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ORIGINAL ARTICLE

The long-term outcome of CyberKnife-based stereotactic radiotherapy for central skull base meningiomas: a single-center experience

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Abstract

Few reports exist demonstrating the effects of stereotactic radiotherapy (SRT) on the central skull base meningiomas (CSMs). A retrospective analysis of 113 patients was performed. The median age was 62 (IQR 50–72) years old, and 78 patients (69%) were female. Upfront SRT was performed in 41 (36%), where 17 (15%) patients were asymptomatic. The other SRT was for postoperative adjuvant therapy in 32 (28%), and for the recurrent or relapsed tumors in 40 (35%) patients. Previous operation was done in 74 patients (66%). Among the available pathology in 46 patients, 37 (80%) were WHO grade I, 8 (17%) were grade II, and 1 (2%) was grade III. The median prescribed dose covered 95% of the planning target volume was 25 (IQR 21–25) Gy, and the median target volume was 9.5 (IQR 3.9–16.9) cm^3. The median progression-free survival (PFS) was 48 (IQR 23–73) months and 84% and 78% were free of tumor progression at 5 and 10 years respectively. The median follow-up was 49 (IQR 28–83) months. PFS was better in grade I than grade II ($p = 0.02$). No other baseline factors including the history of previous operation were associated with PD or PFS. Adverse events of radiation therapy were radiation-induced optic neuropathy (0.9%), and cerebral edema (4.4%). Asymptomatic cavernous carotid stenosis was found in three (2.7%), five (4.4%) underwent ventriculoperitoneal shunt placement for normal pressure hydrocephalus, and five (4.4%) died. SRT is useful for the management of CSMs with a low rate of adverse events.

Keywords CyberKnife · Meningioma · Parasellar · Skull base

Introduction

Meningiomas of parasellar or sellar regions are sometimes difficult to treat. Some of them are surgically inaccessible, and complete excision remains challenging [1, 2]. Although many reports exist regarding the single-fraction radiosurgery with gamma knife, few large series reports exist regarding hypofractionated stereotactic radiotherapy (hSRT) using a CyberKnife system [1]. CyberKnife is a robotic frameless radiosurgery system equipped with real-time imaging guidance, which can deliver non-surgical multisession stereotactic treatments and automated targeting correction with sub-millimeter accuracy [3, 4]. Here, we report our facility's outcome of hSRT on the central skull base meningiomas (CSMs), which are defined as those involving parasellar, sellar, petroclival, planum sphenoidale, and medial third of sphenoid ridge regions.

Methods

Patient selection and tumor characteristics

Consecutive patients who received hSRT for CSMs in the period from 2010 to 2019 were identified and recorded. Inclusion criteria were pathologically confirmed CSMs and central skull base tumors which were most likely to be meningioma (for those not operated on). As the authors' institution was a referral center for SRT, quite a few patients were referred by other hospitals. Consequently, among the previously operated patients in the other institutions, some pathological information was limited to the diagnosis of meningioma, and no further information on the specific subtype, or WHO grade, was available or written in the letter of reference. For non-operated cases, radiological diagnosis of meningioma was made based on contrast-enhanced

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T1-weighted magnetic resonance imaging (MRI) and computed tomography (CT). The typical radiological findings were extra-axial well-demarcated tumors which enhance relatively homogeneously with or without dural tail and calcification. We radiologically supposed the diagnosis of WHO I meningioma if the tumor volume increase is less than 10% of the last volume, in two consecutive MRI at least 6 months apart. Since we aimed to reveal the effects of SRT on radiation-virgin CSMs, we excluded those who had previous radiation therapy for CSMs and those whose follow-up was 6 months or less. Patients with progressive neurological deterioration from CSMs were treated surgically before given SRT.

