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Clinical Study

Radiosurgery for brain metastases and cerebral edema

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ABSTRACT

The objective of this study was to assess reduction in cerebral edema following linear accelerator radiosurgery (LINAC) as first line therapy for brain metastasis. We reviewed the medical records of all patients who underwent LINAC radiosurgery for brain metastasis at our institution during 2010–2012, and who had not previously undergone either surgery or whole brain radiotherapy. Data were analyzed for 55 brain metastases from 46 patients (24 males), mean age 59.9 years. During the 2 months following LINAC radiosurgery, the mean steroid dose decreased from 4.8 to 2.6 mg/day, the mean metastasis volume decreased from 3.79 ± 4.12 cc to 2.8 ± 4.48 cc ($p = 0.001$), and the mean edema volume decreased from 16.91 ± 30.15 cc to 12.85 ± 24.47 cc ($p = 0.23$). The 17 patients with reductions of more than 50% in brain edema volume had single metastases. Edema volume in the nine patients with two brain metastases remained stable in five patients (volume change <10%, 0–2 cc) and increased in four patients (by >10%, 2–14 cc). In a subanalysis of eight metastases with baseline edema volume greater than 40 cc, edema volume decreased from 77.27 ± 37.21 cc to 24.84 ± 35.6 cc ($p = 0.034$). Reductions in brain edema were greater in metastases for which non-small-cell lung carcinoma and breast cancers were the primary diseases. Overall, symptoms improved in most patients. No patients who were without symptoms or who had no signs of increased intracranial pressure at baseline developed signs of intracranial pressure following LINAC radiosurgery. In this series, LINAC stereotactic radiosurgery for metastatic brain lesions resulted in early reduction in brain edema volume in single metastasis patients and those with large edema volumes, and reduced the need for steroids.

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1. Introduction

Metastases are the most common tumors of the central nervous system. The most common primary cancers associated with brain metastases are lung, breast, melanoma, renal and colorectal cancers [1]. The prognosis of patients with brain metastases is generally poor; the median survival ranges from 2.3 to 7.1 months [2]. Thus, the treatment of brain metastases is mainly palliative.

Several hypotheses of tumor related edema have been postulated, including secretion of vascular endothelial growth factor, inflammatory cytokines, arachidonic acid metabolites, and destruction of the blood–brain barrier by the tumor itself [3]. Edema adds to the mass of the tumor, increases intracranial pressure (ICP), and disrupts tissue homeostasis by reducing local blood flow [4]. The symptoms of edema can be related to its location, resulting in hemiparesis, epilepsy, visual field defect, aphasia and other focal neurological deficits; or related to increased ICP, with headache worsening in the morning, nausea and vomiting, abnormal eye movements, and impaired consciousness [5]. Reducing tumor related edema may be as important to quality of life as controlling the tumor.

Stereotactic radiosurgery (SRS) plays a substantial role in brain metastasis tumor control and affords many patients improved survival and quality of life. Radiosurgery can be used to treat multiple metastases during the same procedure and permits treatment of deep deposits considered surgically inaccessible [3,6,7]. SRS enables delivery of a high dose of radiation, precisely focused to the tumor, while minimizing the radiation absorbed by normal surrounding brain tissue. In contrast with whole brain radiotherapy (WBRT), SRS is less likely to cause neurological toxicity. In contrast with surgery, SRS is a minimally invasive outpatient procedure that does not require general anesthesia, has wide applicability, lower costs, shorter recovery time, and lower post-treatment morbidity [2]. SRS has become an increasingly popular procedure, as a first-line therapy, as a repeated therapy, and as an adjunctive therapy to surgery and WBRT.

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Linear accelerator (LINAC) is an SRS technique that has demonstrated effectiveness in controlling brain tumor size [8–10], and in prolonging survival [11]. Nevertheless, only a few studies have investigated the effects of SRS on cerebral edema. Reduction in cerebral edema following Gamma Knife (Elekta AB, Stockholm, Sweden) radiosurgery (RS) was found to be associated with improved quality of life outcomes, though not with prolonged survival [3]. For meningioma, SRS treatment demonstrated a low incidence of toxicity; risk factors for increased post-treatment edema were large tumor volumes and single-fraction SRS treatment [12].

In this study, we assessed the reduction in cerebral edema following LINAC SRS as a first line therapy for brain metastasis.

2. Methods

This was a retrospective study of patients with cerebral edema due to primary metastasis who underwent LINAC SRS during 2010–2012 at a single medical center. Previous treatment for brain metastasis, by means of WBRT and/or surgery, was an exclusion criterion. Data were retrieved from patient medical records, using the medical history, hospitalization records, and letters of hospital discharge, regarding demographic characteristics (age and sex) and disease characteristics (primary disease, location and depth of metastasis, symptoms), steroid dose, and scores on the Karnofsky Performance Scale, which is a measure of functional impairment. MRI were recorded at the time of LINAC SRS as a baseline and 2 months after the performance of SRS treatment. Patients were evaluated at 2 month follow-up to assess symptoms of raised ICP and the need for corticosteroids. The MRI program IPLAN software (BrainLab, Munich, Germany) enables manual marking of the area of metastasis and the area of the edema. All volume calculations were made on axial MRI using T1-weighted with gadolinium images for tumor margin definition and T2-weighted sequences for edema margin definition using IPLAN software. For all cases a 3.0 Tesla MRI machine was used. The slice thickness for the T1-weighted with gadolinium sequence was 1 mm, and for the T2-weighted sequence 2 mm, both without gap. All manual markings of tumor and edema margin definitions were done by authors I.G. and U.N. Volume was calculated by integration of the areas over a contiguous set of axial slices by the software. Volumes were calculated in an identical method before and after SRS treatment.

