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Original Article

Stereotactic intensity-modulated radiotherapy for skull base meningioma using the HybridArc with Novalis STx system

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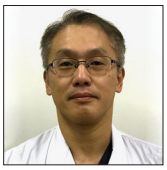

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ABSTRACT

Background: Skull base meningiomas are often difficult to remove completely with preserved nerve function and may require radiation therapy. However, the Gamma Knife is unsuitable for large tumor volume or the optic nerve, which is difficult to identify on imaging. We report the results of stereotactic radiotherapy with HybridArc using Novalis STx for skull base meningiomas.

Methods: We retrospectively examined 28 patients with skull base meningioma who underwent stereotactic radiotherapy (54 Gy/30 fractions) with HybridArc.

Results: The 28 patients, nine males and 19 females, were aged 31–83 years (mean 58.4 years), and the tumor volume was 2.6–97.1 mL (mean 29.7 mL). HybridArc irradiation was performed with D95 54 Gy/30 fractions for all patients with a median follow-up period of 36.0 months (range: 12–78 months). Tumor control rates at 1, 2, and 5 years after radiotherapy were 92.6%, 89.1%, and 82.8%, respectively. Only one non-atypical meningioma remained uncontrolled; thus, the tumor control rate for non-atypical meningioma at 1, 2, and 5 years was 94.1%. Tumor control rates for atypical meningioma at 1, 2, and 5 years were 85.7%, 71.4%, and 53.6%, respectively, significantly worse than for non-atypical meningiomas ($P = 0.0395$). Radiation injury was observed in two cases (7.1%). Visual field defects were observed in 16 patients, and diplopia in 6. Visual field and diplopia improvements were achieved in 5 and 2 patients, respectively (with overlap).

Conclusion: Stereotactic radiotherapy (54 Gy/30 fractions) with HybridArc using Novalis STx is a safe and effective approach for relatively large skull base meningiomas.

Keywords: HybridArc, Intensity-modulated radiotherapy, Novalis STx, Skull base meningioma, Stereotactic radiotherapy

INTRODUCTION

A complete surgical removal of skull base meningiomas with preservation of neurological function is often difficult; radiotherapy may be used in combination or as an alternative to surgery. However, stereotactic radiosurgery (SRS), such as Gamma Knife surgery, is not suitable for large tumors that cause severe compression of the brain stem or optic apparatus due to the high risk of exceeding the tolerable dose of radiation for nearby structures, especially the optic nerve.

Stereotactic multi-fraction radiotherapy using the Novalis STx system is suitable for relatively large lesions that compress the optic nerve/chiasm and brain stem. This system is a high-performance

linear accelerator (Linac), which enables highly accurate irradiation with the Brainlab ExacTrac system, a positioning device that combines X-ray and infrared radiation, and a robotic couch with 6-axis correction. The Novalis STx system enables high-precision SRS incorporating various methods, including normal rotational body irradiation (dynamic conformal arc), intensity-modulated radiotherapy (IMRT) using beams, and Brainlab HybridArc, a method of irradiation combining several dynamic arcs and IMRT beams.[12] HybridArc ensures almost homogeneous dose distribution within the tumor due to the additional IMRT beams and can be adapted to complicated tumor shapes. Furthermore, additional rotary irradiation reduces the irradiation time compared with IMRT using only a large number of beams. However, the efficacy of the HybridArc method for skull base meningiomas is currently unclear. The present study aimed to address this gap in knowledge by investigating the clinical utility and results of stereotactic multi-fraction radiotherapy with HybridArc using the Novalis STx system for skull base meningiomas that were difficult to completely remove surgically.

MATERIALS AND METHODS

We retrospectively investigated 28 patients who underwent stereotactic multi-fraction radiotherapy (54 Gy/30 fractions) using the Novalis STx system and were followed up for 12 months or longer. Patients with treatment failure within 12 months were also included, but those with anaplastic meningioma were excluded from the study. The selection criteria for this treatment were as follows:

1. Skull base meningioma that was difficult to remove by surgery completely or surgery refused by the patient
2. Cases where the tumor volume is so large that SRS or hypofractionated radiotherapy is considered to carry a high risk of radiation injury
3. Cases where it is difficult to identify the optic tract (optic nerve/optic chiasm) on magnetic resonance imaging due to tumor size and/or severe brainstem compression.