Patient evaluation and tumor response

Patients' follow-ups were done almost annually at our institution or primary hospitals for those who live far away. For those whose follow-ups were made in their primary hospitals, the clinical and MRI data were sent to our institution on their every visit. We performed radiological follow-up by contrast-enhanced MRI unless patients had a poor renal function, in which case we performed plain MRI or CT for those with contraindication to MRI. In the regular MRI, magnetic resonance angiography was included in the routine sequence. Based on the MRI or CT, we defined the response to SRT into three categories of partial response (PR), stable disease (SD), and progressive disease (PD) based on the longest diameter of the tumor. PR was defined as a decrease in the diameter of 10% or more, PD was defined as an increase of 10% or more or an increase of 5 mm or more whichever is smaller, and SD as not being PR or PD. The senior author KS evaluated the tumor response into the three categories, which was confirmed by the primary author SH. We defined adverse events (AE) as radiation-induced if no apparent cause other than radiation was identified and radiation was the most likely contributing factor. AE was graded based on the Common Terminology Criteria for Adverse Events (CTCAE) [5].

SRT at our facility

Target volumes were delineated on thin-slice CT with or without gadolinium-enhanced MRI. We illustrate a typical treatment plan in Fig. 1. Since the linear-quadratic model does not apply to hypofractionated therapy (3–5) [6], the dose selection was chosen based on the senior author's (KS) past experiences. In planning the treatment, we selected the prescription dose and fractionation according to the size and site of the lesions. We tried to achieve doses of radiations equivalent to 13 Gy in a single fraction, or 54 Gy in 30 fractions. Generally, 21 Gy/3 fractions were used to treat lesions less than 2 cm, 25 Gy/5 fractions were used for 2–3 cm, and 28 Gy/7 fractions were used for larger than 3 cm. For those which involved or proximal to organs at risk, like optic apparatus and the patients' clinical condition, the prescribed dose

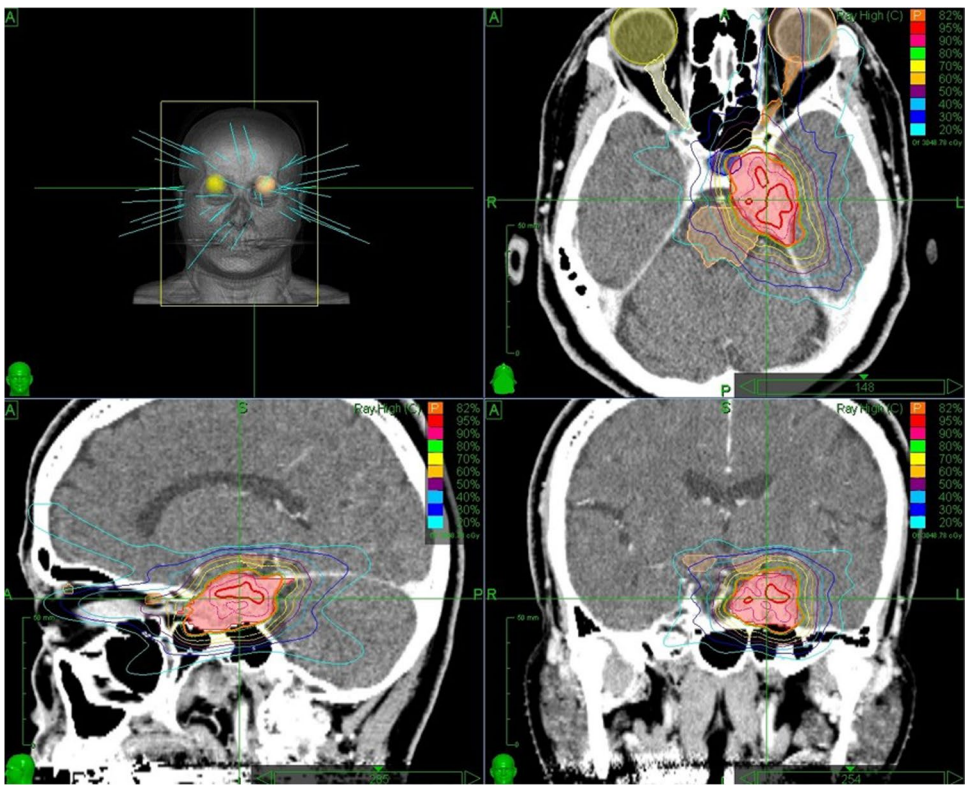


Fig. 1 An example of a treatment plan providing the isodose curves in a 64-year-old female with left petroclival meningioma

and fractionations were further adjusted accordingly. We did not change the prescription dose between WHO grade I and grades II–III. It is our facility's way to treat higher-grade meningiomas in the same way as low-grade ones. The dura or the underlying bone near the CSMs was not included in the target volume.

