Long-term Outcomes of Fractionated Stereotactic Radiotherapy for Intracranial Skull Base Benign Meningiomas in Single Institution

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Objective: To investigate the outcome of linac-based fractionated stereotactic radiotherapy over the last 10 years for intracranial skull base benign meningiomas in patients who were inoperable, who had residual tumors with some components of high mitotic index after surgery and who experienced relapse of the tumor.

Methods: Twenty-seven patients with intracranial skull base benign meningiomas treated with fractionated stereotactic radiotherapy were retrospectively reviewed. Twenty-seven cases were diagnosed as benign meningiomas on pathological (17 cases) or radiological (10 cases) examination. The median follow-up time was 90 months after initial treatment and 63 months after fractionated stereotactic radiotherapy. The median biological equivalent dose calculated using an $\alpha/\beta$ ratio of 2.0 Gy was 82.0 Gy (range, 60–106 Gy).

Results: The 5-year overall survival was 95.7 (95% confidence interval: 87.3–100)% after initial treatment and 96.2 (88.8–100)% after fractionated stereotactic radiotherapy. The 5-year overall survival and local control rate of patients who received fractionated stereotactic radiotherapy alone were both 100%. The 5-year progression-free survival and local control rate after fractionated stereotactic radiotherapy were all 100% with a tumor volume of $<9.1 \text{ cc}$ and 68.2 (37.2–99.2) and 75.8 (45.2–100)% for the tumors 9.1 cc, respectively. The difference was significant in progression-free survival ($P = 0.022$) and local control rate ($P = 0.044$). The local control rate was significantly worse in patients who received fractionated stereotactic radiotherapy for relapsed tumors ($P = 0.01$). No late radiation damage was observed in the follow-up period.

Conclusions: The long-term outcome suggests that fractionated stereotactic radiotherapy is a safe and effective treatment for intracranial skull base benign meningioma, especially for those who have tumors $<9.1 \text{ cc}$ or would receive fractionated stereotactic radiotherapy with or without surgery as the initial treatment.

Key words: radiation therapy – meningioma – stereotactic – skull base – fractionation

INTRODUCTION

Radiotherapy is increasingly being used for the treatment of meningiomas after incomplete resection, after recurrence and when tumor histology is atypical or malignant (1,2). When meningiomas are located in the intracranial skull base region, tumor excision is frequently incomplete and even biopsy can be hazardous (1). Therefore, it is a matter of...
debate whether the use of radiotherapy should be used when the residual tumor is still small as the primary treatment or should be reserved as a potential salvage treatment for the residual tumor enlarged (3).

Stereotactic radiosurgery (SRS) has been proven useful for reducing unnecessary irradiation to the normal tissue surrounding meningiomas and provides an excellent local control rate (LCR) for small to mid-size skull base meningiomas (3,4). Three-dimensional conformal radiotherapy (3D-CRT) and fractionated stereotactic radiotherapy (FSRT) are expected to be useful for further reducing the possibility of late adverse reactions, even for relatively large tumors (5,6). Although there were several precise reports from a few institutions about the long-term outcome after FSRT (5–8), we are still short of knowledge about the treatment results of FSRT with the median follow-up longer than 60 months for intracranial meningioma.

We began using FSRT 15 years ago for patients with intracranial skull base meningiomas, principally for patients who were inoperable, who had residual tumors with some components of high mitotic index or high MIB-1 index, who experienced relapse of the tumor. In this study, we retrospectively reviewed our long-term results for FSRT of intracranial skull base benign meningiomas in order to investigate the usefulness and prognostic factors of this treatment.

PATIENTS AND METHODS

Patients

The outcome of 27 patients with intracranial skull base benign meningiomas treated with FSRT at Hokkaido University Hospital between May 1994 and February 2009 was retrospectively reviewed. Our treatment policy was to apply FSRT principally for those patients with intracranial skull base meningiomas who were inoperable, who had residual tumors with some components of high mitotic index or high MIB-1 index, who experienced relapse of the tumor. In this study, we retrospectively reviewed our long-term results for FSRT of intracranial skull base benign meningiomas in order to investigate the usefulness and prognostic factors of this treatment.

