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Original Article

Fractionated Stereotactic Radiotherapy using CyberKnife for the Treatment of Large Brain Metastases: A Dose Escalation Study

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Abstract

Aims: To evaluate the toxicity and efficacy of fractionated stereotactic radiotherapy (FSRT) with doses of 18–30 Gy in three fractions and 21–35 Gy in five fractions against large brain metastases.
Materials and methods: Between 2005 and 2012, 61 large brain metastases (≥2.5 cm in maximum diameter) of a total of 102 in 54 patients were treated with FSRT as a first-line therapy. Neurological symptoms were observed in 47 of the 54 patients before FSRT. Three fractions were applied to tumours with a maximum diameter ≥2.5 cm and <4 cm, and five fractions were used for brain metastases ≥4 cm. After ensuring that the toxicities were acceptable (≤grade 2), doses were escalated in steps. Doses to the large brain metastases were as follows: level I, 18–22 Gy/three fractions or 21–25 Gy/five fractions; level II, 22–27 Gy/three fractions or 25–31 Gy/five fractions; level III, 27–30 Gy/three fractions or 31–35 Gy/five fractions. Level III was the target dose level.
Results: Overall survival rates were 52 and 31% at 6 and 12 months, respectively. Local tumour control rates of the 102 total brain metastases were 84 and 78% at 6 and 12 months, respectively. Local tumour control rates of the 61 large brain metastases were 77 and 69% at 6 and 12 months, respectively. Grade 3 or higher toxicities were not observed.
Conclusions: The highest dose levels of 27–30 Gy/three fractions and 31–35 Gy/five fractions seemed to be tolerable and effective in controlling large brain metastases. These doses can be used in future studies on FSRT for large brain metastases.

Key words: Cyberknife; fractionated stereotactic radiotherapy; large brain metastases; stereotactic radiosurgery

Introduction

With advances in cancer treatment and improvement in prognosis, increasing attention has been paid to treating brain metastases [1]. Surgery and radiotherapy are two major treatment modalities for brain metastases, and radiotherapy plays the most important role in patients who are not indicated for or refuse surgery [2]. However, a few issues remain to be addressed regarding the treatment of large brain metastases (≥2–3 cm in maximum diameter, ≥4–15 cm^3 in volume), especially in patients with surgical contraindications. These brain metastases have typically been treated with whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), fractionated stereotactic radiotherapy (FSRT) or a combination of these [3–7], but it has not yet been clarified which should be considered the standard treatment. Single-fraction SRS against large brain metastases can lead to severe neurotoxicity, whereas WBRT usually takes 2–4 weeks of overall treatment time and can affect cognitive function. With recent advances in radiotherapy systems, FSRT can now be considered as an important treatment option for a large brain metastasis [8], but the optimal dose and fractionation schedule have not yet been established. The CyberKnife® (Accuray Inc.,

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Sunnyvale, CA, USA) is an image-guided, frameless radiotherapy system with a 6 MV linear accelerator mounted on a flexible robotic arm. This system provides accuracy equivalent to that of SRS and conformity equivalent to that of intensity-modulated radiotherapy. This system also allows easy FSRT approaches. In June 2005, our group began to treat large brain metastases with FSRT using Cyberknife. This treatment protocol for large brain metastases was started using smaller doses than initially planned. After confirming that the toxicity was acceptable, the prescribed dose was escalated step by step. The objective of the present study was to evaluate the feasibility of FSRT dose escalation in large brain metastases with respect to efficacy and toxicity.

Materials and Methods

Patients

Between June 2005 and January 2012, we treated large brain metastases with FSRT (three-fraction or five-fraction schedule) using Cyberknife at the Department of Radiology and Neurosurgery, Tsushima City Hospital. According to previous reports on neurotoxicity after SRS [9,10], we defined a large brain metastasis as one ≥2.5 cm in maximum diameter in the planning target volume (PTV). Patients with previous cranial radiation and/or craniotomy were excluded. This study was approved by the institutional research and ethics committee (Tsushima City Hospital, 2013 No. 02).

Fractionated Stereotactic Radiotherapy Indication Criteria

Brain metastases ≥2.5 cm in maximum diameter were treated according to our FSRT protocol. Indications for radiotherapy and surgery were evaluated by radiation oncologists and neurosurgeons. Patients were treated with FSRT when the brain metastases were located in or adjacent to the eloquent area or deep seated, their general condition made surgery too risky or less beneficial, or they refused surgical treatment. None of them had neurological or radiological evidence of carcinomatous meningitis. Patients with poor Karnofsky performance status (<40) were not treated with this protocol. Informed consent was obtained from all patients.

Radiotherapy Technique

All treatment was carried out using CyberKnife® [11]. The patient was placed in a supine position and a thermoplastic mask was moulded to the head and attached to the head support. Axial contrast-enhanced computed tomography with a slice thickness of 2 mm was conducted for treatment planning. The clinical target volume was defined as an abnormal contrast-enhanced lesion on computed tomography and magnetic resonance imaging (MRI). We extended the clinical target volume by 2 mm to create the PTV. Dose planning was carried out with the Cyberknife On-Target treatment planning system ver. 3.4.2.

Dose Escalation Design

Three levels of prescribed dose were used in successive cohorts with the dose escalation design described below. Dose-limiting toxicity (DLT) was defined as symptomatic brain necrosis (≥grade 3) according to the National Cancer Institute Common Terminology Criteria for Adverse Events; initially, we used version 3.0, but the toxicities were re-evaluated using version 4.0 after 2011. As the DLT is expected to occur more than 6 months after FSRT and many brain metastasis patients die within 6 months, we applied a prudent dose escalation design. At least five patients were allocated to each dose level. Additional patients had to be treated at the same dose level until five patients survived more than 6 months and DLT could be evaluated appropriately. Thus, five plus a few more patients had to be finally allocated to each dose level. In the case of one DLT among the patients, the same dose level was continued until 10 patients in total survived more than 6 months or a second DLT was observed. If there was no DLT among the patients, the dose escalation proceeded to the next level. In the case of two or more DLTs, the dose level was reduced by one level. The maximum tolerated dose was defined as the dose level at which two or more patients experienced DLT. If the target dose level (III) was not reached, the de-escalated level was to be recommended for the next phase II study. If the target dose level was reached, the level was continued until 10 patients in total survived more than 6 months.

Prescribed Dose and Fractionation

The prescribed dose covered 95% of the PTV (D95). The fractionation schedule was determined according to the maximum tumour diameter. Five-fraction treatment was delivered to brain metastases ≥4 cm in maximum diameter and three-fraction treatment to brain metastases ≥2.5 cm and <4 cm. FSRT was delivered daily on consecutive days to the brain metastases. The prescribed doses at each level were as follows: level I, 18–22 Gy/three fractions or 21–25 Gy/five fractions; level II, 22–27 Gy/three fractions or 25–31 Gy/five fractions; and level III, 27–30 Gy/three fractions or 31–35 Gy/five fractions. Dose level III was the target in this study.

Dose constraints were applied to nearby critical structures based on the total dose and fractionation schedules. Accompanying smaller lesions were also treated with a single fraction of 13–20 Gy. The maximum doses to the brain stem, optic nerve and optic chiasm were limited to 21–25 Gy/five fractions or 15–18 Gy/three fractions as described previously [12]. The dose to the lens was also limited to 7–10 Gy. To satisfy these limitations, modification of the total dose was made within the dose range for each level or the number of fractions was increased from three to five.

Follow-up and End Point

We evaluated local tumour control, overall brain control (OBC) and overall survival as end points from the date of