Statistical analysis

Statistical analyses were carried out using SPSS version 25.0 (IBM Inc., Armonk, NY, USA). Shapiro–Wilk test of normality was used to tell parametric data from nonparametric data. From the acquired data, univariate analyses by binary logistic regression were performed to identify prognostic factors for local control (LC). Kaplan–Meier method was used to draw progression-free survival (PFS) curves from the last day of SRT. PFS curves were evaluated by a log-rank test based on various factors (age, sex, the status of the previous operation, pathology grade, and form of SRT). A p-value of 0.05 or less was considered statistically significant.

Our institutional review board did not require informed consent for study participation because this study relied on information obtained as part of routine clinical practice.

Results

A total of 324 patients were identified. Eighty-seven patients were excluded for meningiomas other than the central skull base. One hundred one patients were excluded for the history of previous radiation. And 23 patients were excluded for follow-up data not being available for more than 6 months. As a result, a total of 113 were included in the analysis (Table 1). Females constituted 69% of the patients. The previous operations were performed in 74 cases (66%), which included two biopsies, and pathology information was available in 46 cases. Upfront SRT was performed in 41 (36%) patients, and among them, 17 (15%) were incidentally found asymptomatic CSMs. All the 41 CSMs were clinically and radiologically consistent with WHO grade I meningiomas. The parameters of radiation therapy are summarized in the lower rows of Table 1.

Table 1 Summary of baseline patient characteristics and CyberKnife therapy (CKRT)

Total	113
Age (median) (IQR) (yr)	62 (50–72)
Sex (male:female)	35:78
Previous operation	74 (66%)*
Pathology	46
Grade 1	37 (80%)
Grade 2	8 (17%)
Grade 3	1 (2%)
Form of CKRT	
Upfront Tx	41 (36%)
Asymptomatic	17 (15%)
Adjuvant Tx	32 (28%)
Tx for recurrent or relapsed tumor	40 (35%)
Time from the last surgery to CKRT (mos)	
Adjuvant Tx (median) (IQR)	3.5 (2.5–6.0)
Tx for recurrent or relapsed tumor (median) (IQR)	29.0 (16.0–75.0)
Treatment characteristics (median) (IQR)	
$D_{95\%}$ (cGy)	2500 (2100–2500)
Fraction	5 (3–5)
Target diameter (cm)	2.6 (1.9–3.1)
Prescription isodose (%)	79.5 (76–82)
Target volume (cm^3)	9.5 (3.9–16.9)
Target covered (cm^3)	9.0 (3.7–16.1)
Target covered (%)	95.6 (95.2–96.1)
Prescribed isodose volume/target isodose volume	1.34 (1.22–1.42)
New conformity index	1.39 (1.27–1.49)
Max dose/prescribed dose	1.26 (1.22–1.32)

Abbreviation: *IQR*, interquartile range; *yr*, years old; *Tx*, treatment; *mos*, months

*Includes two biopsy cases, whose CKRT was regarded as upfront CKRT

Progression-free survival and analysis on the prognostic factors

The outcome is summarized in Table 2. LC (PR + SD) was achieved initially in 98%. Out of the 111 tumors in LC, 14 (12%) resulted in PD later. No patients who underwent upfront SRT for incidentally found asymptomatic CSMs resulted in PD. On the other hand, among the postoperative patients with documented growing tumors, 15% (6/40) resulted in PD. For the total of 16 PD cases, 10 (63%) underwent SRT again, five (31%) were treated conservatively, and the other one (6%) was surgically treated.

PFS curves are shown in Fig. 2 (estimated mean PFS 107 months, 95% CI 98–115 months). PFS at 3, 5, and 10 years were 87%, 84%, and 78% respectively. And most of the local control failure occurred within 3 years after SRT (Fig. 2a). PFS showed a difference depending on the pathological grade ($p = 0.06$). The p-value was 0.02 by pairwise comparison between WHO grade I and II (Fig. 2b). PFS showed no significant difference depending on the sex ($p = 0.33$), history of operation ($p = 0.13$), or form of SRT ($p = 0.31$). Regarding the form of SRT, p-value was 0.11 by pairwise comparison between upfront SRT (mean 98 months, 95% CI 89–107 months) and adjuvant SRT (mean 88 months, 95% CI 72–103 months). Univariate analysis for the status of PD resulted in no variables to

