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CLINICAL STUDY

Cranial nerve outcomes after primary stereotactic radiosurgery for symptomatic skull base meningiomas

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Abstract

Objective To evaluate cranial nerve (CN) outcomes after primary stereotactic radiosurgery (SRS) for petroclival, cavernous sinus, and cerebellopontine angle meningiomas.

Methods From our prospectively maintained database of 2022 meningioma patients who underwent Leksell stereotactic radiosurgery (SRS) during a 30-year interval, we found 98 patients with petroclival, 242 with cavernous sinus, and 55 patients with cerebellopontine angle meningiomas. Primary radiosurgery was performed in 245 patients. Patients included in this report had at least one CN deficit at the time of initial presentation and a minimum of 12 month follow up. Median age at the time of SRS was 58 years. Median follow up was 58 months (range 12–300 months), Median tumor volume treated with SRS was 5.9 cm^3 (range 0.5–37.5 cm^3), and median margin dose was 13 Gy (range 9–20Gy).

Results Tumor control was achieved in 229 patients (93.5%) at a median follow up of 58 months. Progression free survival rate (PFS) after SRS was 98.7% at 1 year, 96.4% at 3 years, 93.7% at 5 years, and 86.4% at 10 years Overall, 114 of the 245 patients (46.5%) reported improvement of CN function. Patients with CP angle meningiomas demonstrated lower rates of CN improvement compared to petroclival and cavernous sinus meningioma patients. Deterioration of CN function after SRS developed in 24 patients (10%). The rate of deterioration was 2.8% at 1 year, 5.2% at 3 years, and 8% at 10 years.

Conclusion Primary SRS provides effective tumor control and favorable rate of improvement of preexisting CN deficit.

Keywords Radiosurgery · Skull base · Meningioma · Cranial nerve

Introduction

Complete surgical resection of skull base meningiomas remains difficult due to their proximity to critical cranial nerve and vascular structures. Historically, surgical resection has been the primary management option for symptomatic lesions. Surgery may be associated with additional morbidity, incomplete resection, and delayed progression [1–3].

Stereotactic radiosurgery (SRS) has been used as a primary management option, or as an adjuvant following incomplete resection. The optimal outcome of SRS in the management of meningiomas is the prevention of further tumor growth, while maintaining neurologic function. The success of SRS in achieving tumor control is well established in the literature [4–6]. The goal of this study was to determine tumor control and cranial nerve outcomes following primary SRS in patients with cavernous sinus, petroclival, and CP angle meningiomas.

Methods

Patient population

We reviewed our prospectively maintained Institutional Review Board approved data base of 2022 meningioma patients who underwent SRS during a 30-year interval.

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We identified a total of 659 patients with petroclival (204 patients), cavernous sinus (365 patients), and CP angle meningiomas (90 patients), who underwent Leksell SRS using one of 6 generations of the Gamma knife® at the University of Pittsburgh Medical Center. A total of 414 patients were excluded from the study because they met the following exclusion criteria:

1. No cranial nerve deficit at the time of initial presentation or time of SRS (116 patients).
2. Clinical and imaging follow up duration less than 12 months (105 patients).
3. Patients with multiple meningiomas, and meningiomas related to previous brain radiation therapy or neurofibromatosis (34 patients).
4. Patients with atypical or anaplastic meningiomas (9 patients). In 5 patients this was based on tissue diagnosis following surgical resection due to tumor progression post SRS. In 4 patients this was based on radiographic imaging.
5. Patients who had prior surgical resection (150 patients)

The study cohort consisted of 245 patients, consisting of 55 patients with petroclival meningiomas, 149 with cavernous sinus meningiomas, and 41 patients with CP angle meningiomas. Petroclival meningiomas were defined as tumors with their maximal volume occupying the region between the upper two-thirds of the clivus and the petrous apex [1]. Cerebellopontine angle meningiomas were defined as tumors with maximal volume occupying the junction between the lateral cerebellum, the pons, and the internal auditory meatus [7]. Cavernous sinus meningiomas were defined as tumors with their maximal volume occupying the cavernous sinus [8].

There were 185 female and 69 male patients included in the analysis. For patients with cavernous sinus meningiomas, the most common symptom at the time of initial presentation was diplopia. The most common cranial nerve deficit in patients with petroclival meningiomas was trigeminal neuropathy. The most common cranial nerve deficit in patients with CP angle meningioma was hearing loss.