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RADIATION THERAPY METHOD

The gross tumor volume (GTV) was taken as the gross tumor shown on computed tomography (CT) with or without magnetic resonance imaging (MRI). The clinical target volume (CTV) was equal to the GTV, post-operative tumor bed or both in this study. The planning target volume (PTV) was 2–3 mm geometric expansion of the CTV. In delineating GTV, MRI co-registered with CT was used in 18 recent patients, and only the CT information was used for the remaining 9 patients.

Treatment planning systems were Focus or Xio (CMS Japan). A dose calculation algorithm used for the skull base meningiomas was the Clarkson method or the

<table>
<thead>
<tr>
<th>Table 1. Patients’ characteristics</th>
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<tr>
<td>Factors</td>
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<tr>
<td>Diagnosis</td>
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<tr>
<td>Pathological diagnosis</td>
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<td>Radiological diagnosis</td>
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<td>IV</td>
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<tr>
<td>V</td>
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<td>Radiotherapy alone</td>
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after surgery in 12 patients. The number of surgical procedures before FSRT was 1, 2 and 3 in 10, 5 and 1 patients, respectively. Patients who received open biopsy or surgery were classified according to Simpson’s grade (9). Simpson’s grade II (complete removal and coagulation of dual attachment) and IV (subtotal resection) surgery before radiotherapy was performed in 1 and 15 patients, respectively. Only one patient received biopsy (Simpson’s grade V).
Convolution method. Stereotactic radiotherapy was carried out by using a 6 or 10 MV linear accelerator (LINAC) (2100C: Varian, Palo Alto, CA, USA; EXL15DP: Mitsubishi, Japan) with an in-house developed LINAC-based SRT system. Three-dimensional non-coplanar, single isocenter and the technique using multileaf collimator (MLC) were used. Three to eight static non-coplanar ports with the conformal fields were used in general. The width of these leaves was 5–10 mm at the isocenter. The dose was prescribed at the isocenter and defined as 100% in the dose distribution profile. MLCs were opened to cover PTV by a 90–95% isodose shell. The maximum dose point was always situated near the isocenter with the dose <110% (Fig. 1).

Patients were fixed by using a thermo-plastic mask and a custom-made head rest system. The dose to the optic chiasm was limited to ≤46 Gy. The total dose was 48–54 Gy in 26 cases and 32 Gy in 1 case using 2.0 Gy as the daily dose. When these radiation schedules were converted into the biological equivalent dose (BED) using an α/β ratio of 2.0 Gy, the median BED dose was 82.0 Gy (range: 52–90 Gy).

FOLLOW-UP AND STATISTICAL ANALYSES

The median follow-up time was 90 months (range: 21–209 months) after initial treatment, surgery or FSRT. The median follow-up time was 63 months (range: 19–154 months) after FSRT. More than 70% of patients were followed longer than 36 months after FSRT. Patients were periodically monitored by physical as well as radiographic examination in Hokkaido University Hospital and related hospitals. Local tumor progression (PD) was scored when the maximum diameter of the tumor increased 2 mm or more and partial reaction was scored when the diameter decreased 2 mm or more. The LCR was defined as no change or decrease of the tumor volume in the anatomical region consistent with the PTV of the treatment planning image. When more than 80% of the relapsed tumor volume was outside of the PTV, the recurrence was defined as out of field (10). In-field (≥95% of the relapsed tumor volume in the PTV), marginal (20–95% of the relapsed tumor volume in the PTV), and out-of-field (less than 20% of the relapsed tumor volume in the PTV) recurrence were defined in this study.

Statistical analyses were conducted by using commercially available software (SPSS v18; IBM Inc., Chicago, IL). The overall survival (OS) and LCR were calculated from the date of the initiation of radiotherapy using the Kaplan–Meier method, and statistical evaluations were carried out by the log-rank test.

RESULTS

The OS, progression-free survival (PFS) and LCR at 5 years after initial treatment were 95.7 [95% confidence interval (CI): 87.3–100], 91.6 (80.4–100) and 95.5 (86.9–100)%.

The OS, PFS and LCR at 5 years after FSRT were 96.2 (88.8–100), 84.6 (67.7–100) and 88.6 (72.9–100)%.