Table 2 Outcome after CyberKnife radiation therapy (CKRT)

Radiological outcome	
PR	46 (41%)
SD	51 (45%)
SD➔ PD	6 (5%)
PR➔ PD	8 (7%)
PD	2 (2%)
Radiological outcome based on the form of SRT (PR: SD: PD)	
Upfront Tx	21: 16: 4
Asymptomatic	11: 6: 0
Adjuvant Tx	10: 16: 6
Tx for recurrent or relapsed tumor	15: 19: 6
PFS (median) (IQR) (mos)	48 (23–73)
OS (median) (IQR) (mos)	49 (28–83)
Adverse effects of radiation therapy	
Visual decline	1 (0.9%)
Peritumoral edema	5 (4.4%)
Other post-CKRT outcome	
Cavernous carotid stenosis (asymptomatic)	3 (2.7%)
Ventriculoperitoneal shunt placement	5 (4.4%)
Dead	5 (4.4%)

Abbreviation: *PR*, partial response; *SD*, stable disease; *PD*, progressive disease; *Tx*, treatment; *IQR*, interquartile range; *mos*, months

be statistically significant including age ($p = 0.28$), sex ($p = 0.57$), previous operation ($p = 0.16$), pathology grade ($p = 0.24$), time to SRT ($p = 0.13$), target volume ($p = 0.24$), and form of SRT ($p = 0.49$).

Adverse outcome

Adverse outcomes were classified into AE of radiation therapy and the rest (other post-SRT outcomes) (Table 2). The latter included carotid artery occlusion, normal pressure hydrocephalus requiring ventriculoperitoneal shunt placement, and death, all of which were not solely due to CKT.

As for the AE of radiation therapy, one patient (0.9%) experienced a visual decline (radiation-induced optic neuropathy) at 42 months from the SRT (CTCAE grade 1). She had a CSM involving the tuberculum sella, sella turcica, cavernous sinus, and sphenoid ridge. The maximal dose to the optic pathway, which was outside the prescription isodose line, was 2614 cGy divided into three fractions. The patient's vision improved and stayed good for a while before it deteriorated. No other cranial neuropathies or new or worsening pituitary dysfunction was identified. Peritumoral edema (CTCAE grade 3) occurred in five patients (4.4%), which was found on the regular outpatient visit with scheduled MRI. All of them had tumors attached in the anterior clinoid process. All five tumors were locally controlled (two PR and three SD). Three were symptomatic with headache, who were treated with temporary glucocorticoid steroid administration, and the other asymptomatic two were observed. These peritumoral edemas were observed at the mean of 5 (95% CI 2–8) months and improved at the mean of 12 (95% CI 6–18 months) after SRT. Among the 17 patients who underwent upfront SRT for asymptomatic CSMs, two (11%) patients resulted in AE of radiation therapy (peritumoral edema).

