Linac-based fractionated stereotactic radiotherapy with a micro-multileaf collimator for large brain metastasis unsuitable for surgical resection

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ABSTRACT

The aim of this study was to assess clinical outcomes using linac-based, fractionated, stereotactic radiotherapy (fSRT) with a micro-multileaf collimator for large brain metastasis (LBM) unsuitable for surgical resection. Between January 2009 and October 2018 we treated 21 patients with LBM using linac-based fSRT. LBM was defined as a tumor with ≥30 mm maximal diameter in gadolinium-enhanced magnetic resonance images. LBMs originated from the lung (n = 17, 81%), ovary (n = 2, 9.5%), rectum (n = 1, 4.8%) and esophagus (n = 1, 4.8%). The median pretreatment Karnofsky performance status was 50 (range: 50–80). Recursive partition analysis (RPA) was as follows: Classes 2 and 3 were 7 and 14 patients, respectively. The median follow-up was 5 months (range: 1–86 months). The range of tumor volume was 8.7–26.5 cm³ (median: 17.1 cm³). All patients were basically treated with 35Gy in 5 fractions, except in three cases. The progression-free survival was 3.0 months. The median survival time was 7.0 months. There was no permanent radiation injury in any of the patients. Radiation-caused central nervous system necrosis, according to the Common Terminology Criteria for Adverse Events version 4.0, occurred in one patient (grade 3). One patient received bevacizumab for radiation necrosis. Two patients underwent additional surgical resection due to local progression and cyst formation. For patients with LBM unsuitable for surgical resection, linac-based fSRT is a promising therapeutic alternative.

Keywords: Novalis; large brain metastasis; stereotactic radiotherapy; fractionated radiotherapy

INTRODUCTION

Brain metastasis from systemic cancer is the most common neoplasm among intracranial brain tumors. Stereotactic radiosurgery (SRS) and radiotherapy (SRT) for small brain metastasis are linked to good tumor control and fewer complications [1]. For large brain metastasis (LBM), surgical resection is the only method to urgently obtain cerebral decompression, relieve the effects induced by the mass and rapidly reduce intracranial pressure [2].

Among surgical resection candidates, several patients reject surgery, while others are unsuitable due to poor general condition. Eventually, SRS and SRT, or the best medical treatment option other than surgical resection, is recommended to these patients.
Less attention has been paid to LBM compared to smaller brain metastasis. Several studies have investigated single- or multiple-session SRS, using a Gamma Knife (Elekta Instruments, Stockholm, Sweden), for LBM. The range of local tumor control (LTC) at 1 year was 61–90% [3–6].

In recent studies, fractionated stereotactic radiotherapy (fSRT), using a frameless fixation system for LBM, showed a LTC range at 1 year of 61–100%, with the possibility of less radiation necrosis [7, 8]. However, the optimal treatment in LBM patients for whom surgical resection is unsuitable remains controversial. In this retrospective study, we examined 21 consecutive patients treated with linac-based fSRT for LBM unsuitable for surgical resection to assess clinical and radiographical outcomes and determine the complication rate.

**MATERIALS AND METHODS**

**Patient characteristics**

Clinical data were retrospectively collected to evaluate the efficacy and limitations of fSRT. The institutional review board at Nara Medical University (Nara, Japan) approved this retrospective study in December 2017 (No.1726). Between January 2009 and October 2018, we treated 22 consecutive patients with LBM at Nara Medical University Hospital. Prior to SRT, each patient was evaluated by a multidisciplinary team, including neurosurgeons, neuro-oncologists, neuro-radiologists and radiation oncologists, to determine the most appropriate therapy. LBM was defined as a tumor with a maximal diameter ≥30 mm in axial, coronal or sagittal images of gadolinium-enhanced magnetic resonance imaging (MRI). One patient previously treated with whole brain radiation therapy was excluded from the analysis. Thus, 21 patients were enrolled in this retrospective study. Table 1 lists all patients’ clinical characteristics. Thirteen and 8 patients were male and female, respectively, with a median age of 75.0 years (range: 47–87 years). LBMs originated from the lung (n = 17, 81%), ovary (n = 2, 9.5%), rectum (n = 1, 4.8%) and esophagus (n = 1, 4.8%). Nine LBM were located in the parietal lobe, six in the frontal lobe, two in the cerebellum, two in the temporal lobe, one in the basal ganglia and one in the occipital lobe. The recursive partition analysis (RPA) was as follows: Classes 1, 2 and 3 were 0, 7 (33.3%) and 14 (66.6%) patients, respectively [9]. The ranges of tumor diameter and volume were 30–50 mm (median: 34.0 mm) and 8.7–26.5 cm³ (median: 17.1 cm³), respectively (Table 1). ‘Unsuitable for surgical resection’ was defined as poor general condition for general anesthesia, unsuitable location of the tumor (i.e. basal ganglia and deep-seated) and refusal to undergo surgical resection.

