The Long-Term Outcome of Cyberknife Radiotherapy for Central Skull Base Meningiomas: A Single-Center Experience

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Abstract

Few reports exist demonstrating the effects of CyberKnife radiotherapy (CKRT) on the central skull base meningiomas (CSMs). Retrospective analysis of 113 patients were performed. The median age was 62 (IQR 50 – 72) years old, and 78 patients (69%) were female. Upfront CKRT was performed in 41 (36%), where 17 (15%) patients were asymptomatic. The other CKRT 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%) were grade III. The median prescribed dose covered 95% of the planning target volume was 2500 (IQR 2100 – 2500) cGy and the median target volume was 9.5 (IQR 3.9 – 16.9) cm³. The median PFS was 48 (IQR 23 – 73) months and 84% and 78% were free of tumor progression at five, 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 was 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. CKRT is useful for the management of CSMs with low rate of adverse events.

Introduction

Meningiomas of parasellar or sellar regions are sometimes difficult to treat. Some of them are surgically inaccessible, and complete excision remains challenging.[15, 1] Although many reports exist regarding on the gamma knife radiation treatment, few large series reports regarding on the CyberKnife radiation treatment (CKRT) exist.[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.[4, 3] Here we report our facility’s outcome of CKRT on the central skull base meningiomas (CSMs).

Methods

We defined CSMs as meningiomas involving parasellar, sellar regions as well as petroclival, planum sphenoidale, and medial third of sphenoid ridge regions. Consecutive patients who received CKRT 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). As the authors’ institution were referral center for CKRT, quite a few patients were referred by other hospitals. Consequently, among the previously-operated patients in the other institutions, some pathological information were limited to the diagnosis of meningioma and no further information on the specific subtype, or WHO grade were available or written in the letter of reference. For non-operated cases, radiological diagnosis of meningioma was made based on contrast enhanced magnetic resonance imaging (MRI) and computed tomography. The typical radiological findings were extra-axial well-demarcated tumor which enhance relatively homogeneously with or without dural tail and calcification.
We excluded those who underwent any kinds of radiation treatment (gamma knife, conventional radiation, boron neutron capture therapy) for CSMs and those whose follow-up was six months or less. Based on the MRI, we defined the response to CKRT into three categories of partial response (PR), sustained disease (SD), and progressive disease (PD) based on the longest diameter of tumor. Patients with progressive neurological deterioration from CSMs were treated surgically before given CKRT. We did not change the prescription dose between WHO grade I and II-III. It is our facility's way to treat higher grade meningiomas as the same way as low grade ones. The dura or the underlying bone near the CSMs were not included in the target volume. Patients' follow-up were done almost annually in 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 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. 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).[11]

Statistical analyses were carried out using SPSS version 25.0 (IBM Inc., Armonk, NY, USA). Shapiro-Wilk test of normality was used to tell data parametric from nonparametric. From the acquired data, univariate analysis 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 CKRT. PFS curves were evaluated by log rank test based on various factors (age, sex, the status of previous operation, pathology grade, and form of CKRT). A p-value of .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 138 patients were identified. Twenty five patients were excluded for previous history of radiation to the central skull base or follow-up data not being available for more than six months. And a total of 113 were included in the analysis (Table 1). Female constituted 69% of the patients. Previous operation were performed in 74 cases (66%), which included two biopsy, and pathology information were available in 46 cases. Upfront CKRT was performed in 17 (15%) incidentally found asymptomatic CSMs. The parameters of CyberKnife is summarized at the lower rows of the Table 1.
Table 1
Summary of baseline patient characteristics and CyberKnife therapy

| 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 | 41 (36%) |
| Upfront Tx | 17 (15%) |
| Asymptomatic | 32 (28%) |
| Adjuvant Tx | 40 (35%) |
| Tx for recurrent or relapsed tumor | |
| Time from the last surgery to CKRT (mos) | 3.5 (2.5–6.0) |
| Adjuvant Tx (median) (IQR) | 29.0 (16.0–75.0) |
| Tx for recurrent or relapsed tumor (median) (IQR) | |