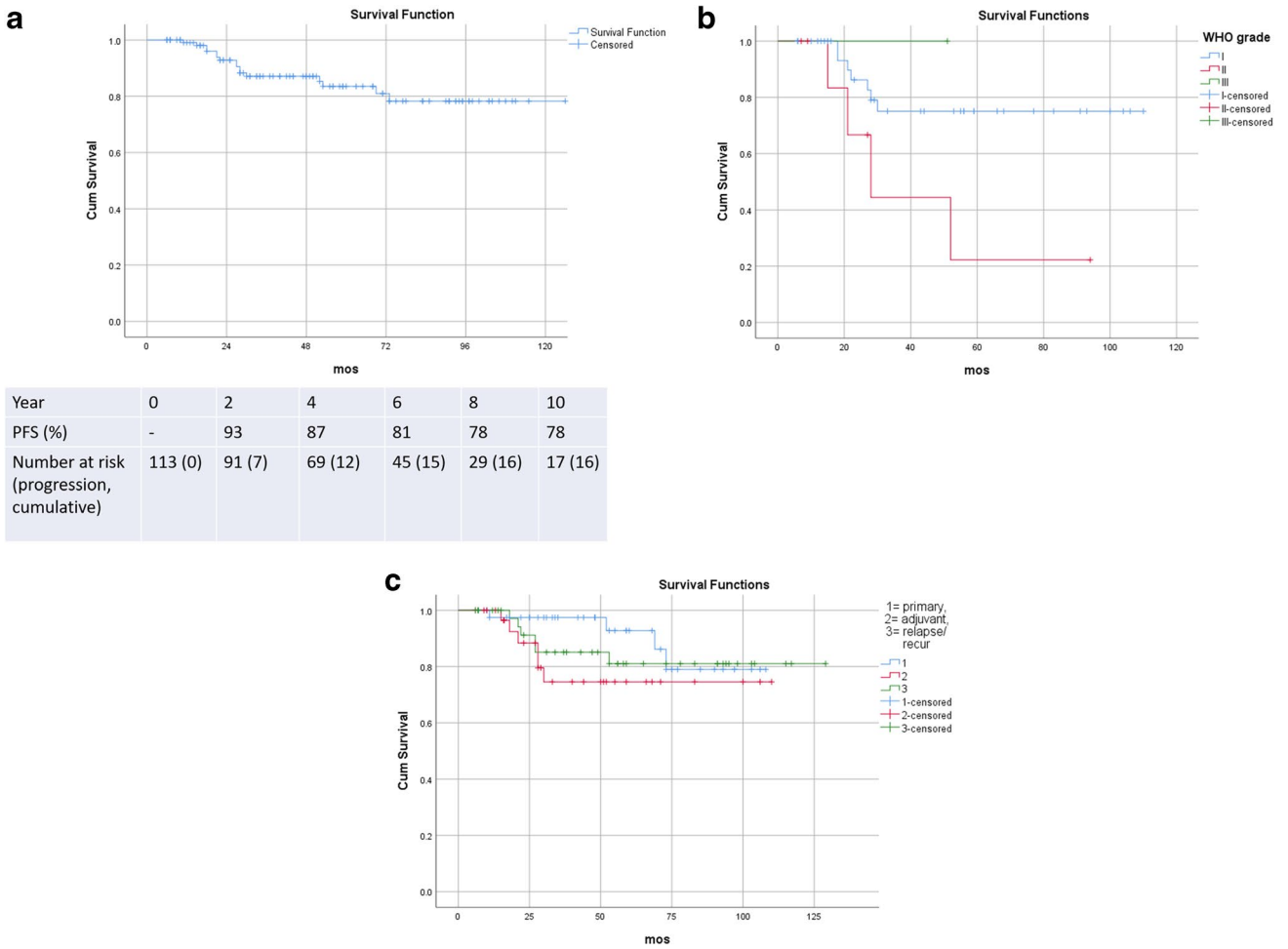
As for other post-SRT adverse outcomes, the stenosis or occlusion of the cavernous segment of the internal carotid artery (CTCAE grade 2 or less in "injury to carotid artery") occurred in three patients (2.7%), which was found incidentally in the regular MRI follow-up, which included magnetic resonance angiography in the routine sequence at the mean of 46 (SD ± 30) months from the SRT. All patients were asymptomatic from the stenosis and their tumor control status was SD. Five patients (4.4%) underwent ventriculoperitoneal shunt (VPS) placement for normal pressure hydrocephalus (NPH) (CTCAE grade 3) at the mean of 6 (95% CI 4–8) months from SRT. All had a history of operation before SRT. Five patients (4.4%) were dead at the last follow-up. Four were due to tumor progression (tumor-related death) and the other one was due to acute exacerbation of chronic congestive heart failure.

Discussion

We analyzed a large series of SRT outcomes on the CSMs. The median of PFS was 48 (IQR 23–73) months with a 5-year local control rate over 80% (Table 2). A significant difference was observed in PFS between grades I and II CSMs (Fig. 2b). There was no difference in PFS depending on the history of previous surgery (Fig. 2c). No variables significantly predicted PD. Cranial neuropathies rarely occurred (0.9%); however, we have to be careful of peritumoral edema (4.4%) especially that the CSMs' main attachment is around the anterior clinoid process. Although CSMs are frequently formidable lesions to deal with, SRT provided an effective local control rate (LCR) with a low rate of AE (Table 2).