Thin-slice imaging was performed; mainly, contrast-enhanced T_1-weighted images, T_2-weighted images, and fluid-attenuated inversion recovery (FLAIR) images were acquired, and patient-specific plastic shells were constructed. Treatment plans were generated using Brainlab iPlan® software. The planning target volume (PTV) varied from case to case, but – in many cases – the PTV was defined as gross tumor volume with a 1–2 mm margin added, and HybridArc irradiation was performed by combining a dynamic conformal arc with two IMRT beams in each arc.

Posttreatment tumor size was evaluated with contrast-enhanced T1-weighted imaging performed every six months, and tumor volume was measured using iPlan®. Occurrence and deterioration of cerebral edema around the tumor were monitored using T2-weighted or FLAIR imaging. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, produced by the U.S. National Cancer Institute, Cancer Therapy Evaluation Program (http://ctep.cancer.gov).[8]

A partial response was defined as a ≥10% decrease in tumor volume, and a stable or partial response was considered to indicate tumor control. Progression was defined as tumor growth of ≥10%. Tumor progression and requirement of salvage therapy due to radiation injury were defined as uncontrolled.

Tissue type (atypical or not), age (≥50 years or < 50 years), sex, and tumor volume (≥30 mL or <30 mL) were analyzed as prognostic factors related to tumor control. The Cox proportional hazards model was used to identify factors affecting survival time. All statistical analyses were performed with EZR (Easy R; Saitama Medical Center, Saitama, Japan; and Jichi Medical University, Shimotsuke, Tochigi, Japan).[4]

RESULTS

Table 1 summarizes the clinical characteristics of the study population. Out of the 28 enrolled patients, nine were male, and 19 were female. The age range was 31–83 years (mean: 58.4 years), and tumor volumes ranged from 2.6 mL to 97.1 mL (mean: 29.7 mL). In four cases, meningioma was diagnosed based on imaging findings without surgical removal, and SRS was administered as the initial treatment, thus precluding histological diagnosis.

Table 2 summarizes the irradiation methods used. HybridArc irradiation was performed for all patients, and all tumors were covered with D_{95} 54 Gy/30 fractions to improve dose homogeneity across the target region. The observation period

Table 1: Summary of patients.

	Value
Sex, male/female	9/19
Age, mean (range), years	58.4 (31–83)
Prior surgery	24
Prior radiotherapy	1
Pathology	
Meningothelial meningioma	15
Fibrous meningioma	1
Transitional meningioma	1
Atypical meningioma	7
None	4
Tumor volume, mean (range), mL	29.7 (2.6–97.1)
Cranial nerve disturbance	
II	16
III, IV, VI	6
V	2
VII	0
VIII	2

after irradiation was 12–78 months (median: 36.0 months), and the tumor control rate at the final follow-up was 85.7% (partial response in 18, stable in 6, and uncontrolled in 4). Tumor control rates at 1, 2, and 5 years after radiotherapy were 92.6% (95% confidence interval [CI]: 0.743–0.982), 89.1% (95% CI: 0.700–0.964), and 82.8% (95% CI: 0.588–0.935), respectively [Figure 1].