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

Abbreviation: PTV, planning target volume
| Treatment characteristics (median) (IQR) | 113 |
|-----------------------------------------|-----|
| 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) |

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

Abbreviation: PTV, planning target volume

**Radiological outcome**

The outcome is summarized in the 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 CKRT for incidentally found CSMs resulted in PD. For the total of 16 PD cases, 10 (63%) underwent CKRT again, five (31%) were treated conservatively, and the other one (6%) was surgically treated.
| Radiological outcome | 46 (41%) |
|----------------------|---------|
| PR                   | 51 (45%)|
| SD                   | 6 (5%)  |
| SD◊ PD               | 8 (7%)  |
| PR◊ PD               | 2 (2%)  |
| PD                   |         |
| Adverse effects of radiation therapy | 1 (0.9%) |
| Visual decline       | 5 (4.4%)|
| Peritumoral edema    |         |
| Other post-CKRT outcome | 3 (2.7%) |
| Cavernous carotid stenosis (asymptomatic) | 5 (4.4%) |
| Ventriculoperitoneal shunt placement | 5 (4.4%) |
| Dead                 |         |
| PFS (median) (IQR) (months) | 48 (23–73) |
| OS (median) (IQR) (months) | 49 (28–83) |

**Adverse outcome**

Adverse outcomes were classified into AE of radiation therapy and the rest (other post-CKRT outcome) (Table 3). The latter included carotid artery occlusion, normal pressure hydrocephalus requiring ventriculoperitoneal shunt placement, and death, all of which were not solely due to CKT.
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 I – III/ central skull base | 113 | 49 | 5-year PFS 83.5% | Worse or new CN deficit 0.9%, transient peritumoral edema 4.4% |
| **Alfredo et al., 2019 [1]** | CyberKnife */ 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% |
| **Patibandla et al., 2017 [12]** | Gamma knife 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[15]** | Gamma knife 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% |

*pathology grade not mentioned in the literature

As for AE of radiation therapy, one patients (0.9%) experienced visual decline (radiation-induced optic neuropathy) at 42 months from the CKRT (CTCAE grade 1). She had a CSM involving the tuberculum sella, sella turcica, cavernous sinus, and sphenoid ridge. The maximal dose to the optic chiasm was 2614 cGy. The patient’s vision improved and stayed good for a while before deteriorated. No other cranial neuropathies or new or worsening of 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 the 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 edema 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 CKRT. Among the 17 patients who underwent upfront CKRT for asymptomatic CSMs, two (11%) patients resulted in AE of radiation therapy (peritumoral edema).

As for other post-CKRT 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 CKRT. All patients were asymptomatic from the stenosis and their tumor control were 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 CKRT. All had a history of operation before CKRT. 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.

**Progression-free survival and analysis on the prognostic factors**

PFS curves are shown in the Fig. 1 (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 three years after CKRT (Fig. 1A). 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. 1B). PFS showed no significant difference depending on the sex (p = 0.33), history of operation (p = 0.13), or form of CKRT (p = 0.31). Regarding the form of CKRT, p-value was 0.11 by pairwise comparison between upfront CKRT (mean 98 months, 95% CI 89–107 months) and adjuvant CKRT (mean 88 months, 95% CI 72–103 months). Univariate analysis for the status of PD resulted in no variables to be statistically significant including age (p = 0.28), sex (p = 0.57), previous operation (p = 0.16), pathology grade (p = 0.24), time to CKRT (p = 0.13), target volume (p = 0.24), and form of CKRT (p = 0.49).

**Discussion**

We analyzed a large series of CKRT outcome on the CSMs. The median of PFS was 48 (IQR 23–73) months with 5-year local control rate over 80% (Table 3). A significant difference was observed in PFS between grade I and II CSMs (Fig. 1B). There was no difference in PFS depending on the history of previous surgery (Fig. 1C). No variables significantly predicted PD. Cranial neuropathies rarely occurred (0.9%), however we have to be careful of peritumoral edema (4.4%) especially CSMs’ main attachment is around the anterior clinoid process. Although CSMs are frequently formidable lesion to deal with, CKRT provided an effective local control rate (LCR) with low rate of AE (Table 2).