Partial response was achieved in two benign patients, and the other patients with local control experienced no change of tumor volume. Three (11%) patients experienced in-field recurrence. These tumors had received Simpson’s grade IV surgical resection. One patient had progression disease out of irradiation field. The recurrent cases were observed at the posterior fossa (at 55 and 81 months) in two patients, and at the cavernous sinus and tuberculum (at 19 and at 27 months) in two patients. These four recurrent cases are summarized in Table 2. No marginal recurrence was observed.

Univariate analyses were performed on OS, PFS and LCR after FSRT for patients with benign meningioma (Table 3). The female patients had significantly better PFS (P = 0.009) and LCR (P = 0.04) than the male patients. The 5-year OS, PFS and LCR after FSRT were all 100% for the benign meningiomas with a tumor volume of <9.1 cc and these parameters were 91.7 (76.0–100), 68.2 (37.2–99.2) and 75.8 (45.2–100)% for the tumors >9.1 cc, respectively. The difference was significant in PFS (P = 0.022) and LCR (P = 0.044) (Fig. 2).

In this study, the 11 patients who received FSRT alone had 100% OS, 88.9% PFS and 100% LCR at 5 years, respectively. The OS, PFS and LCR of patients who received FSRT with or without surgery as the initial treatment (n = 15) were 100, 91.7 and 100%, whereas those of patients who received FSRT for relapse (n = 12) were 90.9, 68.2 and 68.2%, respectively. The LCR was significantly worse in patients who received FSRT for a relapsed tumor (P = 0.01). A higher biological radiation dose, BED, was paradoxically associated with a lower PFS and LCR. The median tumor volume was larger (11.0 vs. 6.7 cc) and the ratio of patients with relapsed tumor was higher (7/11 vs. 5/16) in the higher

Figure 1. Dose distribution of FSRT for an intracranial benign meningioma. FSRT, fractionated stereotactic radiotherapy.
The median dose used in the present study is 48–54 Gy with daily dose of 2.0 Gy. It is lower than the dose used in the Heiderberg study (5,7), in which the mean radiation dose was 56.8 Gy (± 4.4 Gy), and higher than the dose used in the French study (8), in which 45 Gy with daily dose of 1.8 Gy was used. Since a dose–response curve for normal tissues and tumor changes rapidly at the dose range from 40 to 60 Gy with 1.8–2 Gy fractional dose, our results add new biological data for the meningioma and surrounding normal tissue with the long follow-up.

We found that the OS and LCR were 100% at 5 years after FSRT alone for patients with benign skull base meningioma who received FSRT as the initial treatment. This is consistent with a recent article by Korah et al. (6) in which the 8-year LCR was 94% after radiotherapy alone for...
apy (116,17). Previous reports have suggested that delaying the complication rate compared with previous radiotherapy used as the initial treatment than for those who received FSRT for tumors (Table 4). The median tumor volume was 10 cc less in the majority of studies (4,10,11,24–29). The 5-year PFS and LCR values were more than 90% in these series. This study showed that our results contained the largest proportion of the relapsed tumors in these series. The tendency for the outcome to be better in the series with a lower proportion of relapsed tumors was not negligible. The lack of these biases may partly explain the excellent results in the group that received radiotherapy alone. The present study suggested that the selection bias and leading bias must be held in mind when we compare the treatment results of radiotherapy among different institutions or compare it with surgical series.

This study showed that the tumor volume was a significant prognostic factor as reported previously (5,22). We summarized the previous studies of SRS and FSRT which discriminated the tumor volume of benign tumors from atypical and malignant meningiomas (Table 4). The median tumor volume was 10 cc less in the majority of studies (4,10,11,24–29). The 5-year PFS and LCR values were more than 90% in these series. This study showed that our results contained the largest proportion of the relapsed tumors in these series. The tendency for the outcome to be better in the series with a lower proportion of relapsed tumors was not negligible. The lack of these biases may partly explain the excellent results in the group that received radiotherapy alone. The present study suggested that the selection bias and leading bias must be held in mind when we compare the treatment results of radiotherapy among different institutions or compare it with surgical series.

