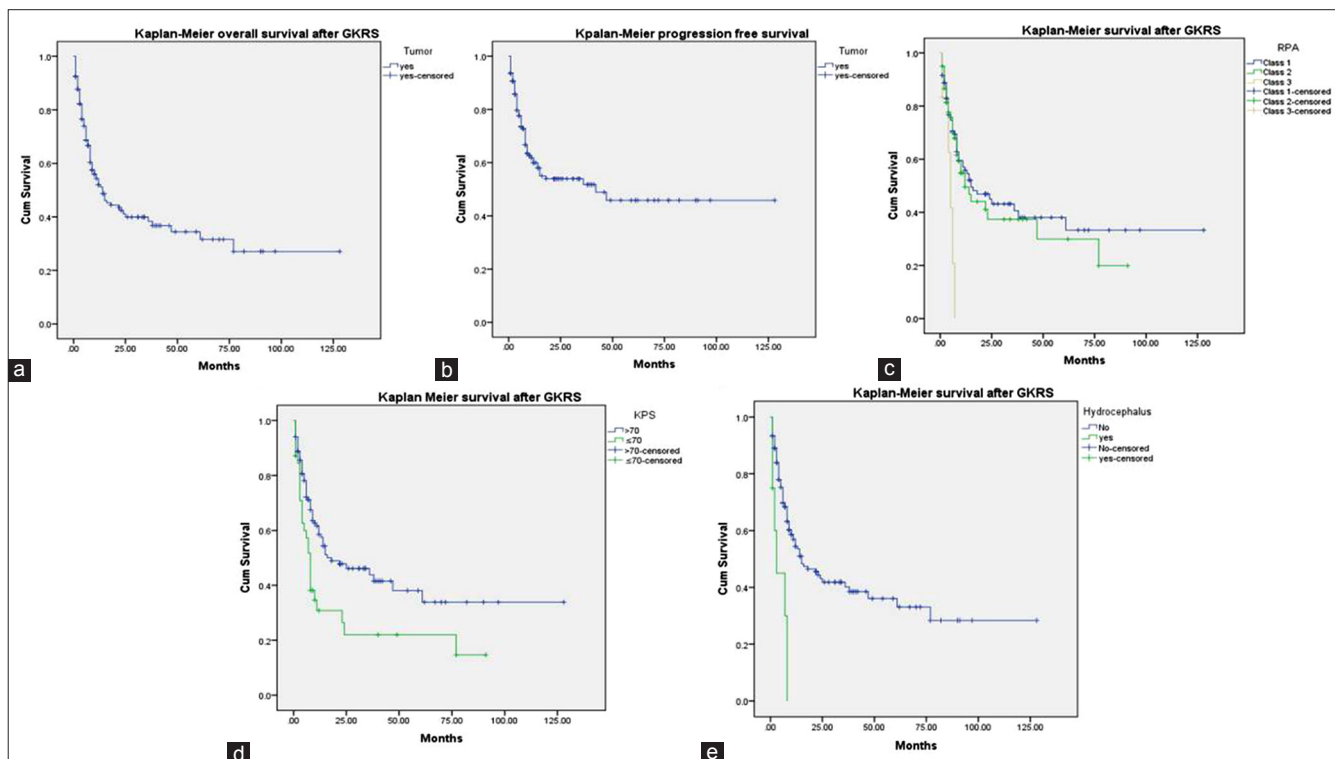

Figure 1: Panels a and b represent the Kaplan–Meier overall and progression-free survival rate, respectively, in all patients with MBTs after GKRS treatment. Panels c, d, and e report the comparison of overall survival based on RPA classification, KPS, and presence or absence of hydrocephalus, respectively, in the patients with MBTs after GKRS treatment. P < 0.05 is considered as significant
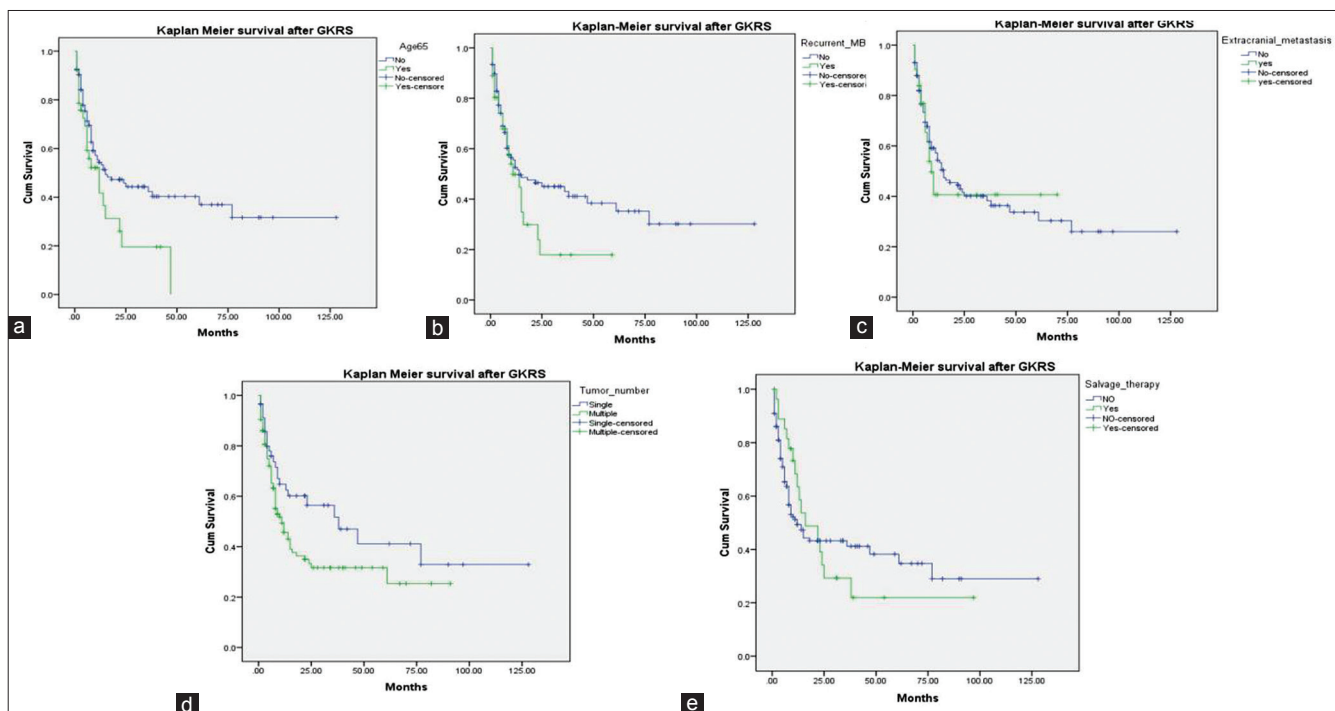

Figure 2: Panels a, b, c, d, and e demonstrate the comparison of overall survival based on age (>65 or ≤65 years), recurrent tumors, presence or absence of extra-cranial metastasis, number of tumors (single or multiple) and with or without salvage therapy, respectively, in the patients with MBTs after GKRS treatment. P < 0.05 is considered as significant

Extra-cranial metastasis
The median survival time for the patients with extra-cranial metastasis was 8 months and in patients without extra-cranial was 15 months. This difference in median survival time between these two groups did not reach statistical significance (log-rank $P = 0.782$) [Figure 2c].

Single or multiple tumors
The median survival time for the patients with single BMTs was 38 months and in patients with multiple BMTs was 11 months. This difference in median survival time between these two groups reached statistical significance (log-rank $P = 0.037$) [Figure 2d].

Survival with or without salvage therapy
The median survival after salvage therapy was 16 months and the median survival without salvage therapy was 12 months. The difference in the median survival did not reach statistical significance (log rank $P = 0.80$) [Figure 2e].

Tumor volume
The median survival time for the patients with tumor size >3 cm was 6 months and for patients with tumor size ≤3 cm was 15 months. This difference in median survival time between these two groups reached statistical significance (log-rank $P = 0.023$) [Figure 3a].