The median age at the time of SRS was 58 years (range 21–93 years). All patients had at least 1 cranial nerve deficit at the time of initial presentation. Patient demographics in each group are demonstrated in Table 1.

Radiosurgery technique

Gamma Knife models U, B, C, 4C, Perfexion, or ICON were used depending on the model available at the time of SRS. The radiosurgical technique utilized has been previously explained in details [9]. The procedure begins by applying a stereotactic head frame under conscious sedation and local anesthesia. After attachment of the fiducial system, patients undergo high definition magnetic resonance imaging (MRI) or CT imaging. Once collected, the images are uploaded to a dose planning software. In all tumors, the treatment volume conformed to the enhancing tumor volume. Beam blocking was used to reduce radiation dose delivered to adjacent critical structures. After the procedure, all patients received 20–40 mg of IV methylprednisolone, and all were discharged within 24 h of SRS. Table 2 summarizes the radiosurgical treatment parameters. Leksell SRS was done in a single session in these patients. The median marginal and maximum SRS doses were 13 and 26 Gy, respectively.

Follow up

Median follow up duration was 58 months (range 12–300 months). Follow up was recommended at 6 months intervals for the first year. If tumor control was achieved, then follow up imaging was performed at 2, 4, 6, 8, and 12 years

Table 1 Patient demographics

Factors	Petroclival (n = 55)	Cavernous sinus (n = 149)	CP angle (n = 41)
Median age, years (range)	61 (37–87)	57 (21–93)	61 (39–83)
Sex (M/F)	10/45	37/112	10/31
Location (R/L)	29/26	77/72	24/17
Median duration of symptoms until SRS (months)	12 (1–300)	8 (1–144)	12 (1–132)
CN involved			
II	0	10	0
III, IV, VI	14	116	4
V	32	53	19
VII	2	3	2
VIII	20	3	25
IX–XII	1	0	1

Table 2 Gamma Knife treatment parameters

Factor	Petroclival	Cavernous sinus	CP angle
Median tumor volume, cm^3	5.35 (0.72–18.3)	7 (0.5–37.5)	3.1 (0.3–17.1)
Median margin dose, Gy	12.5 (11–16)	13 (9–20)	13 (11–16)
Median maximum dose, Gy	25 (22–32)	26 (18–40)	26 (22–32)
Median # of isocenters	10 (3–24)	10 (2–33)	9 (2–20)

intervals. If a patient reported new or worsening symptoms, then an earlier clinical and imaging evaluation was advised. MRI was typically performed to evaluate any changes in tumor volume, or detect any adverse radiation effects.

Improvement in cranial nerve deficit was defined as an improvement in the function of at least 1 preexisting cranial nerve deficit. Hearing status was assessed by performing a pre and post SRS audiogram and using the Gardner-Robertson Hearing Scale [10]. Hearing was considered to be improved if audiogram reveals a positive change in GR grade following SRS. The Barrow International Institute Pain Intensity Score [11] (BNI pain scale) was used to assess the degree of trigeminal pain, and assess for pain change following SRS. Trigeminal pain was considered to be improved if patients are classified into a more favorable BNI pain group. Other determinants for symptom improvement were the patients' subjective sense of symptom change and the identification of any changes on physical examination.

Tumor regression was defined as $>25\%$ reduction of the tumor volume from the time of SRS. Stable tumor volume refers to $<25\%$ change in volume from the time of SRS. Tumor progression was defined as $>25\%$ increase in tumor volume from the time of SRS. All patients included in this analysis had at least 12 months of imaging follow up.

Statistical analysis

Statistical analysis was performed using Chi square test to evaluate the relationship between duration of symptoms, age at the time of SRS, tumor size, tumor locations, radiation dose and tumor response on the likelihood of improvement of cranial nerve deficits. Kaplan–Meier survival plots were plotted for progression free survival, overall improvement rate of cranial nerve deficits, deterioration rate of cranial nerve deficits, and improvement of individual cranial nerve deficits. Suggested cut-off value for variables found to significantly affect CN outcomes was determined by Youden index based on ROC curve analysis. Statistical analysis was performed with IBM SPSS Statistics 24 (IBM, Armonk, NY).