Twenty-four cases (all except the four cases without histological diagnoses) were assessed for atypical or non-atypical meningioma [Figure 2]. The non-atypical meningioma group contained only one uncontrolled case, meaning the tumor control rate for non-atypical meningioma was 94.1% (95% CI: 0.650–0.992) at 1, 2, and 5 years after radiotherapy. The tumor control rates of atypical meningioma were 85.7% (95% CI: 0.334–0.979), 71.4% (95% CI: 0.258–0.20), and 53.6% (95% CI: 0.132–0.825) at 1, 2, and 5 years, respectively. The tumor control rate was significantly worse in the atypical meningioma group (P = 0.0395). Kaplan–Meier analyses revealed tumor volume of <30 mL to be associated with better tumor control than tumor volume of ≥30 mL, although the difference was not statistically significant (P = 0.062) [Figure 3]. Multivariate analysis of tumor control showed that tumor volume of ≥30 mL (P = 0.216, 95% CI: 0.024–2.332), age of 50 years or older (P = 0.999), and sex (P = 0.456, 95% CI: 0.0287–16.100) were not significant factors. Complications were observed in two patients, with deteriorated cerebral edema (CTCAE grade 3) in both cases.

Table 2: Summary of treatments.

Treatment	Value
Irradiation method, no. of cases	
HybridArc	28 (all)
Total dose (D95), Gy	54 (all)
Fraction number	30 (all)
PTV margin, no. of cases	
1 mm	18
1.5 mm	7
2 mm	3

PTV: Planning target volume

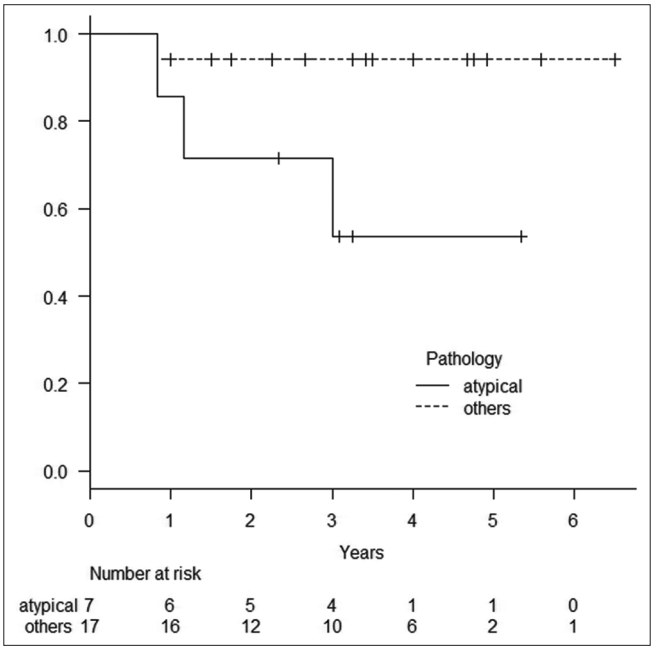

Figure 2: Graph showing the calculated Kaplan–Meier curves for tumor control for atypical meningioma and other histological types (excluding anaplastic meningioma). The tumor control rate was significantly worse in the atypical meningioma group (P = 0.0395).

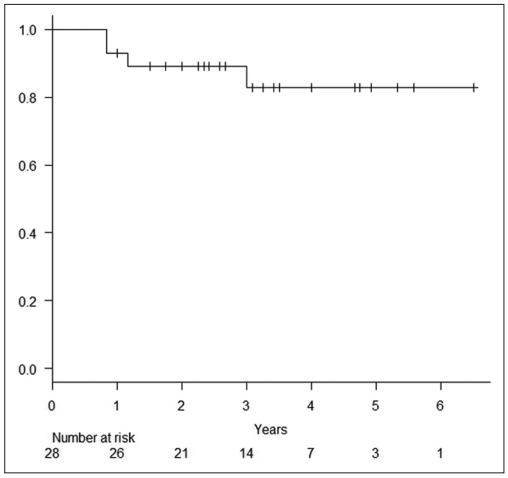

Figure 1: Graph showing the calculated Kaplan–Meier curve for tumor control. The tumor control rates at 1, 2, and 5 years after radiotherapy were 92.6%, 89.1%, and 82.8%, respectively.