Primary tumor (controlled vs. uncontrolled)
The median survival time for the patients with controlled primary tumor was 22 months and for patients with uncontrolled primary tumor was 9 months. This difference in median survival time between these two groups reached statistical significance (log-rank $P = 0.049$) [Figure 3b].

CNS progression vs. systemic progression
The median survival time for the patients with no progression, central nervous system (CNS) progression, systemic progression, and both CNS and systemic progression was 22, 15, 10, and 6 months, respectively. This difference in median survival time among these four groups did not reach statistical significance (log-rank $P = 0.241$) [Figure 3c].

Histological subtype of lung cancer
The median survival time for the patients with nonsmall cell lung cancer was 22 months and for patients with small cell lung cancer was 9 months. This difference in median survival time between these two groups did not reach statistical significance (log-rank $P = 0.748$) [Figure 3d].

Complications

In the present study, 40 (23.12%) patients had progression of MBTs. A total of 29 (16.7%) patients underwent salvage therapy, including 22 (12.7%) and 7 (4%) cases that required GKRS and resection, respectively, after initial GKRS treatment. Two patients (1.15%) experienced intracranial hemorrhage after GKRS; one of these two patients had new symptoms. One patient was under rehabilitative care due to age and tumor-related complications.

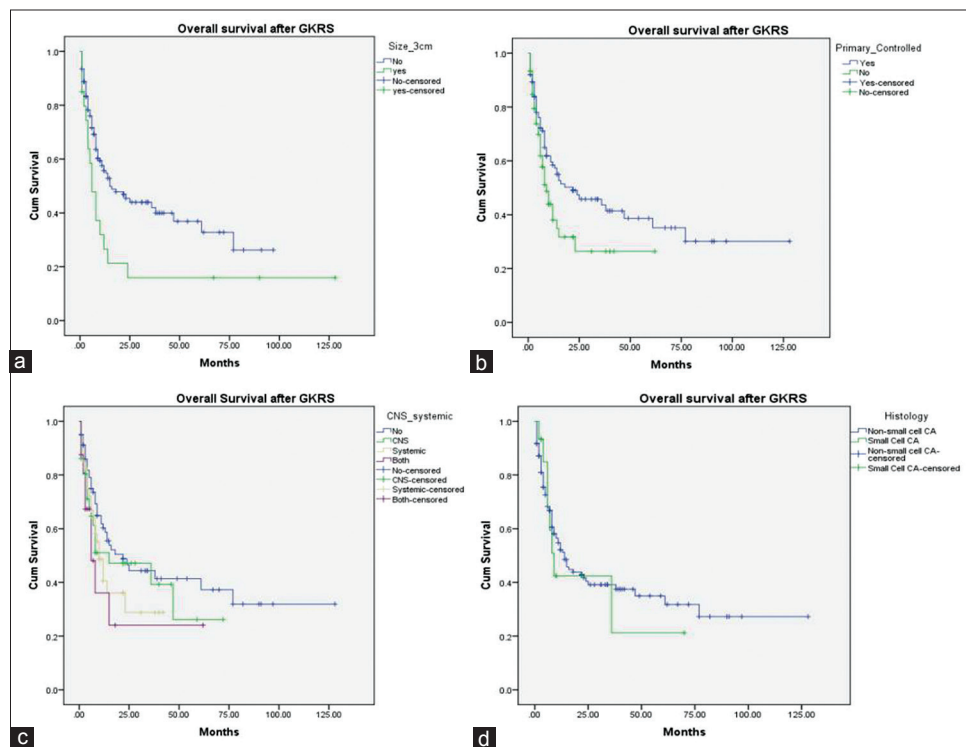**Figure 3: Panels a, b, c, d, represent the comparison of overall survival based on tumor size (>3 vs. ≤3 cm), control of primary tumor (yes vs. no), progression of tumor (no, CNS, systemic or both) and histological subtype of lung cancer (nonsmall cell vs. small cell cancer), respectively, in the patients with MBTs after GKRS treatment. *P* < 0.05 is considered as significant**

