Clinical Neurology and Neurosurgery 187 (2019) 105557

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Gamma Knife stereotactic radiosurgery for cerebellopontine angle meningioma

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ARTICLE INFO

Keywords:
Cerebellopontine angle
Meningioma
Gamma Knife
Radiosurgery
Tumor
Survival

ABSTRACT

Objective: Meningiomas comprise 6–15 % of cerebellopontine angle (CPA) tumors. Surgical treatment is a real challenge because this area is occupied by several critical neurovascular elements. Currently, surgery is the first choice of treatment, however several factors may be present that necessitate choosing the alternative treatments such as Gamma Knife Stereotactic Radiosurgery (GKS).

Patients and Methods: Ninety-three patients with CPA meningioma who were treated by GKS for a period of 8 years, were retrospectively reviewed. Factors affecting clinical and radiological improvement were analyzed.

Results: The median tumor volume was 6 cm^3. The mean values for maximal and marginal dose were 20.2 and 13.6 Gy, respectively. The mean follow-up time was 31.5 months. Tumor control (lack of progression) was achieved in 96.8% of the patients and 55.9% of the patients showed tumor regression on follow-up MRI. The actuarial 3-year progression-free survival (PFS) rate was 96%. Clinical improvement was seen in 49.5% of the patients while 11.8% experienced worsening or new-onset symptoms. Adverse radiation effects were seen in 4.3% of the patients. A worse symptomatic outcome, male sex, a lower tumor coverage, and marginal doses $<$13.5 Gy were associated with worse radiologic outcomes. Worse radiologic outcomes and higher tumor volumes, especially tumor volumes $\geq$8.5 cc, were associated with worse symptomatic outcomes. The male sex was associated with a lower PFS.

Conclusion: Gamma Knife radiosurgery, either primarily or post- operatively, offers a decent long-term tumor control in CPA meningioma, and is associated with an acceptable complication profile, especially in tumors with lower volumes.

1. Introduction

About 1% of all meningiomas occur in the cerebellopontine angle (CPA). Meningiomas comprise 6–15 % of CPA tumors [3,10,12,17,19,26,27]. This area is compactly filled with neurovascular elements, including cranial nerves IV to XII, vertebral and basilar arteries, and their branches. So, any attempts for radical tumor removal might be associated with the risk of strokes, brain stem damage, cranial nerve deficits and other complications [19,20]. Recent advances in understanding anatomic nuances, surgical techniques, and equipment have revolutionized brain microsurgery by increasing the rate of gross total resection while decreasing the rate of complications. However, in the last two decades, with the release of long-term outcomes of the radiosurgical series, it has become clear that radiosurgery can be an effective modality in tumor control with much lower complication rates [1,2,5,9,14,16,25,29]. In a recent study on microsurgical resection of CPA meningiomas, a morbidity of 10.4–35.7% was reported, with gross total resection (GTR) achieved in 82%–86.1% of the patients [4]. Although surgical complications have a wide range including anesthetic, surgical, and post-surgical ones, complications associated with radiosurgery tend to be limited to a smaller and more predictable range. Moreover, for residual or recurrent or small tumors, there is a more tendency towards less invasive treatments such as radiosurgery. Although some authors have suggested that tumors with a diameter less than 3 cm or a volume less than 15 cm^3 are more suitable for primary radiosurgical treatment [11], there is no widely accepted cut-point.

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https://doi.org/10.1016/j.clineuro.2019.105557
Received 7 May 2019; Received in revised form 2 October 2019; Accepted 6 October 2019
Available online 20 October 2019
0303-8467/

Therefore, it is not easy to decide whether to do surgery alone, radiosurgery alone, or adopt a combined approach in many cases.There are very few radiosurgical studies in the literature dedicated solely to CPA meningioma [5,14]. In this study, we retrospectively studied 93 patients who underwent either primary or post-operative Gamma Knife Radiosurgery for CPA meningioma evaluating the factors affecting clinical and radiological improvement and long-term outcome.