The radiological outcome of stereotactic radiotherapy

To the best of our knowledge, no large case series exists that featured SRT outcomes on the CSMs. From similar studies where SRT outcome was assessed on the skull base meningiomas, 1-year, 3- year, and 10-year LCRs were 99.4, 96.8–98, and 80.3% respectively, which was comparable to our results [1, 7]. Another study on intracranial meningiomas showed a 2-year LCR of 81%, which was a bit lower than ours (93.8%) [8]. On the other hand, single-fraction stereotactic radiosurgery (SRS) by gamma



Year	0	2	4	6	8	10
PFS (%)	-	93	87	81	78	78
Number at risk (progression, cumulative)	113 (0)	91 (7)	69 (12)	45 (15)	29 (16)	17 (16)

Fig. 2 Kaplan–Meier curve of progression-free survival (PFS) overall (**a**). Kaplan–Meier curve of PFS based on the pathology grade ($p=0.05$ overall, $p=0.02$ between WHO grades I and II) (**b**). Kaplan–Meier curve of PFS based on different forms of treatment ($p=0.32$ overall, $p=0.11$ between upfront and adjuvant therapy) (**c**)

knife on the sellar and parasellar meningiomas showed LCRs of 98%, 88%, and 82% at 3-year, 5-year, and 10-year respectively. Compared to our results, SRS provided a little better LCR than SRT [2]. Another study of SRS on CSMs showed LCRs of 98.2%, 93.4%, 88.9%, and 76.2% at 2-year, 4-year, 6-year, and 10-year respectively [9]. Comparing their study to ours, their result was a little better than ours as well. However, it must be noted that both studies [2, 9] on SRS included only benign (WHO grade I) meningiomas, and that grade II/III meningiomas were excluded. Consequently, it is understandable that the LCR was better than ours. The comparisons of similar past studies to ours are summarized in Table 3. Having said that, SRS may be better than hypofractionated SRT (hSRT) in terms of LC.

Adverse outcome

The major AE we keep in mind is that on the vision. In our cohort, the visual decline was observed in one patient (0.9%). This rate is lower than 3% in a study of SRS on the sellar and parasellar meningiomas [2]. The risk of damage to the other cranial nerves was 0%. As for the pituitary function, no patients experienced new or worsening hypopituitarism as opposed to the past studies on SRS (0.5–1.8%) [2, 9]. The comparisons of AE are summarized in Table 3. As shown in the table, SRT seems to have a lower AE than SRS. However, since the median follow-up of the SRT is shorter than SRS, further observation of the SRT arm should be done to show that SRT is better in terms of AE. In addition to the visual change,

Table 3 Comparison of our cohort's progression-free survival (PFS) and adverse effects with other recent large case series on the skull base meningiomas

	Treatment modality	WHO grade/locations	*N*	Median follow-up (mos)	Local control rate	Adverse effects
Our study	CyberKnife (hSRT)	I–III/central skull base	113	49	5-year PFS 83.5%, 10-year PFS 78.3%	Worse or new CN deficit 0.9%, transient peritumoral edema 4.4%
Conti et al., 2020 [10]	CyberKnife (hSRT)	I/anterior cranial fossa, parasellar, posterior cranial fossa	156	36	5-year PFS 90%, 10-year PFS 80.8%	Trigeminal neuralgia 5.7%, carotid occlusion 0.6%, peritumoral edema 0.6%
Conti et al., 2019 [11]	CyberKnife (hSRT)	*/Anterior, middle, and posterior skull base	205	33	3-year PFS 96.8%, 10-year PFS 80.3%	New CN deficits 7.8%, carotid artery occlusion 0.5%
Marchetti et al., 2019 [7]	CyberKnife (hSRT)	I/Anterior or a medium skull base close to the optic apparatus	167	51	3-year PFS 98%, 5-year PFS 94%, 8-year PFS 90%	Visual worsening rate 3.7%
Patibandla et al., 2017 [12]	Gamma knife (SRS)	I/central skull base	219	72	6-year PFS 88.9%, 10-year PFS 76.2%	Worse neurologic symptoms 20.5%, worse hypopituitarism 0.5%
Sheehan et al., 2014 [9]	Gamma knife (SRS)	I/Parasellar and sellar	763	66.7	5-year PFS 95%, 10-year PFS 82%	Worse or new CN deficit 9.6%, worse or new hypopituitarism 1.8%

Abbreviation: *hSRT*, hypofractionated stereotactic radiotherapy; *SRS*, stereotactic radiosurgery

*Pathology grade not mentioned in the literature

we need to keep in mind peritumoral edema as a potential side effect. Reviewing the past literature, cerebral edema after therapeutic radiation occurred in 4–19% depending on the studies [11–17]. The risk factors were tumor location, radiation dose, and tumor volume among others [12]. In our case, all the five edemas (4.4%) occurred in CSMs near the anterior clinoid process, and most patients (80%) had some degree of headache.