Predictive factors of survival

Cox regression was performed to identify the predictors of survival in patients with MBTs and the results are shown in Table 5. The following covariates were included in the model: Gender (male vs. female), ethnicity (Caucasians vs. African Americans), age (>65 vs. ≤65 years), and hydrocephalus (yes vs. no), RPA classification (Class I vs. Class II vs. Class III), number of tumors (single vs. multiple), extra-cranial metastasis (yes vs. no) and recurrent MBTs (yes vs. no), and KPS (>70 vs. ≤70). Among the listed factors, hydrocephalus ($P = 0.001$, CI 1.83-8.87), RPA class ($P = 0.005$, CI 0.10-0.66), single number of MBTs ($P = 0.044$, CI 1.04-2.55), KPS >70 ($P = 0.007$, CI 1.89-2.90), and age ≤65 years ($P = 0.041$, CI 1.02–2.65) were identified as the predictors of survival. However, gender, ethnicity, extra-cranial metastasis did not show any significant relation with survival in the studied cases [Table 5].

DISCUSSION

Different treatment strategies including surgical resections, WBRT and GKRS alone or in combination, have been widely used as treatment options for MBTs despite there having been debatable issues on optimal treatment.[31] Although historically, the long-term outcome of MBTs with different treatment strategies was not so satisfactory, rapid advances in radiation techniques for management of MBTs have contributed to improved function and survival rates in these patients with MBTs. This has raised the concern regarding long-term outcomes of GKRS on MBTs.[46] The long-term outcomes of MBTs including the survival benefits, tumor growth control, and quality of life and complications were observed in most of the published reports. Several studies revealed that the overall survival of patients with MBTs originating from

lung cancer after GKRS ranges from 9 to 18 months. Our study also showed that the median survival of patients with MBTs after GKRS was 14 months, which is very consistent with previous reports.[7,19,21,22,23,25] Flannery *et al.* identified that the median survival after GKRS alone was 15.7 months in the patients with MBTs from lung cancer.[7] Similarly, Motta *et al.* and Kong *et al.* showed that the median survival in the patients with MBTs originating from lung cancer was 14.2 and 12 months, respectively.[21,31] Moreover, several randomized control trials revealed the survival benefits of GKRS alone or in combination with WBRT in the patients with MBTs metastasized from lung cancer.[1,41] In these randomized trials on the adjuvant therapy with WBRT versus observation after SRS alone or microsurgical resection did not show any significant differences in term of median survival and neurological deaths.[20,32,33,39] Based on the results of the present study and previous reports, it is obvious that GKRS alone is a more attractive, feasible, and less invasive treatment option combined with high tumor control and survival benefits for the patients with multiple or single brain metastases derived from lung cancer.

As reported in previous studies, our data also showed that the different factors affect the long-term survival benefits of GKRS. The cases in our study were stratified by the RPA classification system, which includes age, status of extra-cranial metastasis, Karnofsky performance status, and primary tumor control. Previous reports revealed that the median survival was highest in the RPA Class I cases with MBTs from lung cancer as compared with Class II and Class III.[24,26,34] Consistent with previous reports, our data showed that the median survival for Class I, II, and III was 15, 12, and 5 months, respectively. Other statically significant variables including KPS scores, hydrocephalus, number of tumors, tumor size, and control of primary tumors affected the long-term outcomes of the GKRS in the patients with MBTs originating from lung cancer. Our study revealed that KPS >70, tumor size ≤3 cm, and good control of primary tumor affected the survival rate positively in the patients with MBTs, and this finding was consistent with previous studies.[31,34,36] In addition, the presence of hydrocephalus, age >65 years, and multiple tumors after GKRS showed negative effects on survivability as already shown by earlier reports.[5,16] Interestingly, findings in our case series showed a downward trend of improved overall survivability in following order: No progression: 22 months, CNS progression: 15 months, systemic progression 10 months, and both CNS and systemic progression: 6 months. Several studies showed that extra-cranial metastasis and female gender have significant effects on the prognosis of MBTs after GKRS.[11,28,37,41] Although our study did not reach any significance difference in median survival related to