2. Patients and methods

2.1. Patient selection

The data of 93 patients with CPA meningioma underwent Gamma Knife stereotactic radiosurgery (GKS) in the Iranian Gamma Knife Center for a period of 8 years were retrospectively reviewed. Twenty nine patients (31%) had a history of previous surgery, while in 64 patients (69%), radiosurgery was the first treatment after radiological diagnosis of CPA meningioma. CPA meningioma was considered when the main bulk of the tumor was confined to this area. Other skull base meningiomas with extension to CPA were excluded from the study. A diagnosis of CPA meningioma in patients without previous surgery or biopsy was made based on typical characteristics of meningioma on CT and MRI including dural base, dural tail, marked enhancement with contrast, calcification, extra-axial location and no extension into the internal acoustic meatus. The indication for post-operative GKS was symptomatic progression or significant tumor remnant after the surgery. All patients had informed consent signed indicating that their information would be used for research purposes. This study is implement in accordance with the Helsinki Declaration of the World Medical Association and all patients have signed an informed consent. This study was approved by the local ethics committee. Demographic characteristics are presented in Table 1.

2.2. Radiosurgical dose planning

The patients were treated using the Elekta Model C, Gamma Knife system Version 5.34 with the Gamma Knife dose planning software (GammaPlan type C). After administration of local anesthesia, a stereotactic Leksel frame was affixed to the patient's head. Then, an MRI was performed with the frame in position to determine the stereotactic coordinates of the treatment target. According to the Gamma Knife planning program, computerized planning was performed. Radiosurgery was performed using 201 cobalt-60 sources. In patients with a history of radiotherapy, the GKRS dose was adjusted accordingly. Table 2 summarizes radiosurgical dose planning.

2.3. Follow-up

The patients were routinely visited every 6 months in the first two years, then annually for three years, and then every 2–3 years. This time table could vary for patient-specific reasons. History taking and physical examination were performed by the first two authors. Tumor progression or regression as in previous studies [5,14] was defined as more than 15% change in the tumor volume on contrast-enhanced MRI. The tumor volume was calculated using the ellipsoid formula, by multiplying the largest x dimension by y and z dimensions divided by two.

2.4. Evaluation of clinical outcomes

For evaluation of clinical outcomes, signs and symptoms that were reported in history and physical examination sheets were considered, and reported both as two-category data (improved vs. not improved or worsened vs. not worsened) and three-category data including "unchanged". The t-test was performed for two categories of continuous variables and ANOVA was performed for three-category variables. Multivariate analysis was performed for data with *p*-values smaller than 0.2. Roc-curve analysis was used to find a discriminative threshold for a continuous variable. The Kaplan-Meier survival curve was used to show the occurrence of progression during the follow-up period. Differences in survival curves were analyzed using Log-rank test and the effect of specific factors on survival curve was analyzed using the Cox proportional hazard model. *P*-values less than 0.05 were considered as significant. All the statistical analyses were performed with SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Demographic information

Of 93 patients with CPA meningioma, 75 (80.6%) were women and with a female to male ratio of 4.17:1. The mean age was 52.2 years (range: 25–79 years). Sixty-four patients (68.9%) had a negative history of previous surgery who were treated by GKS after radiological diagnosis by CT and MRI while 29 patients (31.1%) had a history of previous transcranial surgery. Of these patients, 23 had undergone one operation, while 4 were operated twice, and 2 had a history of three operations. For all of these patients, the pathologic diagnosis was WHO grade I meningioma. Five patients had a history of conventional radiotherapy, of whom 3 patients had one previous surgery, one patient had 2, and one patient had 3 operations. The mean interval between tumor diagnosis and GKS was 2.9 years. There was no difference in tumor volume between non-operated and post-operative patients (p = 0.666).The mean follow-up time was 31.5 months (range: 6–96 months). Ten patients were followed for less than 12 months. The mean follow-up time was 32 months (range: 6–96 months) in the non-operated group and 30.1 (range: 6–84 months) in the post-operative group.The mean tumor volume was 7.5 cm^3 (range 1.5–24.7 cm^3). The mean tumor volume was 8.1 cm^3 (range: 1.5–24.7 cm^3) in the post-operative group and 7.3 cm^3 (range: 1.5-22.9 cm^3) in the non-operated patients, respectively. The mean marginal dose was 13.5 Gy (range: 10–15 Gy) in the post-operative group and 13.6 Gy (range: 12–15 Gy) in the non-operated group. The mean tumor coverage was 98.9% (range: 93–100%) and 99.2% (range: 94–100%) in post-operative and non-operated patients, respectively.

