Salvage Surgical Resection After Linac-based Stereotactic Radiosurgery and Radiotherapy for Newly Diagnosed Brain Metastasis

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Abstract

Purpose: This study aimed to assess the clinical outcomes of salvage surgical resection (SSR) after stereotactic radiosurgery and fractionated stereotactic radiotherapy (SRS/fSRT) for brain metastasis.

Methods: Between November 2009 and December 2018, we treated 427 consecutive patients with 919 lesions with SRS/fSRT for newly diagnosed brain metastasis at our hospital. During the follow-up period, we treated 19 consecutive patients who underwent 21 SSRs for recurrence, radiation necrosis (RN), and cyst formation after SRS/fSRT for newly diagnosed brain metastasis. Two patients underwent multiple surgical resections. Brain metastasis originated from the lung (n=15, 78.9%), breast (n=3, 15.7%), and colon (n=1, 5.2%).

Results: The median time from initial SRS/fSRT to SSR was 14 months (range: 2–96 months). The median follow-up after SSR was 15 months (range: 2–76 months). The range of tumor volume at initial SRS/SRT was 0.121–21.459 cm$^3$ (median: 2.188 cm$^3$). Histopathological diagnosis after SSR was recurrence, RN and cyst formation in 13 and 6 cases, respectively. The median survival time from SSR and from initial SRS/SRT was 17 months and 74 months, respectively. The cases with recurrence had a significantly shorter survival time than those without recurrence (p=0.0453).

Conclusion: The patients treated with SRS/fSRT for brain metastasis need long-term follow-up. SSR is a safe and effective treatment for the recurrence, RN, and cyst formation after SRS/fSRT for brain metastasis.

Background

Brain metastasis from systemic cancer is the most common neoplasm among intracranial brain tumors. Stereotactic radiosurgery and fractionated stereotactic radiotherapy (SRS/fSRT) for brain metastasis are linked to good tumor control and fewer complications[1,2,3]. However, among the long-term survivors, thanks to the advance of chemotherapy, a few patients previously treated with SRS/fSRT have shown recurrence, radiation necrosis (RN), or cyst formation in long follow-up after SRS/fSRT[4,5,6,7,8,9]. The optimum treatment option for patients with recurrence in a previously irradiated field remains controversial. In some studies, re-irradiation for the recurrence of brain metastasis after SRS were reported[4,6,7,10,11,12,13]. In contrast, another study recommended salvage surgical resection (SSR) [5]. Lesser attention has been paid to re-treatment for recurrence, RN, and cyst formation than to initial SRS/fSRT for brain metastasis, because disease progression of the primary cancer may not permit long-term survival in patients treated with SRS/fSRT.

In this retrospective study, we examined 19 consecutive patients treated with SSR for brain metastasis after SRS/fSRT to assess the efficacy and limitations of SSR.

Methods/materials
Patient characteristics

Clinical data were retrospectively collected to evaluate the efficacy and limitations of SSR among patients treated with SRS/fSRT for newly diagnosed brain metastasis. The ethical committee of Nara Medical University (Kashihara, Japan) approved this retrospective study in May 2020 (No. 2634). Between November 2009 and December 2018, we treated 427 consecutive patients with 919 brain metastases with SRS/fSRT for newly diagnosed brain metastasis at our hospital. Patients who needed SRS/fSRT for the recurrence of irradiated brain metastasis and those with resected cavity after surgical resection of brain metastasis were excluded from the study. Then, between February 2011 and January 2020, we treated 19 consecutive patients with SSR after SRS/fSRT for brain metastasis at our hospital. Prior to SRS/fSRT, each patient was evaluated by the tumor board review on brain tumors—a multidisciplinary team including neurosurgeons, neuro-radiologists, and radiation oncologists—to determine the most appropriate therapy. Table 1 lists all patients’ clinical characteristics. Twelve and 7 patients were male and female, respectively, with a median age of 69 years (range: 48–79 years) at SSR. Primary cancers originated from the lung (n=15, 78.9%); breast (n=3, 15.7%); and colon (n=1, 5.2%). Eight brain metastases were located in the frontal lobe, six in the cerebellum, three in the occipital lobe, one in the parietal lobe, and one in the temporal lobe (Table 1).

SRS and fSRT

Planning SRS and fSRT were based on computed tomography (CT) with a slice thickness of 1 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 mm. The planning target volume (PTV) was defined as GTV plus 1–2 mm for all dimensions. Treatment was initiated within 1 week after planning the CT scan. Treatment planning was performed using BrainSCAN or iPlan RT (BRAINLAB AG). The irradiation dose was prescribed to confirm a dose coverage of 90% for the PTV. Dose calculations were performed using a pencil beam algorithm. SRS and fSRT were performed using linacs with a micro multi-leaf collimator: Novalis® (BRAINLAB AG) with a collimator width of 3 mm using 6 MV X-rays.