As for the other adverse outcomes, we found cases with cavernous carotid stenosis (CCS) and cases with NPH which underwent VPS. CCS may be due to chronic occlusion of the artery by the encasing tumor or the late-phase AE of radiation. NPH requiring VPS may be due to high protein contents in the cerebrospinal fluids as a result of the underlying CSMs, AE of surgical resection, AE of radiation, or idiopathic NPH. Consequently, these two adverse outcomes, as well as death, were not necessarily AE of radiation therapy alone (Table 2). CCS was asymptomatic in all three patients (2.7%). In a similar recent study on the effect of SRS on the internal carotid artery, nine patients (5.8%) out of 155 cavernous sinus meningioma patients resulted in CCS [18]. In their cohort, symptomatic CCS were rare, which is in line with our result. Regarding NPH, since all patients developed and underwent VPS within 1 year after the last SRT, we need to monitor them for any signs of NPH in their first year especially if they had a previous history of surgical resection.

Treatment suggestion

Comparing our data and the past literature on SRS, hSRT has a comparable treatment effect on PFS with a low risk of AE. Since gross total resection of CSMs, while preserving important structures, sometimes pose a great challenge, for incidentally found CSMs, in addition to observation and surgical resection, upfront hSRT may be a reasonable choice as well as GKS [10, 19]. All asymptomatic patients who underwent upfront hSRT resulted in local control (100%). However, we need to keep in mind the possibility of transient new-onset or worsening of peritumoral edema (11%, two patients out of 17 in our cohort) especially if the tumor involves the anterior clinoid process. As for symptomatic CSMs, (1) maximal safe resection followed by hSRT or (2) upfront hSRT is a reasonable treatment option depending on the degree of neurologic worsening. Since PFS was better in grade I than grade II CSMs ($p = 0.02$), all grade II CSMs should be followed by adjuvant hSRT to improve PFS. In our cohort, no variables (age, sex, previous operation, time to SRT, target volume, and form of SRT) except pathology grade were found to be statistically significant in affecting PFS. This result is in line with a similar past study [2]. Considering the effectiveness of hSRT on the CSMs regardless of the previous status of the operation, we may not have to stick to achieving Simpson grades I–III

resection at the risk of irreversible surgical complications [20]. Finally, as stated in the result section, although not being significant, we found some *trends* in upfront SRT ($p = 0.11$) having longer PFS than adjuvant hSRT. It may be possible that if pathology data had been available in more patients, the *p*-value would have been significant. For CSMs clinically and radiologically consistent with WHO grade I meningioma, upfront SRT would be suitable for asymptomatic patients.

Limitation

Several limitations exist in this study. First, since our facility is a referred center for hSRT, not all the detailed clinical information was available. We referred the patients' information to their primary hospitals; however, we were not able to obtain a reply from all. For this reason, we excluded those with no more than 6 months' follow-up. Second, the histopathological subtypes (WHO grade) of meningioma were not available in some surgically treated patients. Consequently, information on the WHO grade was missing in the 28 (37%) patients. Finally, since we have many censored data on PFS curves, we have to interpret the data carefully.

Conclusions

SRT is an effective and safe treatment option for CSM management especially for WHO grade I CSMs. PFS is better in grade I patients than grade II CSMs.

Author contribution All authors read and approved the final manuscript. SH made a study design, collected patient data, and drafted and revised the manuscript. KK contributed to revising the original draft. KS and SI were the supervisors.

Data availability Data transparency was confirmed.

Code availability Not applicable.

Declarations

Ethical approval This study was done under our institutional review board's approval and did not require patient consent.

Consent to participate Our institutional review board did not require informed consent for study participation because this study relied on information obtained as part of routine clinical practice.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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