**SRT**

Planning fSRT was based on computed tomography (CT) with a slice thickness of 1–2 mm. All patients were immobilized in a thermoplastic mask (BRAINLAB AG, Munich, Germany). The gross tumor volume (GTV) for each lesion was delineated on MRI with a slice thickness of 1–2 mm. The planning target volume (PTV) was defined as GTV plus 1 mm for all dimensions. The treatment was performed within 1 week after planning the CT. Treatment planning was performed using BrainSCAN or iPlan RT (BRAINLAB AG). The irradiation dose was prescribed to confirm a dose coverage of 90% of the PTV. The dose calculations were performed using a pencil beam algorithm. fSRT was performed using a Novalis® Radiosurgery (BRAINLAB AG) with 6-MV X-rays. Patient positioning and positioning verification were performed using the BrainLab ExacTrac® system (BRAINLAB AG), consisting of two infrared cameras and two dual diagnostic kV X-ray tubes, which moved automatically into the treatment position to minimize setup errors [10, 11]. All patients were treated by Novalis® with 30–42 Gy in 3–10 fractions through non-coplanar multi-beams, non-coplanar multi-arcs or a combination. The treatment methods on fSRT were conformal.

**Table 1. The characteristics of all patients with large brain metastasis**

| Characteristic                  | Value |
|--------------------------------|-------|
| No. of patients                | 21    |
| Male                           | 13    |
| Female                         | 8     |
| Age (years)                    |       |
| Median                         | 75    |
| Range                          | 47–87 |
| Pretreatment Karnofsky Performance Scale |       |
| Median                         | 50    |
| Range                          | 50–90 |
| Tumor origin                   |       |
| Lung                           | 17    |
| Ovary                          | 2     |
| Gastrointestinal               | 1     |
| Esophagus                      | 1     |
| Tumor location                 |       |
| Parietal                       | 9     |
| Frontal                        | 6     |
| Temporal                       | 2     |
| Cerebellum                     | 2     |
| Basal ganglia                  | 1     |
| Occipital                      | 1     |
| Brain metastases               |       |
| Single                         | 12    |
| Multiple                       | 9     |
| Control of primary tumor       |       |
| Yes                            | 3     |
| No                             | 18    |
| Extracranial metastasis        |       |
| Yes                            | 13    |
| No                             | 8     |
| RPA class                      |       |
| 1                              | 0     |
| 2                              | 7     |
| 3                              | 14    |
| Maximum tumor diameter (mm)    |       |
| Median                         | 34    |
| Range                          | 30–50 |
| Tumor volume (cm³)             |       |
| Median                         | 17.1  |
| Range                          | 8.7–26.5 |
beams, dynamic conformal arcs, intensity-modulated radiotherapy (IMRT) and hybrid arcs. This is a novel treatment technique blending aperture-enhanced optimized arcs with discrete IMRT elements, allowing arc selection with a set of static IMRT-beams [12].