3.2. Radiological outcomes

Among 93 patients, tumor control (either radiologic regression or stabilization during the follow- up period) was achieved in 90 patients (96.8%). Radiologic regression was seen in 52 and radiologic progression after GKS was observed in 3 patients, and the tumor remained unchanged in 38 patients. These outcomes are also analyzed for patients with more than 1 year of follow up (Table 3). However, the mean follow-up time and the duration of the follow-up was not statistically different among the patients with various radiologic prognoses. A history of previous surgery or radiotherapy did not affect the radiological outcomes. Radiological outcomes were not significantly affected by any of the presenting symptoms. However, female patients and patients with more radiosurgical tumor coverage tended to have more favorable radiologic outcomes (p = 0.036 and p = 0.010, respectively). Tukey post-hoc test showed that tumor coverage was significantly lower in patients with tumor progression compared to patients with tumor regression or no-change group. However, the difference between the tumor regression group and no-change group was not statistically significant. Other radiosurgical parameters such as age, tumor volume, marginal dose, and maximal dose did not affect the radiological outcomes significantly. Moreover, Tukey post-hoc analysis did not show any significant differences in any of these parameters between the radiological prognosis subgroups. Student t-test was used to evaluate the effect of various factors on radiologic improvement (improved vs not-improved), and only marginal dose was showed to be significant

Table 1
Comparison of studies dedicated to Gamma Knife radiosurgery in CPA meningioma.

Author/year	Ding et al 2014	Park et al 2014	The current study
Number of patients	177	74	93
Female	149	62	75
Male	28	12	18
F/M ratio	5.3	5.2	4.2
Mean age	59	57	52
Number of previous surgeries			
0	124 (70%)	60 (81.1%)	64 (68.8%)
1	46 (26%)	n/a	23 (24.7%)
2	6 (3.4%)	n/a n/a	4 (4.3%)
3	1 (0.6%)		2 (2.1%)
Conventional radiotherapy	3	n/a	5
The most common symptoms			
Dizziness/imbalance	85 (48%)	40 (54%)	38 (41%)
Hearing loss	80 (45.2%)	38 (51%)	53 (57%)
Facial Sensation	69 (39%)	26 (35%)	37 (40%)
Follow-up time (months)	46 (mean)	40 (median)	31.5/24 (mean/median)
Median tumor volume (cm^3)	3.6 (1.9–6.2)	3.0 (0.3–17.1)	6.0 (1.5–24.7)
5-Y progression-free survival	93	95	89
Median Marginal Dose (Gy)	13	13 (11–16)	13.5 (10–15)
Median Maximal Dose (Gy)	26 (26–30)	26 (22–50)	20 (13–37.1)
Radiologic outcomes (%)			
Regression	46.3	62	55.9
Stabilization	45.8	26	40.9
Progression	7.9	12	3.2
Symptomatic outcomes (%)			
improvement	57.4	31	49.5
stabilization	34.1	58	38.7
deterioration	8.5[a]	11[b]	11.8[c]
Most common deteriorated symptoms			
Dizziness/imbalance	11 (6.3%)	N/A	1 (1.1%)
Hearing loss	6 (3.4%)	1 (1.3%)	4 (4.3%)
Facial Sensation	7 (4%)	4 (5.4%)	3 (3.2%)
Adverse Radiation Effect (%)	1.1	9	4.3
Hydrocephalus development	3 (1.7%)	2 (3%)	1 (1.1%)
Death	7	4	1
Factors associated with a worse radiologic outcome	Male sex Previous Irradiation Ataxia at presentation	none	Worse clinical outcome Male sex Lower tumor coverage Marginal doses <13.5 Gy
Factors associated with a worse symptomatic outcome	Facial spasm at presentation Lower maximal dose	Trigeminal neuralgia at presentation	Worse radiological outcome Higher tumor volume Tumor volume ≥ 8.5cc
Factors associated with worse PFS	Male sex Previous irradiation Ataxia at presentation	none	Male sex

[a] 26.7% of these patients had also radiologic progression.
[b] 12.5% of these patients had also radiologic progression.
[c] 18.1% of these patients had also radiologic progression.

Table 2
Radiosurgical dosimetry.

Maximal dose (Gy)	13–37.1
Mean/median	20.2/20
Range	13–37.1
Marginal Dose (Gy)	10–15
Mean/median	13.6/13.5
Range	10–15
Isodose (%)	8–90
Mean/median	61.8/65
Range	8–90
Isocenters	1–50
Mean/median	17.3/13
Range	1–50
Tumor Coverage (%)	
Mean/median	99.1/99
Range	93–100

($p = 0.037$) that also remained significant in multivariate analysis ($p = 0.033$). When performing t-test to investigate the effect of different factors only on radiologic worsening, no factor reached a significant level. ROC curve analysis was performed for various continuous variables and their effects on radiologic improvement (improved vs. not-improved). The only significant factor was the marginal dose (Area under curve: 0.631 ± 0.118, $p = 0.039$). Marginal dose values higher than 13.5 Gy were able to predict radiologic improvement with the highest specificity and sensitivity rate ($p = 0.050$).

