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Gamma Knife radiosurgery in the management of brainstem metastases

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ABSTRACT

Background: Metastases to the brainstem portend a poor prognosis and present a challenge in clinical management. Surgical resection is rarely a viable option.
Methods: Post-treatment MRI scans of patients with brainstem metastases treated with radiosurgery were used to determine local control and disease progression. Median survival was calculated using Kaplan–Meier analysis. Univariate and multivariate analyses were performed using log-rank test and Cox proportional hazards model, respectively.
Results: Thirty-two consecutive patients with brainstem metastasis underwent Gamma Knife radiosurgery. Median age was 50 years. Median tumor volume was 0.71 cm^3 and median tumor margin dose was 13 Gy. Seventeen of 32 patients received WBRT prior to stereotactic radiosurgery. Median survival was 5.2 months. There was a statistically significant difference in survival based on RTOG recursive partition analysis (RPA) class. Median survival of patients categorized as RPA class I was 19.2 months, RPA class II was 8.4 months, and RPA class III was 1.9 months. The overall local tumor control rate was 87.5%. There were no acute complications following stereotactic radiosurgery and no evidence of radiation necrosis noted on post-treatment MRI scans.
Conclusion: Stereotactic radiosurgery is an effective treatment for brainstem metastases and should be considered especially for patients with good performance status.

1. Introduction

Metastatic brain tumors are the most common intracranial neoplasm with approximately 200,000 individuals diagnosed each year in the United States. Recently, our institution reported that the overall population-based incidence of cancer patients with brain metastasis in the Metropolitan Detroit area to be around 9.6% [1]. When analyzing by primary site, 19.9% of all lung cancer patients developed brain metastases, followed by melanoma (6.9%), renal (6.5%), breast (5.1%), and colorectal cancers (1.8%).

Brain metastases occur frequently in the setting of systemic malignancy. Importantly, there is evidence that the frequency of central nervous system metastasis is increasing [2]. With improving imaging, cancer detection, and treatment options, it is likely that cancer patients will continue to survive longer, further increasing the number of patients with brain metastases in the future. Hence, streamlining the optimal management of brain metastases continues to be an area of vital interest.

In particular, metastases located in the brainstem portend a poor prognosis and frequently present a challenge in clinical management. Surgical resection is rarely a viable option due to high risk of developing new or worsening neurological deficits. Patients with brainstem metastases often present with focal neurologic signs and symptoms due to anatomic location and local mass effect, for which stereotactic radiosurgery may provide better symptomatic outcomes than whole-brain radiation therapy (WBRT) alone. However, stereotactic radiosurgery to the brainstem presents unique considerations, mainly due to concerns of toxicity to critical structures. To date, there are a limited number of single institution retrospective studies examining stereotactic radiosurgery for treatment of brainstem metastases. In this study, we report our experience with Gamma Knife radiosurgery (GKRS) for brainstem metastases and provide a review of the literature.

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2. Methods

2.1. Patient selection

After approval from our Institutional Review Board, we retrospectively reviewed our database of patients treated with GKRS (Model 4C, Elekta Instruments, Atlanta, GA) at the Karmanos Cancer Institute in Detroit, Michigan between January 2003 and August 2010. A total of 32 consecutive treated patients were identified.

2.2. Gamma Knife radiosurgery

A Leksell stereotactic head frame was placed using local anesthesia. A volumetric, contrast-enhanced MRI scan was acquired at 1.0–2.0 mm slice thickness. Treatment planning was conducted under the guidance of a medical physicist, radiation oncologist, and neurosurgeon with GammaPlan software (Elekta, Stockholm).

The 50% isodose line was contoured to include the tumor along with 1–2 mm peripheral margin. Conformality was achieved by placing multiple radiation isocenters focused in the target as needed in all 32 patients with a median of 3 isocenters (range 1–16). The prescribed dose to the 50% isodose line was determined by the tumor volume, location, and prior radiation therapy. Several dose matrices were prepared for cases of multiple metastases.

2.3. Whole-brain radiation therapy

In patients who received whole-brain radiation therapy (WBRT), Varian Eclipse Radiation Therapy software was used for treatment planning purposes and plan evaluation. WBRT was delivered using opposed lateral beams or opposed oblique fields to minimize dose to the lenses. All patients who underwent WBRT received 30 Gy given in 10 fractions of 300 cGy prescribed to isocenter.