**Clinical and radiological follow-up**

Follow-up contrast-enhanced MRI was performed every 3 months after the end of SRT, when possible. Tumor volumes were measured before and after SRT using BrainSCAN or iPlan RT software. Each lesion was measured for local tumor response, and tumors were graded according to the following four categories: (i) complete remission (CR), indicating the disappearance of all enhanced lesions on MRI; (ii) partial remission (PR), indicating evidence of >50% reduction in the cross-sectional dimensions of the tumor on MRI images; (iii) progressive disease, indicating >25% increase in size; or (iv) stable disease (SD), indicating all other responses. LTC was defined as CR, PR or SD [13]. Toxicity was recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

**Statistical analysis**

Median survival time and progression-free survival were calculated using the Kaplan–Meier method. The log-rank test was used for the univariate analyses. All of the analyses mentioned above were performed with EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [14] and $P < 0.05$ was considered to be statistically significant.

**RESULTS**

**Radiological and clinical response**

In total, 21 patients underwent fSRT for 21 lesions at our institution during the study period. All the patients were treated with a dose of 30–42 Gy in 3–10 fractions, with 35 Gy in 5 fractions for 17 lesions, 40 Gy in 10 fractions for 1 lesion, 42 Gy in 6 fractions for 1 lesion, 30 Gy in 3 fractions for 1 lesion and 36 Gy in 10 fractions for 1 lesion. The main prescription dose was 35 Gy in 5 fractions. Exceptionally, four patients were not treated with 35 Gy in 5 fractions. The reasons are as follows: treatment suspension in one week because of machine trouble in one case, location of the cerebellar peduncle with severe symptoms in one case, location next to the optic chiasma in one case and rapid growth of
| Reference          | Modality | Tumor volume (average volume) | No. of patients | Treatment                  | Results                      | Complication                          | Other                        |
|--------------------|----------|-------------------------------|-----------------|----------------------------|------------------------------|---------------------------------------|------------------------------|
| Higuchi et al. [15]| GK       | 10 cm³ (17.6 cm³)             | 43              | 30 Gy/3 fractions (max: 20 Gy, marginal 10 Gy) | LTC (12 M) 75.9% LTC (6 M) 89.8% | G3 (1 pt) → edema → OP G2 (1 pt) → nausea/vomiting | G3: 1 pt → OP               |
| Han et al. [16]    | GK       | 14 cm³ (22.4 cm³)             | 80              | Marginal 13.8 Gy                     | OS 7.9 M                    | G3–5 Radiation necrosis (18.8%)      | G3: 7 pt, G4: 6 pt, G5: 2 pt |
| Yomo et al. [3]    | GK       | ≤15 cm³ (supra)               | 27              | 20–30 Gy·2fr                        | LTC (12 M) 61% LTC (6 M) 85% Survival rate (12 M) 45% (6 M) 63% | 2 pt → OP                        | G3: vomiting (2 pt)           |
|                    |          | ≤10 cm³ (infra) (17.8 cm³)    |                 |                            |                             |                                       |                              |
| Hasegawa et al. [5]| GK       | ≤10 cm³ (21 cm³)              | 56              | 2 Sessions: 10–13 Gy/session        | OS 7 M, survival rate (12 M) 42% (6 M) 62% | G3: 1 pt (hemiparesis) Required surgical resection (−) |                              |
|                    |          |                               |                 | 3 Sessions: 10 Gy/session          |                             |                                       |                              |
| Kim et al. [6]     | GK       | >3 cm                         | 36              | 5–11 Gy/2–4 consecutive days        | LTC 90%, OS 16.2 M         | G4 RN: 2.7% → OP                     | G3: 2.7%, G2: 2.7%, G1: 8.3% |

