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Case study

Cumulative volumetric analysis as a key criterion for the treatment of brain metastases

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A B S T R A C T

Background: Recent studies have demonstrated diminished cognitive function, worse quality of life, and no overall survival benefit from the addition of adjuvant whole brain radiation therapy (WBRT) to stereotactic radiosurgery (SRS) in the management of brain metastases. This study analyzes the treatment outcome of SRS, specifically CyberKnife Radiosurgery, based on the total tumor volume compared to the absolute number of lesions.
Methods: A retrospective analysis of hospital records at Virginia Hospital Center for patients with brain metastases who underwent CyberKnife Radiosurgery between June 2008 and June 2014 was performed. Previous treatment history, metastatic tumor dimensions, and outcomes were recorded. Predictors of neurological defects, local tumor progression, and overall survival were assessed with univariate and multivariate analysis.
Results: We identified 130 adult patients with a median age of 61.5 years and a median follow-up of 7.1 months. Unfavorable outcomes such as death, tumor progression, or neurological defect showed correlation with cumulative tumor volume greater than the median volume of 7 cc ($p < 0.05$). Worsening neurological defects showed an association with an increased number of lesions ($p < 0.02$) and age ($p < 0.05$). For local tumor progression, patients who have received WBRT were less likely to progress (.74, 95% CI, .48, 1.10), while those who received chemotherapy (1.48 95% CI, .98, 2.26), or surgery (1.56 95%, CI .98, 2.47) without WBRT were more likely to progress.
Conclusions: Our data suggest that a cumulative tumor volume greater than 7 cc correlates with worse outcomes following CyberKnife Radiosurgery. In addition, WBRT appears to have a role in improved survival for patients with increased tumor burden. A prospective study is warranted to validate these findings.

1. Introduction

Brain metastases are a common secondary malignancy present in 20–40% of metastatic cancer patients and carry a poor prognosis [1–3]. Common treatments include surgical resection, whole brain radiation therapy (WBRT), and stereotactic radiosurgery (SRS). While WBRT has been the main radiation treatment option for brain metastases, recent data displays an association between WBRT and potential neurotoxic effects such as neurocognitive decline, dementia, and brain atrophy. This finding is particularly of concern as systemic treatment options have improved and overall survival has lengthened in patients with brain metastases [4,5]. To minimize radiation-induced side effects and preserve patients' neurocognitive function, WBRT has been increasingly replaced by SRS which delivers high dose radiation to a focal tissue with sub-mm accuracy [1,2,6]. In contrast to WBRT, SRS not only exhibits less radiation-related side effects, it also provides the convenience of shorter treatment duration, faster symptom relief, and customizability of radiation dose and fraction for individual tumors [7]. Furthermore, SRS monotherapy has shown no survival difference from WBRT plus SRS [8,9]. However, studies have also shown limitation of SRS beyond certain numbers of brain metastases and the eventual necessity of WBRT involvement [8,10–12].

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In accordance to these findings, the treatment guidelines based on the number of metastases have been suggested. However, because of the variability in size of each lesion, there is no clear consensus among different studies for the number of metastases as the guideline for SRS [8,10–13]. Due to this discord, physicians have shifted their focus to the total volume of the brain metastases for SRS consideration [10,13], but only a few studies have suggested analysis of treatment effects based on the volume of brain metastases [14–16]. Therefore, in this study, we evaluated a cohort of patients with brain metastases who received treatment with SRS, specifically CyberKnife Radiosurgery, to analyze the effectiveness of the cumulative brain metastases volume as a predictor of prognosis and ultimately a primary treatment criterion.

2. Materials and methods

We retrospectively analyzed a database of patients with brain metastases who underwent CyberKnife Radiosurgery treatment at the Virginia Hospital Center from June 2008 to November 2015. The study was approved by the Institutional Review Boards at the Virginia Hospital Center. We examined the medical records of patients who had prior radiological and clinical confirmation of brain metastases and post-CyberKnife Radiosurgery follow-up. Patients underwent CyberKnife Radiosurgery based on the following treatment algorithm based on the NCCN criteria: smaller (<2 cm), deep, and asymptomatic lesions were offered CyberKnife Radiosurgery, while surgical resection was considered for larger (>2 cm) and symptomatic lesions. Resectable tumors were often considered for CyberKnife Radiosurgery to the tumor bed or WBRT. WBRT was also generally offered for palliation for those with disseminated disease with poor systemic treatment options. As the standard of the practice, the initial follow-up occurred 6 weeks from the CyberKnife radiosurgery treatment at the Virginia Hospital Center where an MRI was performed. Patients were followed thereafter every 3 months with the patient's oncologist or neurosurgeon with a new MRI unless patients displayed new signs or symptoms of progression or recurrence.