Patient positioning and verification were performed using BrainLab ExacTrac® (BRAINLAB AG). This device comprises two infrared cameras and two dual diagnostic kV X-ray tubes, which can be moved automatically into treatment position to minimize setup errors[14,15]. All patients were treated using Novalis® with 18–23 Gy in a single fraction for SRS or 30–42 Gy in 3–6 fractions for fSRT via non-coplanar multi-beams, non-coplanar multi-arcs, or both. The treatment methods in SRS or fSRT were conformal beams, dynamic conformal arcs, intensity-modulated radiotherapy (IMRT), or hybrid arcs. Hybrid arcs is a novel treatment technique blending aperture-enhanced optimized arcs with discrete IMRT elements, thereby allowing arc selection with a set of static IMRT beams[16].

Surgical procedure
All patients treated with SRS/fSRT for brain metastasis were regularly evaluated with MRI at intervals of 3 months after initial SRS/fSRT. Once disease progression was detected, MRI was performed at intervals of 1–2 months. The decision for craniotomy and resection for disease progression was based on evidence of clinical deterioration and associated imaging progression judged by the tumor board review on brain tumors. Neuroimaging indications for SSR included an enlarging lesion, hemorrhage, and symptomatic mass effect unresponsive to medical management with corticosteroids. All SSRs were performed under general anesthesia. Image-guided surgeries using intraoperative ultrasonography (HITACHI ALOKA, Japan) were performed in all cases. In eight cases, the BrainLab navigation system was useful to detect the tumor boundaries even though the lesions were irradiated with SRS/fSRT.

**Clinical and radiological follow-up**

Follow-up contrast-enhanced MRI was performed every 3 months after the end of SRS/fSRT, when possible. Tumor volumes were measured before and after SRT using BrainSCAN or iPlan RT software. After SSR, MRI was repeated every 3 months.

**Statistics**

The median survival time was calculated using the Kaplan–Meier method. The log-rank test was used for univariate analyses. All of the analyses mentioned above were performed with the EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [17], and p<0.05 was considered to indicate statistical significance.

**Results**

**Surgical results and pathological diagnosis**

Between November 2009 and December 2018, 427 consecutive patients with 919 brain metastases were treated with SRS/fSRT for newly diagnosed brain metastasis at our hospital. Nineteen of 427 patients (4.4%) and 19 of 919 brain metastases (2.0%) went on to receive SSR after SRS/fSRT during this study period. The ranges of tumor diameter and volume at the initial SRS/fSRT were 3–36 mm (median: 11 mm) and 0.121–21.459 cm$^3$ (median: 2.188 cm$^3$), respectively. The median time from initial SRS/fSRT to SSR was 14 months (range: 2–96 months). Permanent pathological diagnosis revealed recurrence with viable cancer cells in 13 cases of 919 brain metastases (1.4%). In another six cases out of the 919 brain metastases (0.65%), RN and cyst formation were diagnosed without viable cancer cells (Table 1). The median follow-up after SSR was 15 months (range: 2–76 months). Follow-up MRI was performed every 3 months after the SSR. One patient died due to progression of brain metastases within 3 months; hence, follow-up MRI data at 3 months for this patient is unavailable. Among the remaining 18 patients who underwent follow-up MRI every 3 months, the examination revealed recurrence at the same site of resection in two patients. These patients underwent second-look surgery. Among the other patients with SSR for recurrence, additional fSRT for the cavity was performed in two patients, and whole brain radiotherapy was performed in one patient. Six patients treated with SSR for RN with/without cyst
formation experienced no recurrence during the follow-up period. Before SSR, 12 patients had some symptoms including headache, motor weakness, speech disturbance, disorientation, and cerebellar ataxia. Nine patients had an improvement of their symptoms after surgery.

**Survival rate and prognostic factors**

Eleven patients died at the last follow-up after SSR. Eight patients died because of worsening of systemic cancer, and the remaining three patients died owing to progression of carcinomatous meningitis. The median survival time from SSR and from initial SRS/fSRT were 17 months and 74 months, respectively. The median survival time from SSR in the patients with recurrence was 15 months. Those with recurrence had a significantly shorter survival time than those without recurrence (p=0.0453) (Fig. 1).