3.3. Clinical outcome

Eighty two patients had some neurological symptoms at presentation. The most common presenting symptom was hearing loss (53 patients) followed by ataxia and vertigo (38 patients), facial sensation abnormalities (37 patients), headache (37 patients), tinnitus (33 patients), Hearing loss (26 patients), facial nerve paresis (29 patients), dysphagia (9 patients), diplopia (7 patients), and hoarseness. Neurologic improvement was observed in 46 patients, while 11 patients experienced some symptomatic worsening (deterioration of the previous symptoms or new deficits) and 26 patients remained unchanged. The details of the patients' symptoms and their outcomes after GKS are presented in Table 4. Radiologic outcomes were correlated with clinical outcomes ($p = 0.013$). Using ANOVA test, tumor volume was the only

Table 3
Characteristics of the patients with various radiologic outcomes.

Outcome	#	F:M ratio	Mean age*	Tumor volume	History of radiotherapy	History of surgery	Symptomatic improvement*	Max dose	Margin dose**	Tumor coverage*	F/U (months)
Improved	52	3.3	52.4	7.2	4	15	28	20.3	13.8	99.2	34.8
Unchanged	38	8.5	52.1	7.6	1	14	17	19.7	13.7	98.9	30.8
Worsened	3	0.5	40	12	0	1	0	20.4	13.2	97.3	40
Statistics(P)	–	.036	.262	.323	.527	.725	.013	.894	.108	.010	.650

* Factors with significant statistical effect.
** When performing t-test to investigate the effect in two groups (improved vs not-improved), the marginal dose reached to a significant level in univariate (p = 0.037) and multivariate analysis (p = 0.033).

significant factor affecting radiological outcome (p = 0.004). When performing t-test to investigate the effect of various factors on neurologic worsening (worsened vs. not-worsened), only the tumor volume reached a significant level (p = 0.008) which remained significant after multivariate analysis (p = 0.007). ROC curve analysis showed the only acceptable area-under-the-curve was for the effect of the tumor volume on worsening of clinical outcome (area = 0.797 ± 0.127, p = 0.001). The tumor volume cut-off point with the highest sensitivity and specificity was 8.5cc. Patients with a tumor larger than 8.5 cc were more prone to experience worsening of their symptoms (p = 0.002).

3.4. Survival analysis

We report the survival analysis for a time course near to the mean follow-up time (about 3 years). Radiological Progressive free survival (PFS) at one and three years of follow-up was 100%, 96% (±2%), using the Kaplan-Meier method, respectively (Fig. 1). Log-Rank analysis showed the significant effect of sex on survival. Females tended to have higher PFS (p = 0.011). The maximum follow-up times were different between females and males. However, the mean follow-up was not significantly different between the two sexes. History of previous surgery or radiotherapy did not affect PFS significantly. Moreover, PFS was not significantly affected by any of the presenting symptoms. Comparison of radiological and clinical outcomes in primary and post-operative patients using Log Rank test showed no significant difference. Cox Proportional Hazards analysis showed no significant effect for age, tumor coverage, tumor volume, maximal dose and other continuous variables on PFS.

3.5. Complications

One of the patients died due to myocardial infarction. Adverse radiation effect (ARE), defined as peri-tumoral hyperintensity and edema, was seen in four patients. One patient developed hydrocephalus that required a ventriculoperitoneal shunt. Overall, 11 patients (11.8%) reported either deterioration or onset of a new deficit. Worsening of hearing loss, facial sensory abnormalities, facial paresis, and loss of balance was seen in 4, 4, 3, and 1 patient, respectively. Two patients developed new-onset diplopia.