Conventional 3D-CRT was reported to achieve excellent results in 1980s–early 1990s when CT and MRI had 5 mm slice thickness and very precise fixation did not make sense. However, in the late 1990s, treatment planning using images with 1–2 mm thickness began to require precise fixation of the skull. Although there is no randomized studies to compare 3D-CRT and FSRT, FSRT can reduce the dose to the critical part of brain tissue with higher certainty than conventional 3D-CRT in the era of 1–2 mm slice thickness of the medical images. There are two recent reviews comparing different radiotherapy techniques such as 3D-CRT, SRS delayed irradiation was given for a poor prognosis group with a tendency of enlargement and irradiation was not required at all for the majority of patients in a good prognosis group. Precise selection criteria for the early irradiation after surgery are warranted to reduce the unnecessary irradiation for the good prognosis group.

The poorer outcome for recurrent meningioma is likely due to the progressive nature of some meningiomas or a mixed component of atypical meningioma (4,19,20). Meningiomas have been reported to obtain radioresistance or a component of malignant transformation as a natural course of the disease (20–23).

Considering that relapsed meningiomas often contain a progressive component, the treatment policy of applying radiotherapy only in the case of relapsed tumors causes a selection bias in the treatment outcome. The progressive nature of some meningiomas may also result in a leading bias with the treatment policy. Our study showed that the 5-year OS was 96.3% after any initial treatment and 88.2% after FSRT for the same patients’ group. We summarized the previous studies of SRS and FSRT in Table 4 and found that our results contained the largest proportion of the relapsed tumors in these series. The tendency for the outcome to be better in the series with a lower proportion of relapsed tumors was not negligible. The lack of these biases may partly explain the excellent results in the group that received radiotherapy alone. The present study suggested that the selection bias and leading bias must be held in mind when we compare the treatment results of radiotherapy among different institutions or compare it with surgical series.

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and FSRT (30,31). Elia et al. (30) summarized that FSRT has toxicity equivalent to that of SRS, despite its biased use for larger meningiomas with more complicated volumes. Minniti et al. (31) recommended SRS only for tumors <3 cm away more than 3 mm from the optic pathway because of the high risk of long-term neurological deficits.

Selch et al. (27) reported an encouraging 3-year PFS of 97% after FSRT for patients with a median tumor volume of 14.5 cc using a dose fractionation schedule similar to that in our study. Milker-Zabel et al. (5) have published results of FSRT for 179 skull base meningiomas, achieving 90.5 and 89% recurrence-free survival rates for benign meningiomas and atypical meningiomas, respectively, and using a median dose of 57.6 Gy (range: 45–68 Gy). Their results were excellent considering that the median target volume was as large as 33.6 cm³ (1–412.6 cm³) and as many as 141 (44.5%) cases of recurrent disease were included. Eight (4.4%) patients developed new clinical symptoms, such as reduced vision, trigeminal neuralgia and intermittent tinnitus located at the side of the irradiated meningioma after FSRT in their series. The slightly higher dose used in their study might have been the reason for the better tumor control with a little higher complication rate compared with our study. Korah et al. (6) used FSRT, 3D-CRT and SRS for 9, 11 and 22 patients, respectively, and among these, only 1 patient treated with SRS developed a symptomatic radiation-related neurological complication. There were no late adverse reactions in our series (27). Considering that a lower complication rate is an extremely important issue for patients with benign tumors, FSRT is one of the initial treatment options for patients with intracranial skull base meningioma which locate very close to the critical portion of normal brain tissues.

However, in our relapse cases, the LCR was low. We consider that the 2–3 mm PTV margin was sufficient with our FSRT technique by adding MLC margin to cover the PTV with 90–95% isodose line. However, it is not deniable that the high relapse rate of the larger tumors may also be explained by the small PTV margins used in our study. Goldsmith et al. (32) reported that the PFS rate in the group treated with a minimum tumor dose of >52 Gy was better than the group treated with ≤52 Gy (93 vs. 65%; P = 0.04). When FSRT was used for treating the case of the tumor located near the organ at risk (OAR), we must have reduced the margin for PTV to exclude the OAR from the high-dose area. Thus, the dose concentration for the tumor was gotten worse than an ideal dose distribution. Intensity-modulated radiotherapy (IMRT) is expected to increase the therapeutic ratio by reducing the dose to normal tissue because IMRT can deliver the prescription dose to the targets without worsen the dose concentration. For improvement of the LCR of those relapse cases, IMRT with a fractionated schedule will be more appropriate than simple FSRT to increase the dose for these tumors without increasing the dose to the surrounding normal tissue (33–36). However, higher radiation dose to the rest of the body and higher cost to the patient must be taken into account for each patient to use IMRT.