*Abbreviations: M = month; supra = supratentorial region; infra = infratentorial region; G = grade; pt = patients; OP = operation; RN = radiation necrosis.
Table 4. Cyber Knife radiosurgery for large brain metastasis

| Reference          | Modality | Tumor volume (average volume) | No. of patients | Treatment | Results                  | Complication         |
|--------------------|----------|------------------------------|-----------------|-----------|--------------------------|----------------------|
| Murai et al. [17]  | CK       | ≤25 mm                       | 54              | 18–30 Gy/3 fr | OS (12 M) 31%, (6 M) 52% | G3, G4 :0%           |
|                    |          |                              |                 | 21–35 Gy/5 fr | LTC 12M 69%, 6 M 77%     |                      |
| Inoue et al. [18]  | CK       | ≤10 cm³                      | 88              | 27–30 Gy/3 fr | LSTM 90.2%               | Brain edema: 10/88pts |
|                    |          |                              |                 | (10–19.9 cm³) | OS 9 M                   |                      |
|                    |          |                              |                 | 31–35 Gy/5 fr |                                            |                      |
|                    |          |                              |                 | (20–29.9 cm³) |                                            |                      |
|                    |          |                              |                 | 35–42 Gy/8 fr |                                            |                      |
|                    |          |                              |                 | (30 cm³~)     |                                            |                      |
| Jeong et al. [19]  | CK       | ≤31 mm                       | 37              | 33 Gy/3 fr | LTC 12 M 100% OS 16 M    | G3: 1pt → OP RN: 6/38 lesions (15.8%) |

*Abbreviations: M = month; RN = radiation necrosis; OP = operation; pt = patients; G = grade.

spindle cell carcinoma in the lung in one case. The radiation dose was calculated to a radiobiological equivalent dose of 2 Gy (EQD2) using α/β ratios of 2 and 10 (Table 2). EQD2 (α/β:2) ranges from 50.4–94.5 Gy and EQD2(α/β:10) ranges from 40.8–59.5 Gy. (Table 2).

Eight patients expired due to progression of primary cancer within 3 months; hence, follow-up MRI data at 3 months was not performed for these patients. Among the remaining 13 patients who underwent follow-up MRI at 3 months, the examination revealed PR in 11 patients (84.6%), SD in one patient (7.7%) and progressive disease in one patient (7.7%). During the follow-up period, 5 patients were diagnosed with distant cerebral metastasis; additional radiosurgery and radiotherapy were performed on these patients.

**Survival rate and prognostic factors**
Seventeen patients expired at the last follow-up after radiotherapy. Fifteen patients expired due to worsening of systemic cancer. The remaining two patients expired due to progression of brain metastasis, including status epilepticus in one patient. The progression-free survival was 3.0 months and the median survival time was 7.0 months (Fig. 1). We analysed each prognostic factor, including age (＞75 years vs ＜75 years), sex, tumor volume, extra-cranial metastasis, control of primary cancer and pretreatment Karnofsky performance status. None of the factors showed a significant difference in the median survival time.

**Complications**
There was no permanent radiation injury in any of the patients. Radiation-caused central nervous system necrosis (grade 3) occurred in one patient treated with linac-based SRT using 35 Gy in 5 fractions. The maximum tumor diameter and volume were 36 mm and 19.1 cm³, respectively. This patient with grade 3 necrosis was treated with bevacizumab. One patient underwent additional surgical resection for local progression. This patient suffered from lung cancer diagnosed with spindle cell carcinoma. One patient underwent additional surgical resection for cyst formation 85 months later after initial SRT.

**DISCUSSION**

**LBM**
Based on advances in chemotherapy and radiotherapy against cancer in the modern era, physicians have more options for treating brain metastases. Brain metastasis is the most common intracranial malignant tumor in adults, occurring in up to 8-10% of cancer patients [2].

Treatment for brain metastasis includes whole brain radiotherapy, surgery and SRS. In particular, for managing smaller brain metastases, SRS is the first-line option. In contrast, for larger brain metastases, surgical removal is the first-line option in patients with good general condition. Wolf et al. previously reported management of brain metastasis using Gamma Knife SRS. In this prospective study, LBM > 20 mm is involved in only 4.36% and > 30 mm in only 0.73% of patients [1]. Most LBMs are treatable via surgical removal rather than SRS and SRT. Currently, choosing the best supportive care vs SRS and SRT for treating LBM in patients with poor general condition remains controversial.