4. Discussion

For symptomatic CPA meningioma, especially for those with a noticeable mass effect and hydrocephalus, microsurgical approach is considered the first option. Recent advances in microsurgical techniques and apparatus, as well as post-operative cares, have made the surgical approach more effective and safer than before. Surgical series on CPA meningioma have shown very good results in terms of complete tumor removal and recurrence rate; however, the risk of neurovascular injury is still a serious concern [7,18,20,27]. Baronicini et al. [2] reported the results of microsurgical resection of CPA meningioma in 115 cases. Total or subtotal tumor resection was achieved in 91% of the patients. New facial nerve deficits occurred in 9% and hearing worsened in 17% of the patients. The rate of postoperative facial nerve injury may be as high as 30% [27] and hearing preservation does not usually exceed 77–91% at best [13,18]. The rate of post-operative cranial nerve deficits may be as high as 17–23% [7,22]. These complications that affect the patient's quality of life may be higher in postoperative and post-radiation patients. Therefore, surgical treatment is not always an easy choice for the patient to choose. GKS for CPA

Table 4
Characteristics of the patients with various clinical outcomes.

Outcome	#	F:M ratio	Mean age	Tumor volume*	History of surgery	Radiologic improvement*	Max dose	Margin dose	Tumor coverage	F/U (months)
Hearing loss										
Improved	15	2.7	51.9	6.6	5	10	20	13.7	99	37.6
Worsened	4	3	62	12.1	1	2	18.9	13.2	99.5	31.7
Dizziness/ataxia										
Improved	17	4.7	56.8	7.3	6	14	21.2	13.6	99.1	39
Worsened	1	0	45	22.9	0	0	20	13	94	24
Trigeminal Nerve										
Improved	19	8.5	53.6	8.7	5	11	19.1	13.5	98.7	28
Worsened	4	3	64	13.2	0	4	19.3	13.5	99.2	45
Facial Nerve										
Improved	11	10	56.4	7.4	4	9	18.8	13.3	99.3	29.4
Worsened	3	2	54	8.9	0	2	19.8	13.8	98.7	60
All Symptoms										
Improved	46	6.7	52.4	6.8	13	28	19.7	13.5	99	33.9
unchanged	36	3.1	49.7	7.4	14	17	21	13.6	99.2	29.8
Worsened	11	1.7	56.9	11.1	2	7	17.3	13.6	99.1	43.9
Statistical significance (p)	–	.101	.338	.004	.460	.013	.191	.955	.390	.310

* Factors with significant statistical effect.

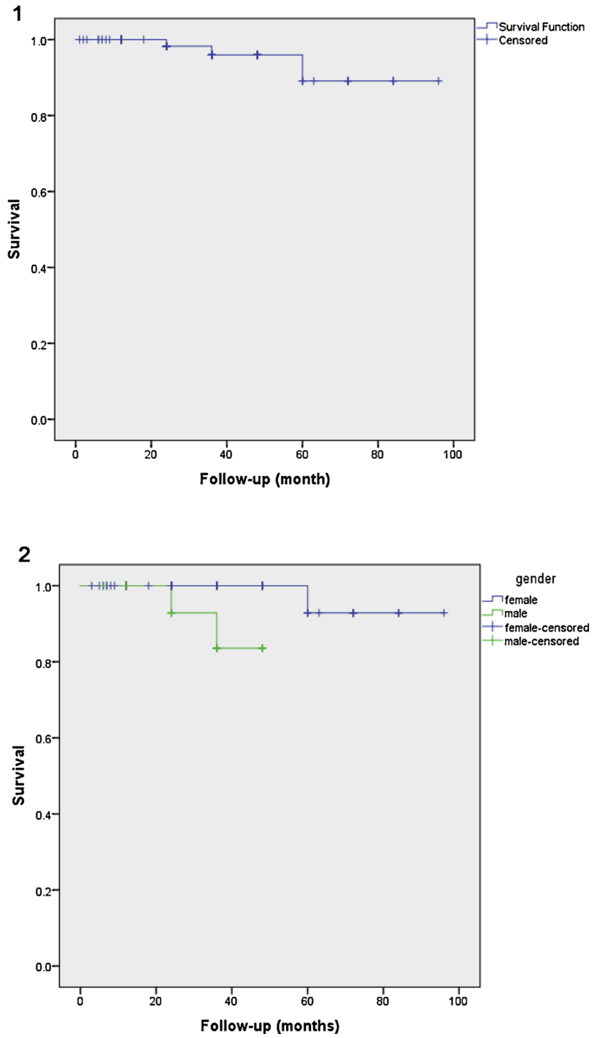

Fig. 1. Kaplan–Meier plot for progression-free survival rate in all patients with CPA meningiomas (1) and separately in two genders (2).