One day before the radiosurgery treatment, a thin-slice MRI was obtained for all patients including a spoiled gradient echo protocol with contrast enhancement and a T2-weighted series. On the day of hospital admission, a stereotactic head frame or a custom-fitted thermoplastic mask was applied to the patient's head. A stereotactic CT scan was then performed, which included the entire head, in consecutive axial sections of 0.6 mm thickness. The data were transferred to the computer and processed in the IPLAN software for treatment planning. The MRI was fused to the stereotactic CT scan. The tumors were outlined and three-dimensional dosimetry was designed. After completion of the programming, the patient was placed supine on the LINAC (Novalis Tx; BrainLab). The target was positioned at the LINAC isocenter, and position precision and stability were monitored throughout treatment by the ExacTrac system (BrainLab) [13]. Radiosurgical treatment was administered by means of the dynamic rotation paradigm [13]. Treatment was administered in five (or occasionally four) dynamic arcs. Metastases were treated with a marginal dose of 20 Gy for renal cell carcinoma and malignant melanoma (set for 80% from maximal dose), and 18 Gy for all other metastases (set for 80% from maximal dose).

2.1. Statistical analysis

To assess the effect of radiosurgery on brain edema volume, we used the paired *t*-test; each variable before treatment was compared to the same variable following treatment. Logarithmic transformation was performed to approach normal distribution. To examine the effect of radiosurgery on the intake and dosage of corticosteroids, we used the Wilcoxon signed-rank test. The one-way analysis of variance test was used to examine the effect of SRS on metastases from different primary cancers, and to examine the effect of SRS on different locations of brain metastases. The Mann–Whitney U test was used to examine the effect of SRS on the depth of the metastases, and the Pearson correlation to examine associations with age, sex, metastasis volume, and radiation dose.

3. Results

A total of 46 patients with 55 lesions who were available for 2 month follow-up were analyzed, and represent the cohort of this study. Fifteen patients were excluded from analysis. Of these, two had undergone surgical treatment for cerebral metastasis, one had undergone craniotomy due to sub-acute hemorrhage inside the metastasis, and one other had undergone an Ommaya drainage procedure of a cystic metastasis. The remaining 13 excluded patients died during the 2 month follow-up period, 12 due to their cancer and one due to hemorrhagic cerebral metastasis. Clinical characteristics of the lesions are presented in Table 1. The mean age of the 46 patients was 59.9 years. Twenty-four were male (52%) and 22 female (48%). The mean steroid dose for these patients decreased from 4.8 to 2.6 mg/day in the 2 month period following SRS ($p = 0.002$). Non-small-cell lung carcinoma and melanoma were the most common primary diseases, followed by breast cancer.

The mean volume of the 55 metastases investigated decreased from 3.79 ± 4.12 cc to 2.8 ± 4.48 cc ($p = 0.001$) and the mean volume of the edema decreased from 16.91 ± 30.15 cc to 12.85 ± 24.47 cc ($p = 0.229$) during the 2 months following LINAC treatment. Edema volume decreased by >50% in 17 metastases, by 10–50% in six, remained stable (volume change <10%) in 15, and increased by >10% in 17. All 17 reductions of more than 50% in brain edema volume were for single metastases. Edema volume in nine patients with two brain metastases remained stable in five patients (volume change <10%, 0–2 cc) and increased in four patients (by >10%, 2–14 cc). For eight metastases the baseline edema volume was greater than 40 cc. Analysis of the change in

Table 1
Clinical characteristics of the 55 brain metastases included in the analysis

Characteristic	Metastases (n = 55)
Primary disease	
Colon	2 (3)
NSCLC	19 (35)
Melanoma	21(38)
breast	11 (20)
RCC	2 (3)
Location of metastases	
Hemispheres	40 (73)
Basal ganglia	7 (13)
Cerebellum	8 (14)
Depth of metastases	
Cortical	40 (73)
Deep	15 (27)
Baseline symptoms	
Asymptomatic	26 (47)
Focal deficit	21 (38)
Increased ICP	3 (6)
Focal + ICP	5 (9)
KPS, mean ± SD Range	89.43 ± 12.35 70–100

Data are presented as number (percentage) except where stated otherwise.
ICP = intracranial pressure, KPS = Karnofsky Performance Status, NSCLC = Non-small-cell lung carcinoma, RCC = renal cell carcinoma, SD = standard deviation.

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