Results

Patient survival and tumor control

Overall survival after SRS was 99.6% at 1 year, 98% at 6 years, 95.2% at 10 years, and 85% at 15 years. Thirty-six patients were deceased at the time of data collection. None of the deaths were related to the treated tumor or as a SRS complication. Tumor location did not affect overall survival (log rank test $P=0.4$). Overall tumor control as observed on serial follow up imaging was achieved in 225 patients (93.5%) at a median follow up of 58 months. Tumor volume reduction was demonstrated in 149 patients (61%) tumor volume was stable in 74 patients (30%), and tumor growth was observed in 22 patients (9%). Tumor progression developed at a median of 47 months after SRS (range 5–150 months). Based on Kaplan Meier analysis, progression free survival rate (PFS) after SRS was 98.7% at 1 year, 96.4% at 3 years, 93.7% at 5 years, and 86.4% at 10 years (Fig. 1). Tumor location, margin dose, and tumor size were not associated with better or worse PFS ($P=0.34$, $P=0.29$, and $P=0.64$ respectively). None of the patients developed a radiation induced malignant transformation of the tumor.

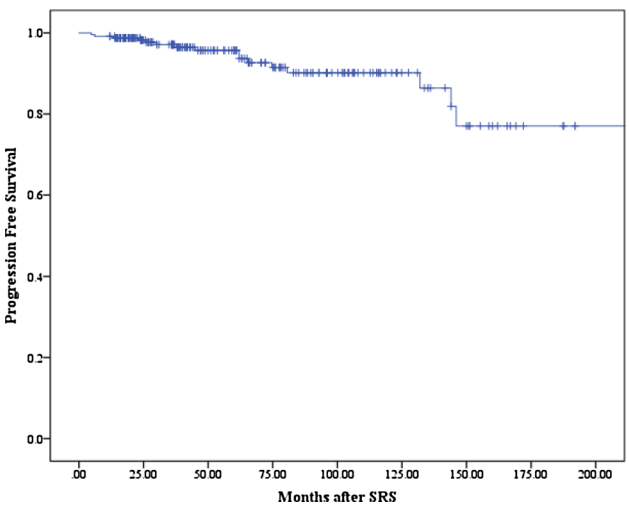

Fig. 1 Kaplan Meier graph demonstrating the PFS curve for 245 patients with petroclival, cavernous sinus, and CP angle meningiomas treated with primary SRS

Table 3 Cranial nerve outcomes after SRS

Factors	Petroclival (n = 55)	Cavernous Sinus (n = 149)	CP angle (n = 41)
Improved (%)	32 (58%)	66 (44%)	16 (34%)
Unchanged (%)	22 (40%)	67 (45%)	18 (49%)
New onset or worsening preexisting deficit (%)	1 (2%)	16 (6.5%)	7 (17%)

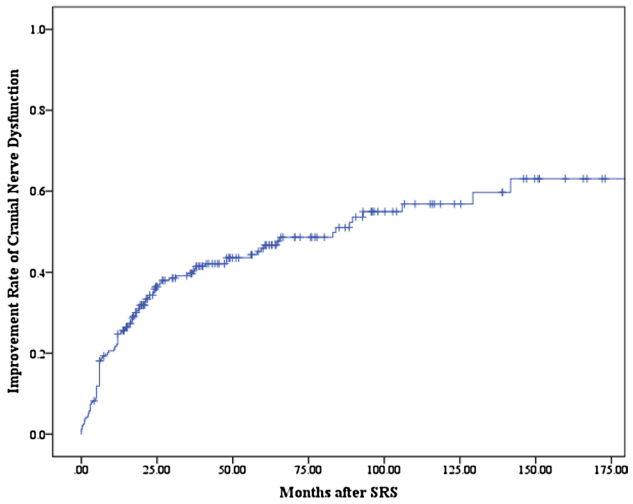

Fig. 2 Kaplan Meier graph demonstrating the cranial nerve improvement rate in patients treated with primary SRS