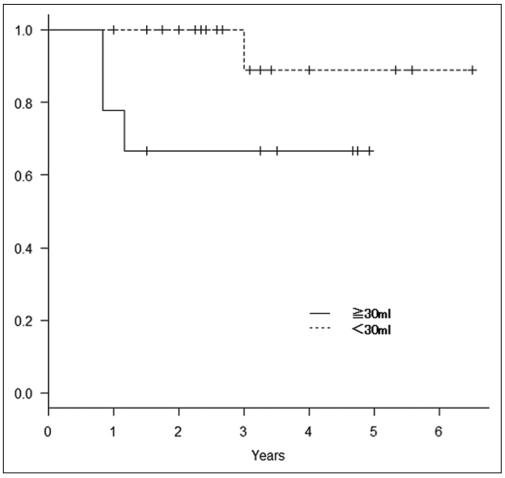

Figure 3: Graph showing the calculated Kaplan–Meier curves showing tumors of <30 mL tended to show better control than tumors of 30 mL or more (P = 0.062).

Four cases were uncontrolled in this study. Two cases (one case was an atypical meningioma) developed deteriorating cerebral edema around the tumor ten months after radiotherapy. However, this condition was present in both cases before treatment, so one patient underwent direct surgery while the other was transferred to the referring physician. The other two uncontrolled cases were categorized as such because salvage radiotherapy was required: One due to intracranial disseminated metastasis and the other due to tumor growth. Both of these cases were atypical meningiomas.

Compression of the optic nerve/chiasm or invasion of the cavernous sinus by the tumor was observed in 27 of the 28 cases. Visual field defects or visual impairment were observed in 16 patients, and diplopia was observed in six patients [Table 1]. Improvements in the visual field were observed in five cases, and improvement in diplopia was obtained in two cases (with overlap). No patients suffered deterioration of nerve function.

Radiation injury, identified by the presence of hyperintensity on T2-weighted imaging, was observed in two patients (7.1%, including the uncontrolled cases). Cerebral edema around the tumor was already present in both patients before radiotherapy, and deterioration occurred in both cases 10 months later.

Imaging follow-up at ≥36 months postoperatively was carried out for 15 patients. For these patients, the tumor volume before irradiation was 21.1 ± 15.2 mL, and the tumor volume at the final follow-up (rage: 36–78 months, mean: 49.2 months) was 15.3 mL ± 13.6 mL. A significant reduction in tumor volume was obtained in these 15 patients ($P = 0.01$, paired t-test).

DISCUSSION

Radiation tolerance of the optic nerve/optic chiasm

The most clinically significant issue in radiotherapy for parasellar-sphenoid ridge meningioma is avoidance of radiation damage to the optic nerve and optic chiasm. SRS studies show that these structures can tolerate around 8–12 Gy.[11] The optimal SRS dose for meningioma is 13–16 Gy or more;[10] therefore, delivering an adequate dose and preserving visual function is not possible in cases where the tumor compresses or involves the optic nerve and/or optic chiasm.[13]

The α/β values of the brain and optic nerve are thought to be as low as ~2 Gy, so each fraction must be <2 Gy to preserve visual function when treating large parasellar meningiomas. An analysis of 34 papers concluded that delivery of 10 Gy in a single session, 20 Gy in three fractions, or 25 Gy in five fractions resulted in a 1% risk of radiation-induced optic nerve/chiasm neuropathy (RION).[7] The optic nerve, however, can tolerate about 50 Gy with single 2 Gy conventional fractionated irradiation [2], and we have found RION to be extremely rare using the irradiation schedule of 54 Gy/30 fractions (1.8 Gy/fraction). Indeed, in the present study, although 16 patients had visual dysfunction before radiotherapy, none suffered deterioration of visual function during the irradiation period or follow-up period.

Stereotactic hypofractionated radiotherapy for meningioma

Stereotactic irradiation provides a steep dose gradient. Thus, if the tumor volume is not large and the distance between the tumor and optic nerve/optic chiasm is 2–3 mm or more, SRS with a marginal dose of 13–16 Gy is possible. However, if the tumor is in contact with or compressing the optic nerve/optic chiasm, the dose to the optic nerve on the tumor surface is almost equal to the marginal dose. Therefore, the dose in each fraction must be reduced to avoid RION. The optimal dose for meningiomas is about 25–30 Gy delivered in five fractions, and good tumor control can be expected.[3,9] If the tumor is only slightly in contact with or only partially compressing the nerve, treatment with hypofractionated irradiation is possible and desirable due to the short treatment period.