**Complications**

One patient had a postoperative hemorrhage in the cavity, on day 4 after SSR for recurrence of brain metastasis from lung spindle cell carcinoma. This patient had received anti-coagulant medication to prevent pulmonary embolism. He restarted the anti-coagulant therapy on day 3 after surgery. However, the next day, the patient became unconscious and head computed tomography revealed postoperative hemorrhage in the cavity. We performed urgent evacuation of the hematoma. He recovered and was discharged without any deficits. Eventually, he died because of progression of lung cancer 10 months later after the initial fSRT and 7 months later after SSR.

No patients experienced any postoperative surgical site infection. One patient developed hydrocephalus after SSR, for which a ventriculo-peritoneal shunt was placed.

**Illustrative case 1**

A 55-year-old male patient with spindle cell carcinoma in the lung presented with headaches. MRI revealed the presence of a large brain tumor in the left frontal lobe. The maximum tumor diameter and volume was 36 mm and 21.4 cm$^3$, respectively. Because of the previous pulmonary embolism under the administration of anti-coagulate drug, the patient was treated with linac-based fSRT using 30 Gy in 3 fractions. Nine weeks after the fSRT, MRI revealed a significant increase in the tumor size (Fig. 2). The patient underwent SSR for brain metastasis. Permanent pathological diagnosis was recurrence of spindle cell carcinoma. On the third day, heparin administration was started, but he became unconscious the next day. Head CT showed postoperative hemorrhage in the surgical cavity, for which an emergency hematoma evacuation was performed. The patient recovered uneventfully, and follow-up MRI revealed no recurrence at the same site. However, the patient died due to progression of lung cancer 10 months after the initial fSRT and 7 months later after SSR.

**Illustrative case 2**

A 63-year-old female patient with breast cancer. MRI revealed the presence of a small metastatic lesion in the left cerebellum. The maximum tumor diameter and volume was 13 mm and 1.24 cm$^3$, respectively.
The patient was treated with linac-based SRS using 23 Gy. Three months after SRS, MRI revealed a significant decrease in tumor size (Fig. 2). During the follow-up period, the lesion gradually increased in size. Eventually, the patient underwent SSR for cyst formation 8 years after the initial SRS. The patient experienced no recurrence of cyst formation for 2 years.

**Discussion**

**SRS/fSRT for brain metastasis**

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 8–35% of all cancer patients[18].

Treatment for brain metastasis includes whole brain radiotherapy, surgery, and SRS/fSRT. In particular, to manage smaller brain metastases, SRS is the first-line option. SRS/fSRT for brain metastasis are linked to good tumor control and fewer complications[1,2,3]. In our previous studies, SRS and fSRT, using a frameless fixation system for brainstem metastasis and large brain metastasis with unsuitable surgical resection, showed good tumor control with the possibility of reducing RN[19,20].

**Recurrence after SRS/fSRT for brain metastasis**

SRS is an effective, routinely used treatment modality for brain metastasis, achieving high local tumor control (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%[2]. Nevertheless, the efficacy of SRS using a Gamma Knife (GK), in terms of LTC and complications, depend 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 cm$^3$ were associated with shorter overall survival[2]. McKay et al. reported the recurrence of brain metastasis after GK SRS. Among 738 patients treated with GK SRS, 58 (7.85%) patients had a recurrence with local failure. Of these 58 patients, 32 underwent a second course of GK SRS[4]. Among them, 24% developed symptomatic RN and the 1-year control rate was 79%. Rana et al. reported that 32 brain metastases with recurrence after linac-based SRS/fSRT were treated with linac-based salvage SRS. The median interval time between initial SRS/fSRT and second SRS was 9.7 months. The overall control rate was 84.4% with 18.8% RN[6]. Balermpas et al. reported 32 recurrent brain metastasis after GK SRS and Cyber Knife SRS. The one-year local control rate was 79.5%, and the overall rate of radiological RN was 16.1%[7]. Repeated SRS for the recurrent brain metastasis after SRS or SRT are summarized in Table 2 [4,6,7,10,11,12,13].

**Radiation necrosis after SRS/fSRT for brain metastasis**

RN is an inflammatory reaction that occurs between a couple of months and several years following SRS and is one of the most common adverse effects after SRS/fSRT. In previous studies, RN occurred in 5-25% patients[21,22,23,24,25]. The definition of RN varies across studies and is based on radiological
findings including MRI perfusion, MR spectroscopy, and positron emission tomography with fluorodeoxyglucose and other tracers, and pathological findings after surgical resection. Therefore, it is difficult to compare the reported incidence of RN in each study.

Kohutek et al. reported that the median time from initial SRS to RN was 10.7 months (2.7–47.7 months) [21]. RN is seen as a contrast-enhancing lesion with peri-lesional edema at the site of previous SRS radiologically and can be asymptomatic or cause neurological symptoms. Commonly cited risk factors for RN include target dose and volume, previous radiotherapy, and the concurrent use of systemic agents[22].