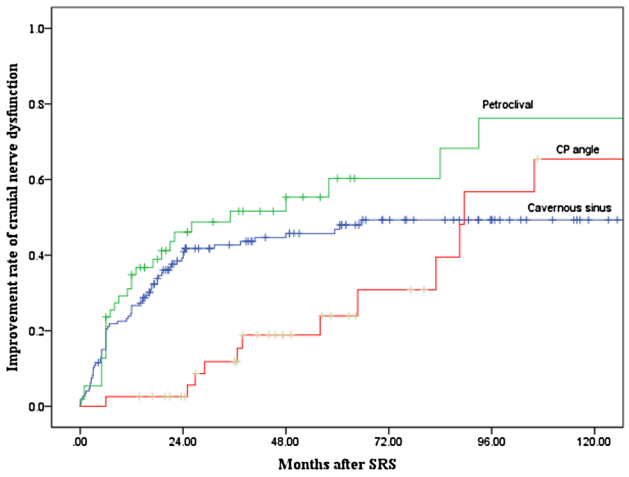

Fig. 3 Kaplan Meier graph demonstrating the cranial nerve improvement rate. Patients with petroclival and cavernous sinus meningiomas demonstrated significantly higher rates of improvement compared to patients with CP angle meningiomas (log-rank test, P = 0.03)

Cranial nerve outcomes

Improvement of cranial nerve deficits

At final follow up, 114 (46.5%) patients reported improvement in preexisting CN deficits. One hundred and seven (44%) patients reported no change in preexisting CN deficit, and 24 patients (10%) reported worsening or a new onset CN deficits (Table 3). Patients with a shorter duration of symptoms until SRS were more likely to report an improvement in CN deficit (P = 0.018). Based on ROC curve analysis, patients who underwent SRS < 12 months after onset of symptoms demonstrated a higher likelihood of improvement of CN symptoms. Patients with tumor regression on imaging reported more favorable CN outcomes (P = 0.041). Margin dose, gender, tumor size, and age at the time of intervention did not significantly affect the likelihood of improvement of CN deficit. Based on the Kaplan–Meier analysis, the improvement rate was 25% at 1 year, 36% at 2 years, and 47% at 5 years (Fig. 2).

Cavernous sinus and petroclival meningioma patients demonstrated more favorable CN outcomes compared to patients with CP angle meningiomas (P = 0.035 and P = 0.033, respectively). Table 3. Summarizes CN outcomes based on tumor location.

The improvement rate in patients with cavernous sinus meningioma was 26.6% at 1 year, 40.9% at 2 years, and 48% at 5 years. The improvement rate in patients with petroclival meningioma was 34.8% at 1 year, 48.8% at 2 years, and 60.3% at 5 years. The improvement rate in patients with CP angle meningioma was 15.3% at 1 year, 23.9% at 2 years, and 30.8% at 5 years. Patients with cavernous sinus and petroclival meningiomas had significantly higher rates of improvement of cranial nerve deficits compared to patients with CP angle meningiomas (log-rank test, P = 0.03). Figure 3 demonstrates the rate of improvement of cranial nerve deficit based on tumor location.

In the entire series, the most common preexisting symptom was diplopia. Of the 134 patients with diplopia, 61 patients (45.5%) reported improvement at a median of 65 months after SRS. Based on Kaplan Meier analysis, the improvement rate of diplopia was 20% at 1 year, 37% at 2 years, and 44% at 5 years (Fig. 4). Tumor location did not affect improvement rate of diplopia (P = 0.885).

Trigeminal neuropathy/neuralgia was the second most common symptom in the entire series. Forty two of 104 (40.4%) patients reported improvement of trigeminal

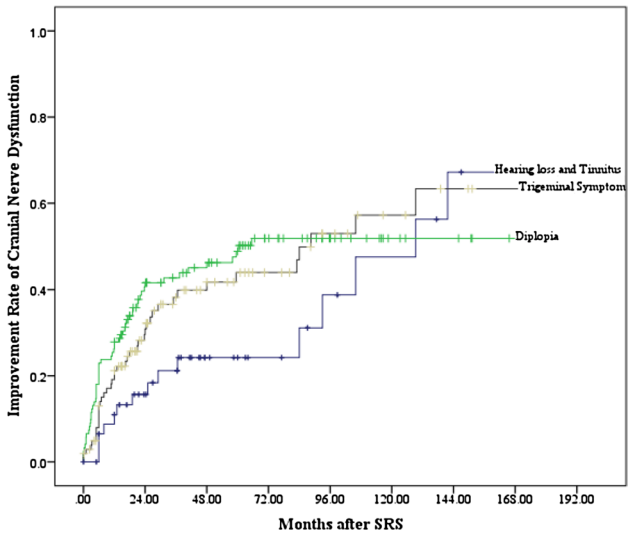

Fig. 4 Kaplan Meier graph demonstrating the improvement rate of diplopia, trigeminal symptoms, and hearing loss and tinnitus. No significant difference in improvement rate between the different CN symptoms (log-rank test, P = 0.123)

