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Brain metastases

Clinical outcomes of patients with limited brain metastases treated with hypofractionated (5 × 6 Gy) conformal radiotherapy

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ABSTRACT

Background and purpose: Hypofractionated conformal radiotherapy (hfCRT) is used for larger brain metastases or metastases near critical structures. We investigated hfCRT outcomes for newly diagnosed brain metastases.

Materials and methods: We identified 195 patients with 1–3 brain metastases who underwent 5 × 6 Gy hfCRT for 231 lesions from 2007 to 2013. Associations among clinical factors, local control (LC), distant brain control (DC) and overall survival (OS) were tested using univariate and multivariate (MVA) Cox regression analysis and Kaplan–Meier method.

Results: Median follow-up was 12.8 months. One hundred forty-three (62%) lesions were treated with hfCRT post-operatively, and 88 (38%) with definitive hfCRT. LC for all lesions was 83% at 1 year. For lesions treated with post-operative hfCRT, tumor size (HR = 4.7, $p = 0.04$) and subtotal resection (HR = 2.7, $p = 0.02$) were predictive of local failure on MVA. For lesions ≥2.8 cm in size, LC was 61% at 12 months for lesions status-post subtotal resection, compared to 84% status-post gross total resection ($p = 0.004$). Extracranial disease presence was associated with worse DC (HR = 1.8, $p = 0.008$) and OS (HR = 3.1, $p < 0.001$).

Conclusions: We showed 5 × 6 Gy hfCRT provides acceptable LC at 1 year for limited brain metastases. For large lesions not grossly resected, more aggressive strategies can be considered to improve LC.

The incidence of brain metastases in cancer patients is approximately 25% [1], and the incidence is increasing with improvements in systemic therapy resulting in prolonged patient survival as well as earlier diagnosis [2]. The mainstay of treatment of brain metastases has largely included surgery and radiation due to poor penetrance of many chemotherapeutic agents across the blood brain barrier [3]. Patients who undergo surgery for brain metastases often receive post-operative whole brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS) for improved local disease control [4,5]. Alternatively, patients who do not require surgery or are not surgical candidates may be treated with radiation alone. Lesions amenable to single fraction SRS typically measure less than 3 cm in maximum dimension, and SRS combined with WBRT has been shown to improve survival and local control compared to WBRT alone for patients with 1–4 brain metastases [6]. However, SRS alone without WBRT has surfaced as a preferred modality to WBRT in patients with limited brain metastases due to high rates of locoregional control and similar survival rates with minimal toxicity and shorter interruption of systemic therapy [7–10].

Tumors treated with lower doses (<18 Gy) have been shown to have inferior local control rates after single-fraction SRS due to inferior doses required to meet normal structure constraints [11,12]. For patients with limited number of brain metastases measuring greater than 3 cm in size or located within eloquent cortex or brainstem, hypofractionated conformal radiation therapy (hfCRT) has emerged as an alternative to single-fraction SRS in both the post-operative and definitive settings [13–15]. One retrospective study reported superior local control for brain metastases >2 cm treated with 3 × 9 Gy compared to singe fraction SRS [16]. However, the optimal hypofractionated regimen is still unclear. In this study, we investigated the efficacy and predictors of outcomes in patients who received hfCRT using 5 × 6 Gy for newly diagnosed brain metastases at a single center.

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Materials and methods

Study population

Patients with the presence of 1–3 newly diagnosed brain metastases treated with hypofractionated conformal radiotherapy (hfCRT) to a dose of 30 Gy in 5 fractions at our institution from 2007 to 2013 were eligible. At our institution, patients with lesions >3 cm in size or near critical structures generally receive hfCRT either definitively or postoperatively, while lesions <3 cm in size generally receive single fraction stereotactic radiosurgery (SRS). Patients with prior cranial radiotherapy were excluded. Institutional Review Board approval was obtained. Medical records were reviewed and clinical information including patient age, primary tumor histology, Karnofsky performance status (KPS), extracranial disease (ECD, present versus absent within 60 days of hfCRT), concurrent systemic therapy (systemic treatment within 30 days of hfCRT), number of brain metastases (1 versus 2–3), brain metastasis size, tumor location (supratentorial versus infratentorial) and clinical outcomes including pathological diagnosis of radiation necrosis following radiotherapy were collected. Brain metastasis size was defined as the largest dimension of the lesion prior to surgical resection for patients who received hfCRT following craniotomy, or at the time of definitive hfCRT for patients who did not undergo surgical resection. We chose presurgical size for analysis as it was shown to be predictive of local control in a prospective trial at our institution [4].