**Radiosurgery and fractionated radiotherapy for LBM**
SRS is an effective, routinely used treatment modality for brain metastasis, achieving high LTC rates and typically avoiding the neurocognitive toxicities associated with whole brain radiation therapy. Based on a recent systematic review, the reported 1-year LTC rates vary from 71 to >90% [1]. Nevertheless, the efficacy of SRS using a Gamma Knife, in terms of LTC and complications, depended on the tumor size. In a large cohort treated with SRS, patients whose tumors at first SRS had a maximal diameter ＞10 mm or a volume of 0.25 cm³ were associated with shorter overall survival (OS) [1].

We summarized the efficacy and adverse events of radiosurgery and radiotherapy against LBM for each treatment modality as follows: Gamma Knife in Table 3 [3, 5, 6, 15, 16], Cyber Knife (Accuray, Sunnyvale, CA) in Table 4 [17–19] and linac-based radiotherapy in Table 5 [7, 13, 20–22]. In several reports, a single session of fSRT for LBM was compared to multiple sessions in terms of LTC and the development of radiation necrosis. Kim et al. published comparative data between
| Reference            | Modality | Tumor volume | No. of patients | Treatment               | Results                        | Complication              | Other          |
|----------------------|----------|--------------|-----------------|-------------------------|-------------------------------|---------------------------|-----------------|
| Jiang et al. [13]    | Novalis  | ≤3.1 cm      | 40              | 20–53 Gy/4–15 fr       | LTC(12 M) 94.2%               | G3–5: Spts (12.5%)         | Prior WBRT     |
|                      |          |              |                 | 40 Gy/10 fr             | OS:15 M                       | Brain edema:             | 11/40 pts      |
|                      |          |              |                 |                         |                               | dead (1 pt)               |                 |
| Wiggeraad et al. [20]| Novalis  | ≤13 cm³      | 92              | 15 Gy/1 fr             | LTC(12 M) 54%(2004–2007)      | Pseudo-progression        | Prior WBRT     |
|                      |          |              |                 | 24 Gy/3 fr             | LTC(12 M) 61%(2007–2009)      |                           | 30% (2004–2007) |
|                      |          |              |                 |                         |                               | 15%(2004–2007)            |                 |
|                      |          |              |                 |                         |                               | 25% (2007–2009)           |                 |
|                      |          |              |                 |                         |                               | 37% (2007–2009)           |                 |
| Feuvret et al. [21]  | Novalis  | >3 cm        | 12              | 33 Gy/3 fr             | LTC (12 M) 100%               |                           |                 |
| Navarria et al. [22] | Linac    | ≤2.1 cm      | 102             | 27 Gy/3 fr             | LTC (12 M) 96%                |                           |                 |
|                      |          |              |                 | (2.1 cm ~ 3.0 cm)      | OS 16.8 M                     |                           |                 |
|                      |          |              |                 | 32 Gy/4 fr             |                               |                           |                 |
|                      |          |              |                 | (3.1 cm ~ 5.0 cm)      |                               |                           |                 |
| Minniti et al. [7]   | Novalis  | ≤2 cm        | 289             | 16 Gy(2–3 cm) 15–16    | LTC (12 M)                     | RN: 5.8%                  |                 |
|                      |          |              |                 | Gy (3 cm ~)            |                               |                           |                 |
|                      |          |              |                 | SRT 27 Gy/3 fr         |                               |                           |                 |
|                      |          |              |                 |                         |                               |                           |                 |

*Abbreviations: M = month; RN = radiation necrosis; WBRT = whole brain radiotherapy.
single-dose 20 Gy and 36 Gy in six fractions. In general, fsRT is used for large lesions and lesions near critical structures. The results showed that OS and LTC were not significantly different between the two groups. However, toxicity, including radiation necrosis, occurred more frequently in the SRS group vs the SRT group [8]. Minniti et al. conducted a retrospective analysis between SRS and SRT for LBM >2 cm. The analysis showed that fsRT was superior to SRS in terms of LTC and risk of developing radiation necrosis [7]. Navarria et al. stated the five advantages of fsRT compared to other treatment modalities: (i) the possibility of treating large brain lesions with a lower risk of important radiation-induced neurotoxicity vs single-dose SRS; (ii) the feasibility of treating lesions located near critical structures using few fractions of radiotherapy; (iii) a theoretical advantage due to re-oxygenation of hypoxic tumor cells between fractions; (iv) a reduced risk of brain radiation necrosis vs SRS; and (v) short treatment time vs whole brain radiotherapy [22].