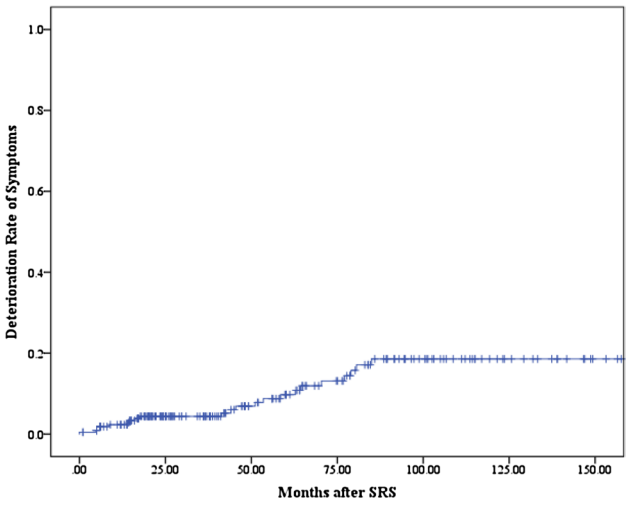

Fig. 5 Kaplan Meier graph demonstrating the deterioration rate of cranial nerve symptoms after SRS

neuropathy at a median of 48 months. Based on Kaplan Meier analysis, the improvement rate was 11% at 1 year, 22.5% at 2 years, and 41% at 5 years (Fig. 4).

Eighteen of 32 patients (56%) with trigeminal symptoms secondary to petroclival meningioma reported improvement of their TN symptoms at a median of 48 months. In contrast, 16 out of 53 of patients (30.2%) with cavernous sinus tumors reported improvement at a median of 61.2 months. Eight out of 19 patients (42%) with CP angle meningioma reported improvement of their trigeminal symptoms at a median of 56 months. Tumor location significantly impacted the likelihood of improvement of trigeminal symptoms (P = 0.03). In addition, the rate of improvement of trigeminal symptoms was significantly higher in patients with petroclival meningioma compared to patients with CP angle and cavernous sinus meningiomas (log-rank test P = 0.039).

Forty-eight patients had symptoms related to vestibulocochlear nerve involvement, with hearing loss and tinnitus being the most common symptoms. Of the 48 patients, 15 patients (31.1%) reported improvement of symptoms at a median of 43.7 months. Based on Kaplan–Meier analysis, the improvement rate was 15.7% at 1 year, 25.2% at 2 years, and 31.3% at 3 years. Tumor location did not significantly influence the likelihood of improvement of vestibulocochlear nerve dysfunction.

New onset or worsening preexisting cranial nerve deficit

After SRS, 24 patients (10%) developed new or worsening cranial neuropathies. Fifteen patients had delayed tumor volume progression associated with the worsening cranial nerve symptoms. Tumor progression was associated with higher likelihood of developing new or worsening symptoms (P = 0.01). In 6 patients, the reason for worsening was attributed to adverse radiation effects (ARE). In 3 patients, there was no evidence of tumor progression on imaging, and it was not possible to determine the cause of the worsening symptoms. Thirteen patients developed worsening trigeminal nerve symptoms at a mediation duration of 41 months after SRS. Six patients had worsening diplopia at a median duration of 45 months after SRS. Five patients had worsening vestibulocochlear nerve deficit at a median of 52 months after SRS. Based on Kaplan–Meier analysis, the deterioration rate was 2.8% at 1 year, 5.2 at 3 years, and 10.8% at 5 years (Fig. 5). Patients who had tumor progression on imaging were more likely to have worsening or new onset symptoms after SRS (P = 0.0001). Patients with CP angle meningiomas were more likely to develop new onset, or worsening CN deficits compared to petroclival and cavernous sinus meningiomas (P = 0.03). A higher margin dose demonstrated a trend towards a higher likelihood of new onset or worsening CN deficit (P = 0.08). Based on ROC curve analysis, a margin dose of 14 Gy was the cut-off dose point for a higher likelihood of new onset or worsening CN symptoms. The cut-off dose was not influenced by tumor location.