For the management of symptomatic RN including headache, cognitive impairment, seizures, or focal deficits related to the location of RN, oral steroids are the first line of treatment[23]. Some patients need oral steroids for a long duration, but cannot continue to take steroids because of the unfavorable side effects. When RN following SRS/fSRT is resistant to oral steroids, bevacizumab—a humanized antibody inhibiting the vascular endothelial growth factor—may improve patient status and reduce the use of corticosteroids[26]. For symptomatic patients with RN resistant to medication including oral steroids and bevacizumab or those with suspected recurrence, we performed SSR.

**Cyst formation after SRS/SRT for brain metastasis**

Alattar et al. reported that cyst formation after linac-based SRS occurred in 0.9% of 1106 treated lesions. Among the nine patients, four who had neurologic deterioration despite steroid treatment underwent surgical fenestration and biopsy of the cyst wall[8]. Ishikawa et al. reported that the incidence of cyst formation was estimated as 10% in long-term survivors (>3 years) without tumor recurrence[27].

In the present study, there were two cases with cyst formation. The time from initial SRS/fSRT to cyst formation was 85 months and 96 months, respectively. We performed fenestration of the cyst wall and removed the necrotic tissue surrounding the cyst wall. No recurrence of cyst formation occurred in these two cases. Aizawa et al. reported that cyst formation occurred 10 years after initial SRS[28]. In the long-term survivors treated with SRS/fSRT, even though follow-up MRI revealed no new brain metastasis and no recurrence, physicians should pay more attention to the development of cyst formation >10 years after SRS/fSRT. Cyst formation after SRS or SRT is summarized in Table 3.

The mechanism of development of cyst formation is unclear. Ishikawa et al. hypothesized that cyst formation is essentially the same as or very similar to those in patients treated with SRS for arteriovenous malformation and thus are not the result of disease progression. Breakdown of the blood-brain barrier appears to play an important role in the cyst formation process. The relatively high blood flow volumes and increased permeability of injured blood vessel walls in the irradiated lesion, may also promote cyst formation within the area of radiation-induced degeneration continuing for several years after SRS/fSRT[27].

**Limitations**
The small sample size included in the present study and retrospective analyses do not allow us to evaluate the proper treatment for recurrence, RN, and cyst formation after SRS/fSRT. Although similar clinical studies have been recently conducted, each study involved different criteria, such as for the definition of RN and treatment modalities, hence lacking consistency in analysis.

**Conclusion**

The patients treated with SRS/fSRT for newly diagnosed brain metastasis require long-term follow-up. In this study, the mean survival time of all patients and of those with recurrence was 17 months and 15 months, respectively. SSR is a safe and effective treatment for the recurrence, RN, and cyst formation after SRS/fSRT for brain metastasis.

**Declarations**

**Author contributions:** Conception and design: RM, MH, HN. Acquisition of data: RM, TM, NI, TT. Analysis and interpretation of data: RM, TM, MH, TT. Manuscript draft: RM, MH, TT. Critical revision for important intellectual content: TO, TM, KY, SM, YT, KM, SY, FN, IN, YM, YP. Final approval: All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Data availability:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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**Conflict of interest:** None.

**Ethical approval:** Data was collected retrospectively, in accordance with the ethical committee of Nara Medical University (No: 2634).

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**Tables**

Due to technical limitations, table 1, 2 and 3 is only available as a download in the Supplemental Files section.

**Figures**
Figure 1

Overall survival time since SSR (A), overall survival since initial SRS/fSRT (B), and overall survival time since SSR in the recurrence group and in RN/cyst formation, estimated using the Kaplan–Meier method.
Figure 2

Illustrative case 1: This patient is a 55-year-old man with lung spindle cell carcinoma. MRI revealed the presence of a large brain tumor in the left frontal lobe. The maximal tumor diameter and volume were 36 mm and 21.46 cm³, respectively. (A) Because of anti-coagulant medication for the prevention pulmonary embolism, the patient was treated with linac-based fSRT using 30 Gy in 3 fractions. MRI revealed recurrence of the tumor 9 weeks after SRT (B) and one month after salvage surgical resection (C).
Figure 3

Illustrative case 2: This patient is a 63-year-old woman with breast cancer. MRI revealed the presence of a brain tumor in the cerebellum. The maximal tumor diameter and volume were 13 mm and 1.24 cm³, respectively. (A) This patient was treated with linac-based SRS using 23 Gy in single fraction. Three months after treatment, MRI revealed a considerable decrease in tumor size. (B) Eight years after treatment, MRI revealed cyst formation. (C) Two years after SSR, MRI revealed no recurrence of cyst formation. (D)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.
- Table120210223.xlsx
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