Radiotherapy technique

A T1-weighted magnetic resonance imaging (MRI) scan with gadolinium contrast (dosing 0.1 mg of gadolinium per kg of body weight) at 3 mm slice thickness was obtained prior to radiotherapy and reviewed by a board-certified neuroradiologist at the time of simulation. Patients were immobilized with a three-point face mask and a computed tomography (CT) scan was obtained with intravenous contrast at the time of simulation. The CT images were transferred to in-house treatment planning system (Top Module) and fused to the post-gadolinium T1-weighted MRI for target delineation. The gross target volume (GTV), defined as the contrast-enhancing lesion, was delineated on T1-weighted MRI and on the planning CT (contrast enhancement on MRI and CT). Surrounding areas of edema were not considered part of the target volume. For patients who had undergone resection, the postoperative cavity was defined as clinical target volume (CTV). The planning target volume (PTV) was defined as a 3-dimensional 2–5 mm margin around the GTV or CTV. The prescribed dose was 30 Gy given over 5 daily fractions with either 3D-conformal radiation or intensity modulated radiation therapy (IMRT) (Fig. 1). All patients received the same dose. The treatment plan typically consisted of 5–7 coplanar and non-coplanar IMRT fields. The plans were normalized so that 100% of the prescription dose is delivered to 95% of the PTV and with a PTV Dmax <110%. The plans were designed to meet our departmental dose criteria for normal tissues with maximum point dose constraints of 31.2 Gy, 30 Gy, and 23 Gy to the brainstem, spinal cord, and optic structures, respectively. Dose–volume histograms were used to document coverage for target volume and normal structures. Treatment was delivered either on a Trilogy, C-2100EX or C-600EX LINAC (Varian Medical Systems, Palo Alto, CA).

Statistical analysis

Patients were followed up with MRI following radiation according to standard clinical practice: 6–8 weeks after radiotherapy then 3–4 months thereafter. Clinical outcomes examined included local control (LC), distant brain control (intracranial control outside of treatment target, DC) and overall survival (OS). Outcomes were measured from the initiation of radiation until last follow up or death. LC was defined as absence of recurrence within the treatment target, determined both clinically by the treating physicians' consensus and radiographically, including the use of advanced imaging modalities such as brain positron emission tomography and MRI perfusion imaging. DC was defined as absence of new bran lesions outside of the treatment target. Association between clinical factors and outcomes were tested using univariate and multivariate Cox regression analysis. The Kaplan–Meier method was used to assess actuarial LC, DC and OS. Analyses were performed with IBM SPSS Statistics (IBM, Armonk, New York).

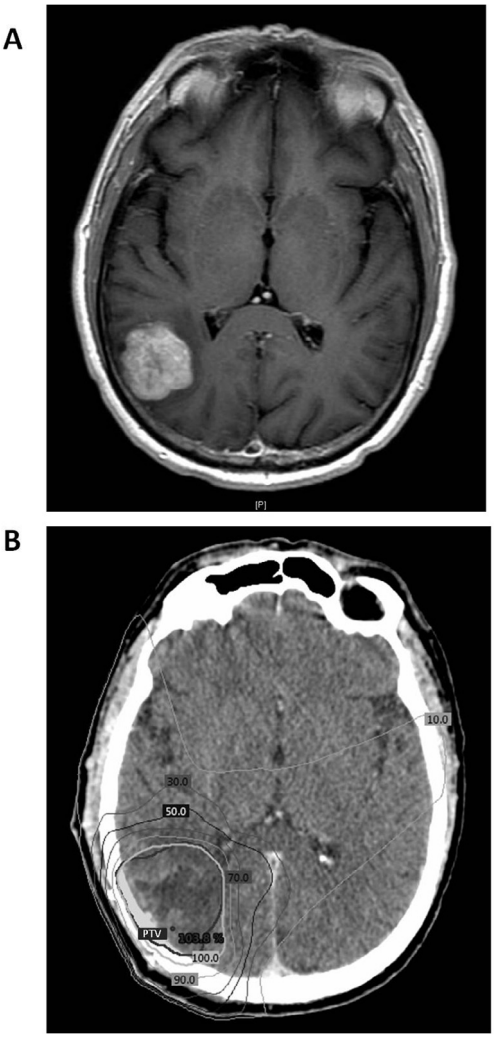

Fig. 1. Representative intensity modulated treatment (IMRT) plan of hypofractionated conformal radiotherapy. A 58 year-old man with squamous cell carcinoma of the lung presented with 3.5 × 3.4 cm right parietal lobe metastasis status-post gross total resection for post-operative radiation to dose 5 × 6 Gy. (A) Pre-operative axial T1-weighted MRI with gadolinium contrast. (B) IMRT treatment plan with axial post-operative planning CT scan. Planning target volume (PTV) and isodose lines (%) showing rapid dose fall off are labeled.

Results

A total of 195 consecutive patients with 231 newly diagnosed limited brain metastases treated with hfCRT between 2007 and 2013 were identified for the study. Patient and lesion characteristics are summarized in Table 1. The median follow-up time was