Stereotactic multi-fraction radiotherapy with the Novalis STx system

Tumor control of large skull base meningiomas that are difficult to remove completely surgically can often be obtained using stereotactic multi-fraction radiotherapy with fractions of 1.8–2 Gy and a total dose of 50–54 Gy [Table 3].[5,14,15] Such tumors often have an irregular shape, and the optic nerve and optic chiasm are impossible to identify. Optic-nerve-sheath meningiomas usually enclose the optic nerve, almost in the center of the tumor. Postoperative recurrence of tumors may involve the nerve, so homogeneous dose distribution is important to prevent over-irradiation of the involved optic nerve and optic chiasm. In such cases, IMRT using Novalis STx is the most suitable technique. Rotational body irradiation (dynamic conformal arc) is also possible. Still, IMRT offers the advantage of avoiding over-irradiation of the optic nerve and optic chiasm due to the almost homogenous dose distribution.[1]

Improvements in visual function can be expected after irradiation.[6] In our study, we observed visual field/visual impairment in 16 of 28 patients and diplopia in 6. Improvement of visual field defect and diplopia was obtained in five and two patients, respectively (with overlap). This study shows that in patients with skull base meningiomas with visual dysfunction, our treatment has the potential not only to control tumor growth but also to improve visual function.

Table 3: Summary of the reported studies of fractionated stereotactic radiotherapy for skull base meningiomas.

Author, Year	Method (no. of patients)	Total dose, Gy	Tumor volume (range), mL	Median follow-up period (range), months	Local control rate	Complication rate
Tanzler *et al*., 2011[15]	FSRT (103) CRT (41) IMRT (2)	Median 52.7	Greatest tumor dimension median 3 cm (0.1–9)	87.6 (7.2–264)	10 years: 96%	Radiation necrosis: 1%, Ophthalmologic complication: 2%, Peritumoral edema: 1%
Soldà *et al*., 2013[14]	FSRT (222)	50–55	Median 12.0 (0.4–183)	43 (3–144)	10 years: 86%	Transient mild visual deterioration: 1%, Deterioration of preexisting clinical features: 3.5%, Cognitive impairment: 1%, Cerebrovascular accident: 1%
Kaul *et al*., 2014[5]	FSRT (136)	Mean 56.95	Mean 22.4 (0.4–190.85)	44.9 (1–135)	10 years: 91.5%	CTCAE grade I and II symptoms (fatigue, headache, vertigo): 37.5%
Our series	HybridArc (28)	54	Mean 29.7 (2.6–97.1)	36 (12–78)	5 years: 82.8%	Radiation injury: 7.1%

FSRT: Fractionated stereotactic radiotherapy, CRT: Conventional radiotherapy, IMRT: Intensity-modulated radiotherapy, CTCAE: Common terminology criteria for adverse events.

Imaging follow-up data were available for a significant proportion of the study population, and the tumor volumes observed at the final follow-up indicated a gradual and long-term reduction in size.

In our series, four out of five uncontrolled cases were atypical meningiomas. However, SRS using HybridArc (54 Gy/30 fractions) proved highly effective for grade 1 meningiomas, suggesting a high likelihood of tumor control. Our findings indicate that the HybridArc technique is particularly effective for skull base meningiomas.

One drawback of this approach is the extended treatment timeline, which exceeds six weeks due to treatment plan preparation and verification. Radiation-induced injuries, manifested as T2-weighted hyperintensity, occurred in only two cases within our series. These injuries were observed in relatively large tumors that already exhibited cerebral edema before irradiation, necessitating careful management.