Additional management

Fourteen patients with tumor progression on imaging required additional treatment. Nine patients underwent repeat SRS at a median of 80.6 months (range 12–288 months) after initial SRS. Five patients underwent delayed

surgical resection at a median of 62 months (range 16–62 months) after initial SRS.

Discussion

Choosing the appropriate management strategy for skull base meningiomas is challenging. Given the indolent nature of some of these tumors, observation may be considered, particularly when patients are asymptomatic [12]. However, given the proximity of these tumors to critical structures, growing skull base meningiomas lead to new neurological deficits caused by compression of adjacent cranial nerves or vascular structures [13]. The Rates of complete tumor resection reported in the literature range between 12 and 80%, with tumor progression reported as 10 and 26.8% within 2–7 years after surgery [14–16]. Post-operative complication rates reported in the literature range between 5 and 66.8%, while mortality is reported in up to 7.3% of patients [3, 14–21]. Sughrue et al. conducted a meta-analysis studying the factors predicting outcomes following treatment of patients with cavernous sinus meningiomas. In their series of 2065 patients, patients treated with primary SRS demonstrated higher tumor control rates when compared to patients managed surgically with either complete or partial resection. In addition, the rate of post-operative CN deficits was higher in patients with prior resection compared to primary SRS [22]. Natarajan et al. reported 48 patients with petroclival meningiomas, and noted that in patients with "complete resection", tumor progression was observed in 15% of patients at 12 years [23]. In their series on petroclival meningiomas, Nanda et al. [15] report that 44% of patients who underwent surgical resection developed post-operative deficits, and that 19% of patients demonstrated tumor progression. Tumor debulking followed by adjuvant SRS have been used by some neurosurgeons to avoid the high risk of complications encountered with complete resection [2, 24].

Tumor control

In this report, tumor control was achieved in 225 patients (93.5%) at a median follow up of 58 months. In addition, the 5 year PFS was 94%. Published reports have indicated that the 5 year PFS after SRS for skull base meningiomas ranges between 91 and 100% [4, 5, 25–30]. In the current report, we confirmed tumor control at 10 years in 86.4% of patients. This outcome suggests that SRS can provide results that are comparable to recurrence after a Simpson grade I resection at 10 years [6, 31–33]. Tumor location was not predictive of long term tumor control.

Fractionated radiotherapy and fractionated stereotactic radiotherapy are also used for the management of patients with skull base meningioma. Chung et al. systemically analyzed the outcomes of benign meningioma patients treated with SRS and radiotherapy, and found similar tumor control, symptomatic improvement, and complication rates [34]. Five year PFS rates reported in the literature range between 93 and 98.1% [35–37]. Such tumor control rates are similar to what is reported in patients treated with SRS. However, the rates of tumor regression are higher in patients managed with SRS [35, 38]. The volumes of meningiomas treated with radiotherapy are often larger than those treated with SRS. In addition, a limitation of SRS is related to the volume of the tumor adjacent to the optic apparatus [26].

Cranial nerve outcomes

All patients included in this series had CN deficits at the time of SRS. We found that 46.5% of patients reported improvement of deficits after SRS. We found that patients who underwent SRS less than 12 months after onset of symptoms were more likely to report improvement. Tumor regression on imaging was associated with higher likelihood of symptom improvement. Flannery et al. suggested that one potential mechanism for improvement of trigeminal nerve symptoms includes tumor regression leading to pressure relief on the nerve root [6].

Patients with cavernous sinus or petroclival meningiomas were more likely to experience improvement of CN deficits compared to patients with CP angle meningiomas. In this report, 34% of patients with CP angle meningiomas reported symptom improvement. Park et al. reported on 74 patients who underwent SRS for the management of CP angle meningiomas. Improvement in symptoms was reported in 31% of patients [7]. In a multicenter study, Ding et al. reported an overall improvement of neurologic function in 57% of patients with cp angle meningiomas who underwent SRS [27].