**Radiological outcome of CKRT**

To the best of our knowledge, no large case series exist that featured CKRT outcome on the CSMs. From a similar study where CKRT outcome was assessed on the skull base meningiomas, 1-, 3-, and 10-year LCR were 99.4, 96.8, and 80.3% respectively, which was comparable to our results.[1] Other study on intracranial meningiomas showed 2 year LCR of 81%, which was a bit lower than ours (93.8%).[8] On the other hand, gamma knife radiation surgery (GKS) on the sellar and parasellar meningiomas showed LCR of 98%, 88%, and 82% at 3-, 5-, and 10-year respectively. Compared to our results, GKS provided a little better LCR than CKRT.[15] Another study of GKS on CSMs showed LCR of 98.2%, 93.4%, 88.9%, and 76.2% at 2-, 4-, 6-, and 10-year respectively.[12] Comparing their study to ours, their result was a little better than ours as well. However, it must be noted that both studies[12, 15] on GKS included only benign (WHO grade I) meningiomas, and that grade II/ III meningiomas were excluded. Consequently it is
understandable that LCR was better than ours. The comparisons of similar past studies to ours is summarized in the Table 3. Having said that, GKS may be better than CKRT in terms of LC.

**Adverse outcome**

The major AE we keep in mind is that on the vision. In our cohort, visual decline was seen in one patient (0.9%). This rate is lower than 3% in a study of GKS on the sellar and parasellar meningiomas [15]. 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 gamma knife (0.5–1.8%). [15, 12] The comparisons of AE is summarized in the Table 3. As shown in the table, CKRT seems to have lower AE than GKS. However, since the median follow-up of the CKRT is shorter than GKS, further observation of CKRT arm should be done to show that CKRT is better in terms of AE. In addition to the visual change, 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. [10, 5, 9, 2, 17, 7, 16] The risk factors were tumor location, radiation dose, and tumor volume among others. [9] In our case, all the five edema (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 were asymptomatic in all three patients (2.7%). In a similar recent study on the radiosurgery's effect on the internal carotid artery, nine patients (5.8%) out of 155 cavernous sinus meningioma patients treated with stereotactic radiosurgery resulted in CCS. [6] In their cohort, symptomatic CCS were rare, which is in line with our result. Regarding NPH, since all patients developed and underwent VPS within one year after the last CKRT, 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 GKS, CKRT has comparable treatment effect on PFS with 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 CKRT may be a reasonable choice as well as GKS [13]. All asymptomatic patients who underwent upfront CKRT 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 CKRT, or 2) upfront CKRT are reasonable treatment options depending on the degree of neurologic worsening (Fig. 2). Since PFS was better in grade I than grade II CSMs (p = 0.02), all grade II CSMs should be followed by adjuvant CKRT to improve PFS. In our cohort, no variables (age, sex,
previous operation, time to CKRT, target volume, and form of CKRT) except pathology grade were found to be statistically significant in affecting PFS. This result is in line with a similar past study.\[15\] Considering the effectiveness of CKRT on the CSMs regardless of previous status of operation, we do not have to stick to achieving Simpson grade I – III resection at the risk of irreversible surgical complications.\[14\] Finally, as stated in the result section, although not being significant, we found some trends in upfront CKRT (\(p = 0.11\)) having longer PFS than adjuvant CKRT. It may be possible that if pathology data had been available in more patients, the p-value would have been significant. If we were able to identify WHO grade I meningiomas by radiological findings, upfront CKRT would be suitable for asymptomatic patients.

Limitation

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

Conclusions

CKRT is an effective and safe treatment option for CSMs management. PFS is better in grade I patients than grade II CSMs.

Declarations

Funding: Not applicable.

Conflicts of interest/Competing interests: Not applicable.

Availability of data and material: Data transparency was confirmed.

Code availability: Not applicable

Ethical approval: This study was done under our institutional review board 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.
Authors’ contributions: All authors read and approved the final manuscript. SH made a study design, collected patient data, drafted and revised the manuscript. KK made a contribution to revising the original draft. KS, and SI were the supervisors.

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