meningioma has led to an acceptable tumor control rate. In the most salient series consisting of cases with CPA meningioma [21,22,25], the 5-year PFS, radiologic tumor control, and complication rate has been reported to be 92–96%, 86–91.2%, and as low as 9%, respectively. Starke et al reported the CPA meningioma had better symptomatic outcomes compared to petroclival or parasellar meningiomas [25]. Very few studies have solely evaluated CPA meningioma [5–14]. This study is the fourth GKS series dedicated to CPA meningioma. Ding et al [5] conducted a multi-center study of 177 patients with CPA meningioma treated by GKS. Details are presented in Table 1. They reported significantly worse radiologic outcomes in males. Similarly, in our study, female patients had a higher progression-free survival. The maximum follow-up time was different between female and male patients. However, the mean follow-up was not significantly different between the two sexes. In another study, Park et al. [14] evaluated 74 patients with CPA meningioma treated with GKS, either primarily or post-operatively (Table 1). After analyzing their data, only the association between trigeminal neuralgia at presentation and a worse symptomatic outcome was significant [14]. In our study, the female to male ratio was a little lower than the other two studies, but still higher than the usual 2:1 ratio in all meningiomas [28]. The mean age of the patients was comparable to the other two studies. Three main symptoms seen in all three studies were hearing loss, balance problems, and facial sensory abnormalities. The median tumor volume was higher in our study versus the other two studies (6 cm^3 compared to 3.6 cm^3 and 3 cm^3). The tumor volume was not statistically different between non-operative and post-operative groups. In our study, tumor control was achieved in 96.8% of the patients in a mean follow-up of 33.1 months. Tumor regression was 55.9% which is comparable to other studies [5,14,21,24,25]. Analysis of various factors showed that only male sex and the tumor coverage had significant effects. Male sex was associated with worse outcomes as reported by Ding et al. [5]. A higher tumor coverage was associated with a better radiologic response, indicating the importance of dose planning to include all tumor volumes in the radiation field. Moreover, ROC curve analysis showed a critical value of 13.5 Gy for marginal dose. When data are separated by this cut point, with the highest specificity and sensitivity, they would differ in radiologic regression. In most other studies, for evaluation of presumed effective factor, the outcomes are considered as two-category data, i.e. improved vs. not improved or worsened vs. not worsened. We believe that by this kind of categorization and merging two categories, we would miss the value of “unchanged” in statistical analysis. We report the results of statistical analyses in both ways to be comparable with other studies. However, it seems that a three-category ANOVA test is more reliable statistically. Neurologic deterioration was encountered in 11 patients, of whom two also had a radiologic progression. Therefore, the symptomatic deterioration in these patients could be attributed to tumor progression, while it was probably the result of the radiosurgery complications in the other 9. Only one of these 11 patients developed ARE and hydrocephalus. In contrast to the previous two studies, presenting symptoms had no significant effect on the overall symptomatic outcome. The only factor associated with a worse neurological outcome, other than a worse radiologic response, was a higher tumor volume. With a higher tumor volume, removal of neurovascular elements from the radiation field would be more difficult. We also found a cut-off point for tumor volume (8.5 cm^3) above that, post-radiosurgery neurological deterioration was more probable. Actuarial 5-year progression free survival was 89% in our study. However it is more accurate to consider the 3-year PFS (96%) because it is near the the mean follow-up time. The reported 5-year PFS for radiosurgical treatment in skull base meningioma range from as low as 80–87% [6,15] to 96–100%8, [23–25]. However, all of these PFS rates are in an acceptable range in comparison with microsurgical series [2,7,18,20,27]. In our study, the only factor that significantly affected the PFS was the male sex which predicted a lower PFS. However, it is not easy to compare different studies because of differences in their patients' characteristics such as age, tumor volume, etc. The mean age of the patients in our study was slightly lower than the two previous studies which can affect morbidity and mortality profile. The larger mean tumor volume in our study, which may be due to the patients' preferences or more conservative criteria for selecting surgery, makes it difficult to compare our findings with other studies in terms of survival and tumor control outcomes.

5. Conclusion

This retrospective study presents the outcomes of gamma knife radiosurgery in 93 patients with in CPA meningioma. Tumors with lower volumes tend to have fewer radiosurgical complications, specifically those smaller than 8.5 cm^3. Higher tumor coverage and marginal doses in radiosurgical dose planning are associated with better results.

No significant difference was found in outcomes of primary and adjuvant GKRS. The both groups had good long-term tumor control with an acceptable complication profile. Neurologic deteriorations in radiosurgical treatment of CPA meningioma seems to occur less often when compared to the microsurgical series; however randomized controlled studies are needed for better comparison of complication rates and tumor control.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of interest

None.

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