Clinical results of multiple sessions of Gamma Knife and fsRT using Cyber Knife or Novalis have accumulated over the last decade. Generally, multiple sessions of Gamma Knife and fsRT exhibited improved clinical results vs single-session SRS in terms of LTC and radiation necrosis. However, it is difficult to determine the best treatment for LBM because different treatments were compared for different groups in terms of tumor size (20, 25, 30 mm), tumor volume (10, 13, 14 cm³), fractions, patient condition and treatment schedule in each study.

Clinical results of radiotherapy for LBM

In the present study, we analysed 21 consecutive patients with RPA Classes 2 and 3. Based on the RPA classification, the median OS time was 2.3 months in Class 3 and 4.2 months in Class 2 [9].

Of note, in our study, the median OS time following fsRT in patients with RPA Class 3 was 5 months, and 8 months in those with RPA Class 2. In previous studies, using radiosurgery and radiotherapy in patients with LBM and poor general condition attracted limited attention. Surgical resection for LBM is not recommended in elderly patients, patients with poor respiratory function, those receiving anti-coagulant therapy for deep venous thrombosis, those with pulmonary embolism etc. and deep location and eloquent area. For such patients, fsRT is a less invasive treatment alternative.

Navarria et al. reported hypo-fSRT for LBM (>2.1 cm) unsuitable for surgical resection. In this analysis, ‘unsuitable’ was defined as poor general condition, uncontrolled extra-cranial metastasis and metastasis located in a critical area. They reported that the median OS was 14 months with less radiation necrosis (estimated 5.8%). The investigators concluded that hypo-fSRT was a safe and feasible treatment option, with good local control and limited toxicity [22].

Adverse events after radiosurgery and radiotherapy for LBM

The most common adverse event after radiosurgery and radiotherapy for LBM is radiation-induced necrosis. For single-session Gamma Knife, Han et al. reported that the high radiation necrosis rate may be attributed to the increased volume of normal tissue surrounding the LBM, which is also exposed to the dose gradient. Radiosurgery using an 11–12 Gy marginal dose may be beneficial for patients with LBM when used as primary or salvage treatment. A tumor volume of 26 cm³ appears to be the upper limit for single-session radiosurgery [16].

In previous studies, radiation necrosis occurred in 0–20% [3, 5–7, 13, 15–22]. However, this percentage depends on defining the degree of radiation necrosis. It is very difficult to compare between the treatment modalities and fractionation. In recent studies, fractionation led to a lower incidence of radiation necrosis [5, 23]. Conventional medical treatments against radiation necrosis include corticosteroids, anti-coagulants or hyperbaric oxygen therapy. When radiation necrosis following radiosurgery and radiotherapy is resistant to these therapies, bevacizumab—a humanized antibody inhibiting vascular endothelial growth factor—may improve patient status and reduce the use of corticosteroids [24].

In this study, grade 3 radiation necrosis occurred in one patient. They received bevacizumab, which improved their symptoms without recurrence.

Limitations

The small sample size and the short follow-up period included in the present study and retrospective analyses do not allow us to compare between treatments against LBM unsuitable for surgical resection. Although similar clinical studies have been conducted recently, each study involved different criteria, such as the definition of LBM, treatment modalities and patient condition. A randomized trial to determine the conditions for treating LBM unsuitable for surgical resection is warranted. Our results demonstrated the potential benefits of fsRT in terms of good tumor control and reduced toxicity in this setting. In this study, fsRT for LBM unsuitable for surgical resection provided good tumor control without the occurrence of serious complications. The median survival time was 7 months. Therefore, fsRT for LBM unsuitable for surgical resection is a promising therapeutic alternative.

CONFLICT OF INTEREST

None declared.

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