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Clinical Study

Long term outcome of Gamma Knife radiosurgery for metastatic brain tumors

Shyamal C. Bir, Sudheer Ambekar, Anil Nanda *

Department of Neurosurgery, LSU Health-Shreveport, 1501 Kings Highway, Shreveport, LA 71130-3932, USA

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ABSTRACT

Gamma Knife radiosurgery (GKRS; Elekta AB, Stockholm, Sweden) has emerged as an important treatment option for metastatic brain tumors (MBT). However, the long term outcome of GKRS on MBT is not well understood. We reviewed the treatment of MBT with GKRS at our institution. We performed a retrospective review (2000–2013) of 298 patients with MBT who received GKRS. The study population was monitored clinically and radiographically after GKRS treatment. Survival benefits and predictive factors of the outcome were analyzed using the Kaplan–Meier test and Cox regression model, respectively. GKRS in MBT showed significant variation in tumor growth control (decreased in 135 [45%] patients, arrested growth in 91 [37%] patients and increased tumor size in 72 [24%] patients). The median survival in the study population was 17 months. Overall and progression free survival after 3 years were 25% and 45%, respectively. The predictive factors for improving survival in the patients with MBT were recursive partitioning analysis class I ($p < 0.0001$), absence of hydrocephalus ($p < 0.0001$), Karnofsky Performance Status (KPS) >80 ($p = 0.007$) and absence of recurrent MBT ($p = 0.01$). Forty (12%), 15 (4.3%) and two (0.6%) patients required GKRS, resection and whole brain radiation, respectively, after initial GKRS due to tumor progression and worsening of signs and symptoms. Our findings revealed that GKRS offers a high rate of tumor control and good survival benefits in both new and recurrent patients with MBT. Thus, GKRS is an effective treatment option for new patients with MBT, as well as an adjuvant therapy in patients with recurrent MBT.

1. Introduction

Metastatic brain tumors (MBT) are the most common intracranial neoplasms, with an incidence of nearly 200,000 new patients diagnosed each year in the USA [1,2]. Moreover, the incidence of MBT is increasing as the survival of patients with brain metastases is increasing with rapid advances in cancer therapy. Conventionally, resection and whole brain radiation (WBRT) were widely practiced for the treatment of MBT [3–6]. Stereotactic radiosurgeries including Gamma Knife radiosurgery (GKRS; Elekta AB, Stockholm, Sweden) have emerged as important treatment options for the management of brain metastases [7–12]. Radiosurgery has been used as an adjunct therapy with WBRT to irradiate distant micrometastases [3,13]. Numerous studies, including retrospective and prospective series, have reported the safety and efficacy of GKRS alone on MBT [8,9,14]. In addition, research based evidence has also suggested that GKRS is more beneficial than other treatment options, including WBRT and resection, in terms of excellent local control, shorter hospital stay, lower cost, lower mortality and morbidity, minimum invasiveness, and wide access of GKRS for repeated treatments [4,14–16]. However, little information is available in the literature regarding long term survival benefits of GKRS on brain metastases. In the present study, we retrospectively evaluated our experience in the management and long term outcomes of MBT, focusing particularly on tumor control, survival and the predictive factors for survival.

2. Materials and methods

This study was carried out after approval by the Institutional Review Board at our institution. Information related to clinical history, surgery, neuroimaging, and outcomes of the patients with MBT between January 2000 and December 2013 were collected retrospectively by review of each patient's case notes, follow-up chart and radiology reports. We had information regarding outcome for all the patients.

* Corresponding author. Tel.: +1 318 675 6404; fax: +1 318 675 6867.
E-mail address: ananda@lsuhsc.edu (A. Nanda).

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2.1. Patient and tumor characteristics

The median age of patients in this study was 56 years (range 30–87 years). Out of 298 patients, 145 (48.7%) were males and 153 (51.3%) were females. Sixty-eight (22.8%) patients had recurrent brain metastases. According to recursive partitioning analysis (RPA classification), 190 (63.1%) patients had class I MBT, 97 (32.2%) patients had class II MBT and 11 (3.7%) patients had class III MBT (Table 1). The common source of primary tumors included 168 (56%) from the lung, 47 (16%) from the breast, 24 (8%) from malignant melanoma, 21 (7%) from the colon and 18 (6%) from the kidney. Ninety-six (32%) patients had single MBT and 208 (68%) had multiple MBT. Other characteristics of the MBT including location in the brain are listed in Table 2.