In this report, 44% of patients with cavernous sinus meningiomas reported improvement of CN deficits. Nicolato et al. 2002 reported symptom improvement in 78.5% of cavernous sinus meningioma patients who had SRS as a primary management modality [29]. Kano et al. reported that 37% of patients who underwent primary SRS reported improvement of preexisting CN deficits [26]. Azar et al. reported that 40.4% of their patients with cavernous sinus meningiomas treated with SRS reported improvement in symptoms at final follow up [39]. In this report, patients who had symptoms for less than 12 months before SRS were more likely to report improvement. Using linear accelerator-based SRS, Spiegelmann et al. reported that 39% of patients reported improvement after SRS. In addition, they found that patients who had SRS less than 1 year from the onset of symptoms were more likely to report symptom improvement [40].

Fifty-eight percent of patients with petroclival meningiomas reported improvement in symptoms [5]. Flannery et al. reported an overall symptom improvement in 26% of petroclival meningioma patients [6]. Starke et al. reported symptom improvement in 27.1% of patients with petroclival meningiomas. It is worth to note, however, that both reports included patients with and without history of prior microsurgical resection.

The most common symptom reported in all patients was diplopia. Almost 46% of patients reported improvement of diplopia at final follow up. The improvement rate of diplopia was 20% at 1 year, 37% at 2 years, and 44% at 5 years. Hasegawa et al. report that 29% of patients with diplopia related to cavernous sinus meningioma reported symptom improvement [41]. Diplopia was most commonly seen in patients with cavernous sinus meningiomas. However, tumor location did not influence the likelihood of improvement of diplopia.

Trigeminal neuralgia/neuropathy was the second most common complaint. Forty percent of patients reported improvement of their trigeminal symptoms. The improvement rate was 11% at 1 year, 22.5% at 2 years, and 41% at 5 years. Hasegawa et al. 2007 reported that 30% of patients with trigeminal symptoms reported improvement [41]. Huang et al. 2008 reported that 57% of patients with facial pain reported improvement after SRS for petroclival meningiomas [42]. Patients who had trigeminal symptoms related to a petroclival meningioma were more likely to improve compared to patients with trigeminal symptoms related to cavernous sinus or CP angle meningiomas.

The third most common, and least likely symptoms to improve were hearing loss and tinnitus, with only 31% of patients reporting improvement at final follow up. Improvement rate after primary SRS was 15.7% at 1 year, 25.2% at 2 years, and 31.3% at 3 years.

Complications

After SRS, 24 patients (10%) reported worsening or new onset CN dysfunction. Fifteen patients had tumor progression demonstrated on imaging. The published incidence of delayed cranial nerve dysfunction after SRS ranges between 0 and 25% [3, 5, 6, 21, 26]. Six patients (2.4%) developed symptomatic ARE, defined as new neurological signs or symptoms in the absence of tumors growth, with new changes in tumor contrast enhancement on MRI [26]. In three patients there was no evidence of tumor progression on imaging, and it was not possible to determine the cause of worsening symptoms. New or worsening CN V function was the most common dysfunction following SRS. In this report, tumor progression was associated with a higher likelihood of symptom worsening. Williams et al. reported that new onset or worsening CN deficit occurred in 10% of patients. They found that factors such as larger tumor volume, lower margin doses, longer follow up, and tumor progression, were significantly associated with new onset or worsening CN deficits [43].

Study limitations

In the majority of patients, improvement or worsening of symptoms was based on patients' subjective sense of change and the changes identified on physical examination. The use of a validated grading systems to quantify improvement would have definitely enhanced the value of the results. Additionally, patients with chronic symptoms may have adapted to the deficits, which may be confused for improvement. The retrospective nature of this study and referral bias may limit the overall findings of this report. This study is enhanced by the long-term outcome analysis.

Conclusion

In this report, SRS was associated with high tumor control rates, high rates of improvement of preexisting CN deficits, and low complications rates. The results of this report demonstrate that SRS for skull base meningiomas is highly effective for both tumor control and symptom relief.

Compliance with ethical standards

Disclosures Dr. Lunsford is a consultant for and stockholder in Elekta AB.

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