Conversely, grade 1 meningiomas without preexisting cerebral edema carried a significantly lower risk of radiation injury, even in the case of large tumors. Therefore, stereotactic multi-fraction radiotherapy utilizing HybridArc with Novalis STx is considered a safe treatment method for these tumors.

CONCLUSION

Stereotactic multi-fraction radiotherapy (54 Gy/30 fractions) with HybridArc using the Novalis STx system minimizes the risk of radiation damage, leading to visual dysfunction when treating relatively large skull base meningiomas that compress the optic nerve and optic chiasm. A high tumor control rate can be expected with the application of this system.

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Ethical approval

Not applicable.

Declaration of patient consent

Patients' consent not required as patients' identities were not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the

writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Eckert F, Clasen K, Kelbsch C, Tonagel F, Bender B, Tabatabai G, *et al.* Retrospective analysis of fractionated intensity-modulated radiotherapy (IMRT) in the interdisciplinary management of primary optic nerve sheath meningiomas. Radiat Oncol 2019;14:240.
2. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, *et al.* Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991;21:109-22.
3. Han J, Girvigian MR, Chen JC, Miller MJ, Lodin K, Rahimian J, *et al.* A comparative study of stereotactic radiosurgery, hypofractionated, and fractionated stereotactic radiotherapy in the treatment of skull base meningioma. Am J Clin Oncol 2014;37:255-60.
4. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013;48:452-8.
5. Kaul D, Budach V, Misch M, Wiener E, Exner S, Badakhshi H. Meningioma of the skull base: Long-term outcome after image-guided stereotactic radiotherapy. Cancer Radiother 2014;18:730-5.
6. Maclean J, Fersht N, Bremner F, Stacey C, Sivabalasingham S, Short S. Meningioma causing visual impairment: Outcomes and toxicity after intensity modulated radiation therapy. Int J Radiat Oncol Biol Phys 2013;85:e179-86.
7. Milano MT, Grimm J, Soltys SG, Yorke E, Moiseenko V, Tomé WA, *et al.* Single- and multi-fraction stereotactic radiosurgery dose tolerances of the optic pathways. Int J Radiat Oncol Biol Phys 2021;110:87-99.
8. National Cancer Institute. Common terminology criteria for adverse events (CTCAE) v5.0. Available from: https://ctep.cancer.gov/Protocoldevelopment/electronic_applications/ctc.htm#ctc_50 [Last accessed on 2022 Mar 17].
9. Navarria P, Pessina F, Cozzi L, Clerici E, Villa E, Ascolese AM, *et al.* Hypofractionated stereotactic radiation therapy in skull base meningiomas. J Neurooncol 2015;124:283-9.
10. Patibandla MR, Lee CC, Tata A, Addagada GC, Sheehan JP. Stereotactic radiosurgery for WHO grade I posterior fossa meningiomas: Long-term outcomes with volumetric evaluation. J Neurosurg 2018;129:1249-59.
11. Pollock BE, Link MJ, Leavitt JA, Stafford SL. Dose-volume analysis of radiation-induced optic neuropathy after single-fraction stereotactic radiosurgery. Neurosurgery 2014;75:456-60.
12. Robar JL, Thomas C. HybridArc: A novel radiation therapy technique combining optimized dynamic arcs and intensity modulation. Med Dosim 2012;37:358-68.
13. Shrieve DC, Hazard L, Boucher K, Jensen RL. Dose fractionation in stereotactic radiotherapy for parasellar meningiomas: Radiobiological considerations of efficacy and optic nerve tolerance. J Neurosurg 2004;101 Suppl 3:390-5.
14. Soldà F, Wharram B, De Ieso PB, Bonner J, Ashley S, Brada M. Long-term efficacy of fractionated radiotherapy for benign meningiomas. Radiother Oncol 2013;109:330-4.
15. Tanzler E, Morris CG, Kirwan JM, Amdur RJ, Mendenhall WM. Outcomes of WHO Grade I meningiomas receiving definitive or postoperative radiotherapy. Int J Radiat Oncol Biol Phys 2011;79:508-13.

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