In conclusion, the long-term outcome suggests that FSRT is a safe and effective treatment for intracranial skull base benign meningioma, especially for those who have tumors <0.1 cc or would receive FSRT with or without surgery as the initial treatment.

### Table 4. Previous studies of stereotactic radiosurgery and fractionated stereotactic radiotherapy for skull base benign meningioma in which the median or mean tumor volume was described for benign tumors

<table>
<thead>
<tr>
<th>Institution</th>
<th>SRS or FSRT</th>
<th>No. of patients</th>
<th>Tumor volume median (range) (cc)</th>
<th>Recurrent cases (%)</th>
<th>Follow-up period median (range) (months)</th>
<th>PFS</th>
<th>LCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Clinic (30)</td>
<td>SRS</td>
<td>88</td>
<td>10 (2.3–30)</td>
<td>&gt;3 (3%)</td>
<td>35 (12–83)</td>
<td>95.0%</td>
<td>—</td>
</tr>
<tr>
<td>University of Pittsburgh (24)</td>
<td>SRS</td>
<td>60</td>
<td>13.7 (0.8–56.8)</td>
<td>&gt;13 (21%)</td>
<td>35 (12–101)</td>
<td>—</td>
<td>86.7%</td>
</tr>
<tr>
<td>University of Pittsburgh (10)</td>
<td>SRS</td>
<td>155</td>
<td>6.5 (0.5–52.4)</td>
<td>Unknown</td>
<td>39 (2–145)</td>
<td>—</td>
<td>93.1%</td>
</tr>
<tr>
<td>University Hospital, Verona (25)</td>
<td>SRS</td>
<td>111</td>
<td>8.1 (1–20)</td>
<td>0 (0%)</td>
<td>48.2 (12.1–82.5)</td>
<td>96.0%</td>
<td>97.0%</td>
</tr>
<tr>
<td>CHU La Timone (4)</td>
<td>SRS</td>
<td>32</td>
<td>2.28 (0.25–60)</td>
<td>2 (6%)</td>
<td>56 (24–118)</td>
<td>100.0%</td>
<td>—</td>
</tr>
<tr>
<td>University of Pittsburgh (26)</td>
<td>SRS</td>
<td>219</td>
<td>5.0 (0.47–56.5)</td>
<td>0 (0%)</td>
<td>29 (2–164)</td>
<td>—</td>
<td>93%</td>
</tr>
<tr>
<td>Medical University Graz (28)</td>
<td>SRS</td>
<td>200</td>
<td>6.5 (0.38–89.8)</td>
<td>Unknown</td>
<td>94.8 (60–144)</td>
<td>98.5%</td>
<td>—</td>
</tr>
<tr>
<td>Seoul National University (11)</td>
<td>SRS</td>
<td>63</td>
<td>6.3 (0.5–18.4)</td>
<td>1 (2%)</td>
<td>77 (48–112)</td>
<td>90.2%</td>
<td>—</td>
</tr>
<tr>
<td>University of Pittsburgh (29)</td>
<td>SRS</td>
<td>168</td>
<td>6.1 (0.3–32.5)</td>
<td>35 (21%)</td>
<td>72 (2–254)</td>
<td>91.0%</td>
<td>97% (at 10 years)</td>
</tr>
<tr>
<td>University of California (27)</td>
<td>FSRT</td>
<td>45</td>
<td>14.5 (1.4–65.66)</td>
<td>8 (31%)</td>
<td>36 (12–53)</td>
<td>97.4% (3 years)</td>
<td>—</td>
</tr>
<tr>
<td>Hokkaido University (9.1 cc &gt;)</td>
<td>FSRT</td>
<td>14</td>
<td>4.7 (1.1–9.0)</td>
<td>4 (28.6%)</td>
<td>79 (0–154)</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Hokkaido University (all cases)</td>
<td>FSRT</td>
<td>27</td>
<td>9.1 (1.1–86.1)</td>
<td>12 (44.1%)</td>
<td>63 (19–154)</td>
<td>84.6%</td>
<td>88.6%</td>
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SRS, stereotactic radiosurgery.

*Mean.
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Conflict of interest statement
None declared.

References