2.4. Follow-up evaluation

Follow up evaluation was conducted at 3 month intervals after Gamma Knife treatment by the treating physician in the Department of Neurosurgery. Patient medical records were reviewed to assess symptomatic and systemic disease changes. Post-treatment contrast-enhanced MRI scans with 1.5 mm slice thickness were used to determine local control, tumor recurrence, and disease progression. Nearly all patients received a post-treatment MRI scan at 3 months or earlier. Contrast-enhanced MRI scans were ordered every 3 months thereafter, unless more frequent neuroimaging was deemed necessary.

2.5. Statistical analysis

Tumor size was measured in 3 dimensions (anterior–posterior, transverse, and cranio-caudal) for volumetric analysis for all patients. A complete response was defined as the no evidence of residual contrast enhancement of the treated lesion on T1-weighted images. A partial response was defined as ≥50% reduction in tumor volume. Progressive disease was defined as ≥25% increase in the size of the lesion. All others were considered stable disease. Median survival was calculated using Kaplan–Meier analysis. Univariate and multivariate analyses were performed using log-rank test and Cox proportional hazards model, respectively. Chi-square test was used to evaluate symptomatic improvement variables. Statistical analysis was performed using SPSS software version 14.0 (SPSS Inc., Chicago, IL).

Table 1
Patient demographics.

Patients (%)	32 (100)
Gender (%)	
Male	15 (47)
Female	17 (53)
Age (years)	
Median	50
Range	33–80
Follow-up (months)	
Median	12.5
Range	1–26
Histologic type	
NSCLC	13 (40)
Breast	6 (19)
Melanoma	5 (16)
Renal cell carcinoma	3 (9)
Other	5 (16)
Location	
Midbrain	9 (28)
Pons	18 (56)
Medulla	5 (16)
Tumor volume (cm^3)	
Median	0.71
Range	0.01–20.01
Dose (Gy)	
Median	13
Range	8–20
<13	17 (53)
≥13	15 (47)
RPA	
Class I	7 (22)
Class II	15 (47)
Class III	10 (31)
Tumor count	
Median	2
Range	1–22
Single metastasis	11 (34)
Prior WBRT	17 (53)

Gy, gray; NSCLC, non-small cell lung cancer; RPA, recursive partitioning analysis; WBRT, whole-brain radiation therapy.

3. Results

Table 1 summarizes the demographics of the study population. The median age at time of radiosurgical treatment was 50 years (range 33–80). The most common primary tumor type was non-small cell lung cancer ($n = 13$), followed by breast cancer ($n = 6$), melanoma ($n = 5$), and renal cell carcinoma ($n = 3$). Other histologies included small cell lung cancer ($n = 2$), colon cancer ($n = 1$), squamous cell carcinoma involving the orbit ($n = 1$), and Hodgkin's lymphoma ($n = 1$). Nine lesions were located in the midbrain, 18 in the pons, and 5 in the medulla. The median tumor volume was 0.71 cm^3 (range 0.01–20.01). The median tumor margin dose was 13 Gy (range 8–20), and the maximum point dose to the tumor was 26 Gy (range 16–40). Median survival was 5.2 months (95% CI, 1.6–8.8) (Fig. 1). The 1-year overall survival was 37.5%. Median follow-up time was 12.5 months (range 1–26). A total of 5 patients were lost to follow up.

Univariate analysis demonstrated a statistically significant difference ($p < 0.001$) in survival based on RTOG RPA class of the patients at time of treatment. Median survival of patients categorized as RPA class I was 19.2 months ($n = 7$), RPA class II was 8.4 months ($n = 15$), and RPA class III was 1.9 months ($n = 10$) (Fig. 2). There was a difference in survival for patients who received a marginal dose of <13 Gy (9.7 months) versus ≥13 Gy (2.3 months, $p = 0.022$) (Fig. 3). There was no correlation between dose and initial tumor volume size ($p = 0.213$) or dose and RPA class ($p = 0.540$). Patients who had a single brainstem lesion at time of treatment had longer overall survival compared with patients with synchronous brain metastases (19.2 months vs. 3.9 months, $p = 0.005$) (Fig. 4). Smaller initial tumor volume ($p < 0.001$) and younger age ($p = 0.036$)