2.2. Radiosurgical techniques

Gamma Knife stereotactic radiosurgery was performed using the Leksell stereotactic unit; model "C" with an automatic positioning system (Elekta AB). The Leksell head frame was applied under intravenous sedation and local anesthesia. The patient was then transferred to the MRI suite for imaging. High resolution contrast enhanced axial pictures of the brain were taken using the three-dimensional spoiled gradient echo sequence. The imaging data were 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 (Elekta AB). The mean marginal dose to the tumor was 16 Gy (range 10–20), the maximum dose to the tumor was 23 Gy (range 14–40) and the mean isodose line was 50% (range 40–70%). Mean radiation exposure time was 34 minutes (range 10–90 minutes) (Table 3). The head frame was removed after the procedure and a single dose of intravenous methylprednisolone (40 mg) was given to the patient. The patient was transferred to the Neurosurgery service ward for overnight observation.

Table 1
Baseline characteristics, clinical features and treatment of metastatic brain tumor patients

Variables	Value, n (%)
Age	
Median	56
Range	30–87
Sex	
Male	145 (48.7%)
Female	153 (51.3%)
Ethnicity	
Caucasian	208 (69.8%)
African American	90 (30.2%)
Age	
>65 years	65 (22%)
⩽65 years	233 (78%)
Hydrocephalus	
Yes	10 (3.5%)
No	288 (96.5%)
RPA class	
Class 1	190 (63.1%)
Class 2	97 (32.2%)
Class 3	11 (3.7%)
Treatment policy	
GKRS	218 (73.2%)
Prior resection (Sx + GKRS)	68 (22.8%)
Prior radiation (WBRT)	17 (6%)

GKRS = Gamma Knife radiosurgery (Elekta AB, Stockholm, Sweden), RPA = recursive partitioning analysis, Sx = surgery, WBRT = whole brain radiation.

Table 2
Tumor characteristics for metastatic brain tumors

Variables	Value, n (%)
Tumor size	
Mean size	2.25 cm
Median size	2.0 cm
Size range	0.7–6.0 cm
Number of tumors	
Single MBT	96 (32%)
Multiple MBT	202 (68%)
Primary tumor source	
Lung	168 (56%)
Breast	47 (16%)
Melanoma	24 (8%)
Colon	21 (7%)
Renal	18 (6%)
Tumor location	
Frontal	84 (28%)
Parietal	60 (20%)
Temporal	40 (13.4%)
Occipital	39 (13%)
Insular	3 (1%)
Basal ganglia/thalamus	2 (0.6%)
Cerebellum	70 (24%)
Extra-cranial metastasis	
Yes	45 (15%)
No	253 (85%)

MBT = metatstatic brain tumor.

2.3. 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 pre-existing signs and symptoms, development of any new signs or symptoms, and any change in MRI appearance. The median duration of follow-up was 9 months (range 1 month–137 months).

2.4. Statistical analysis

Commercially available software, the Statistical Package for the Social Sciences version 21.0 (SPSS, Chicago IL, USA) 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 patients. The Cox regression model was used to demonstrate the predictive factors of the outcome. A p value < 0.05 was considered as significant.

3. Results

3.1. Tumor growth control and brain edema response after GKRS

Tumor growth control after GKRS is listed in Table 4. The average tumor size was 2.25 cm (range 0.7–3.5 cm). The most recent

Table 3
Dose used during Gamma Knife radiosurgery[a] treatment of metastatic brain tumors

Parameter	Mean (range)
Marginal dose, Gy	16 (10–20)
Maximum dose, GY	23 (14–40)
Isodose line, %	50 (40–70)
Radiation time, minutes	34 (10–90)

[a] Elekta AB, Stockholm, Sweden.