Inclusion criteria included patients with primary neoplastic diagnosis with radiologic and clinical confirmation of brain metastases. Patients who were lost in follow up were excluded. The following information was obtained from the chart reviews: sex, age, primary diagnosis, number and volume of metastases, previous chemotherapy treatment, surgical resection, radiation therapy, neurological symptoms and KPS score before and after the CyberKnife Radiosurgery treatment, recurrence, survival, and the dates of diagnosis, treatment, follow-up, and death. The CyberKnife radiation dose and fraction which were prescribed customarily based on the size and location of the individual tumors were also obtained. Increased fractions were used for patients with prior radiation or tumors involving an eloquent location to stay within tissue tolerance. Isodose line was determined to maximally cover 95% of the gross tumor volume with prescribed dose while minimizing normal tissue tolerance. The volume of metastases was calculated based on axial plane contours from gadolinium enhanced MRI images fused to the planning CT simulation study using MIM software for multiple image fusion. Tumor volumes on follow-up images were measured in a similar fashion.

Statistical analyses of categorical variables were carried out using Chi-square and Fisher's exact test. Statistics of means were carried out using Wilcoxon rank sum test. The following dependent variables were assessed in univariate and multivariate analysis: overall survival, tumor free progression, worsening or new decline in neurological function, and favorable outcome (no tumor progression or worsening or new decline in neurological function). Progression was defined as local progression of treated lesions and new metastatic brain lesions. Neurological function was assessed by notes of headache, dizziness, speech defect, visual deficit, gait imbalance, motor deficit, sensory deficit, cranial nerve deficit, and KPS. Any new or worsening deficits were defined as neurological function decline.

Kaplan–Meier risk of tumor progression and overall survival was also calculated. Factors predictive of tumor progression ($p < 0.20$) were entered into multivariate Cox regression analysis to assess hazard ratios. Clinical covariates predicting new or worsening decline in neurological function with a univariate p-value <0.20 were included in multivariable logistic regression analysis. Additionally, clinical covariates predicting unfavorable outcome with a univariate p-value <0.20 were included in multivariable logistic regression analysis. Clinically significant variables and interaction expansion covariates were further assessed in both Cox and logistic multivariable analysis as deemed relevant. Youden indices were calculated to determine cutoffs for the dichotomized continuous variable tumor volume that yielded the optimal discrimination of overall outcome. In all cases, a p-value of $\leqslant 0.05$ was considered statistically significant.

3. Results

Inclusion criteria for the study included 132 patients with brain metastases treated with CyberKnife however, two patients were excluded because they were lost to follow-up. As such, 130 patients with a median age of 61.5 years were identified to be included within the cohort (Table 1). The cohort was comprised of 43 males and 87 female with median ages of 60 and 64 years, respectively. The median number of cranial metastases was 2 (range 1–13) while the median total volume was 7.0 cm^3 (range .3–67.8 cm^3). The median prescription radiation dose was 2100 cGy (range 1500–3500 cGy) with the median fraction of 3 (range 1–5).

The patients had a median overall follow-up of 7.1 months and a median overall survival of 6.7 months. For the patients that displayed progressive intracranial disease, median progression-free survival was 9.2 months. By the last follow-up, 40 patients had survived (30.8%) and 35 patients had shown progression (26.9%).

Survival had correlation with the number of lesions treated by CyberKnife Radiosurgery ($p < .05$) (Table 2). The patients with 1 lesion treated with CK displayed better survival outcome compared with those with >1 lesions (Fig. 1). Progression-free survival analysis showed that the patients with a history of WBRT (.74, 95% CI, .48, 1.10) were less likely to show progression than those with the history of surgery (1.56 95% CI, .98, 2.47) or chemotherapy (1.48 95% CI, .98, 2.26) (Fig. 2).

For the analysis of favorable outcomes of survival, no tumor progression, or no worsening neurological function, history of WBRT ($p < .005$) and tumor volume ($p < .05$) were the predictive factors (Table 2). Youden indices were calculated to determine the tumor volume that yielded the optimal discrimination of favorable outcome. A tumor volume less than the median volume of 7 cm^3 provided the best predictor of favorable outcome (OR .10, 95% CI .01–1.0; $p < .05$) with sensitivity of 98.3%, specificity of 10.7%, positive predictive value of 52.3%, and negative predictive value of 86.3%. The area under the ROC curve for the model is .83 (Fig. 3).

4. Discussion

4.1. Treatment by number of metastases

Currently, the number of brain metastases is commonly used as the criterion for SRS treatment and many studies have been