Table 5: Prognostic factors for improve survival

Variables	B	SE	Wald	Sig	HR	95% CI for HR	
						Lower	Upper
RPA classification							
Class I	−1.35	0.48	7.98	0.005	0.26	0.10	0.66
Class II	−1.23	0.49	6.32	0.012	0.30	0.11	0.76
Hydrocephalus (yes)	1.39	0.40	11.99	0.001	3.97	1.80	8.75
Number of MBTs	0.48	0.24	4.06	0.044	1.61	1.04	2.55
Extra-cranial metastasis	0.08	0.28	0.73	0.79	1.08	0.62	1.85
Recurrent tumor	0.34	0.25	1.85	0.173	1.39	0.86	2.27
Gender	0.19	0.21	0.84	0.36	1.21	0.81	1.81
Ethnicity	−0.25	0.24	1.12	0.29	0.78	0.49	1.23
Age > 65 years	0.50	0.24	4.1	0.041	1.64	1.02	2.65
KPS (>70)	0.62	0.23	7.37	0.007	1.86	1.89	2.90

CI: Confidence interval, HR: Hazard ratio, MBTs: Metastasis brain tumors, KPS: Karnofsky performance scale

variables including extra-cranial metastasis (yes, 8 months vs. no, 15 months), or gender (female, 11 months vs. male, 15 months), there was marked difference in median survival. This data is comparable with previously published reports.[8,17] In addition, there was possibility that histological subtypes of lung cancer might have contributed to the outcomes of GKRS in the patents with MBTs. However, previous reports suggested that there was no difference in overall survival and tumor control rate in histological subtypes (e.g. small cell carcinoma [SCLC] and nonsmall cell carcinoma [NSCLC]) of lung cancer.[35] This study also revealed that histological subtype of lung cancer (NSCLC, 14 months vs. SCLC, 9 months) did not have significant effect on survivability of patients with MBTs.

Molecular studies revealed that continuous activation of receptor tyrosine kinase (RTKs) and intracellular signaling molecules play major role in fundamental cellular mechanism including survival, proliferation, differentiation, and migration, which in turn leads to lung cancer growth and survival.[2,9] Different molecular target genes including epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (FGF) platelets derived growth factor (PDGF), k-RAS, mesenchymal-epithelial transition factor (MET), analplastic lymphoma akinase (ALK), and mammalian target of rapamycin (mTOR) are involved in lung cancer growth and development and represent the potential parameter to guide treatment decision.[2] Therefore, inhibitors of these RTKs and intracellular molecules have potential positive effect on overall survival in the patients with lung cancer. Recently, EGFR-RTKs inhibitors have been used with chemotherapy for improvement of overall survival in the patients with lung cancer.[27] Although, we have not reviewed the effect of inhibitors of RTKs and intracellular signaling molecules on overall survival in our case series, these inhibitors might have effect on better survival of our cases.

Another objective for treatment of MBTs is to demonstrate the tumor growth control. Our study showed that the tumor growth control was 76.9%, which is very consistent with the range of 70-100% reported by previous studies.[18,25,40] In the present study, most of these responses were in the form of complete resolution of the tumor (45.7%) vs. tumor stabilization (31.2%), which is also consistent with previous reports.[40,46]

In this study, complications including hemorrhage were also observed in our study but with lower frequency as reported in earlier studies.[30,43,44,45] Importantly, not a single patient experienced any mental or memory impairment in our study, which is in partial agreement with an earlier report.[13] In a recent follow-up, adverse radiation effects were observed in 12.1% with neurological symptoms and in 10.9% patients without neurological symptoms after GKRS. Similarly, a previous report also suggested that symptomatic adverse radiation effects and asymptomatic adverse radiation effects were in 11% and 9% patients, respectively. Twenty-two (12.7%) patients required GKRS and seven (4%) patients required resection after the initial GKRS.[32]

Limitation

This study has a few limitations including: (i) it is a retrospective study and (ii) lack of control group confines us in assessing the full benefits and complications of GKRS.

In conclusion, given the good tumor growth control, good overall survival period and lesser number of complications, GKRS can be an ideal treatment option for the patients with MBTs originating from lung cancer. In addition, GKRS can be also a good treatment option for recurrent patients to avoid repeated resections along with craniotomy-related complications. Further study in a large volume of patients with MBTs and a randomized controlled trial are required to accomplish a good comparison of treatment modalities.

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