Gamma Knife Radiosurgery for Tuberculum Sellae Meningiomas: A Series of 78 Consecutive Patients

Yavuz Samanci (✉ mysamanci@hotmail.com)

Koç Üniversitesi <https://orcid.org/0000-0001-8952-6866>

Gokce Deniz Ardor

Koç University Hospital

Selcuk Peker

Koç University <https://orcid.org/0000-0003-3057-3355>

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Abstract

Background: Outcomes of Gamma Knife Radiosurgery (GKRS) for tuberculum sellae meningiomas (TSMs) have not been reported explicitly within any meningioma series. We present the first and largest TSM series with clinical, radiosurgical, and outcome features for 78 consecutive patients managed with GKRS.

Methods: Patients who underwent GKRS for TSMs between 2005 and 2021 and had a minimum of 6 months of follow-up were included. Medical records, imaging studies, and follow-up examinations were evaluated retrospectively.

Results: A total of 78 patients with a median age of 50.5 years were included. SRS was conducted as an upfront treatment for 38 patients (48.7%). The median target volume was 1.7 cm³ (range, 0.1-14.6). During a median follow-up of 78.5 months, the cumulative PFS rates of the whole cohort at 1, 5, and 10 years by Kaplan-Meier analysis were 100%, 97.9%, and 94.5%, respectively. Of 47 patients with impaired vision, improvement and/or preservation of visual acuity and visual field were achieved in 55.3% and 42.6%, respectively. No new-onset hormonal deficits were observed.

Conclusions: Based on our data, SRS represents an effective and safe modality for unresected or recurrent/residual TSMs. SRS should be offered to patients who are not willing or not ideal candidates for surgery.

Introduction

Meningiomas originating from the anterior cranial fossa floor make up almost 40% of all intracranial meningiomas, and tuberculum sellae meningiomas (TSMs) constitute approximately 25% of these tumors [7]. TSMs originate from the dura of the tuberculum sellae, chiasmatic sulcus, limbus sphenoidale, and diaphragma sellae [18]. The proximity to vital structures such as optic nerves, hypothalamus, and pituitary gland complicates the clinical condition and management of these tumors, even when they are small in size.

The management of TSMs is multifaceted. Although surgery is usually the standard treatment choice, anatomical vicinities usually prevent gross-total resection (GTR), independent of the surgical technique used [36]. Stereotactic radiosurgery (SRS) is an accepted treatment alternative to surgery, as it has been involved in the management of skull base parasellar meningiomas as upfront or adjuvant treatment for the past 30 years [5, 38, 40].

This single-surgeon, retrospective study aimed to describe the effectiveness and safety of Gamma Knife Radiosurgery (GKRS) in treating both unresected and residual/recurrent TSMs using radiological and clinical outcomes.

Materials And Methods

This retrospective study with prospectively managed data was authorized by the Institutional Review Board of Koç University (2020.190.IRB1.058) and was performed based on the principles of the Declaration of Helsinki. Written informed consent was obtained from the participants.

The study cohort included 78 consecutive TSM patients who underwent GKRS between December 2005 and April 2021. Inclusion criteria were as follows: a) diagnosis of meningioma based on a radiological or histopathological study, b) meningioma localized in tuberculum sellae, and c) treatment with single-session (sfGKRS) or hypofractionated GKRS (hfGKRS). Patients with previous radiotherapy (RT) or SRS and inadequate follow-up information (<6 months) were excluded. Medical records with clinical and ophthalmological reports, imaging studies, and follow-up evaluations were evaluated retrospectively.

GKRS was conducted with Leksell Gamma Knife® model 4C (2005–2012), Perfexion™ (2012–2017), and Icon™ (2017–2021) (Elekta Instrument AB, Stockholm, Sweden). A contrast-enhanced MRI was obtained before or after the application of a Leksell stereotactic frame, based on the available Gamma Knife® model. The frameless approach was also used for hypofractionated GKRS during the Leksell Gamma Knife® Icon™ era. The target volume was delineated with multiple isocenters, and the marginal dose and fractionation scheme were chosen depending on the tumor size, location, and the projected risk to the adjacent structures.

Unless otherwise specified (in case of poor pre-GKRS vision), the initial imaging and clinical follow-up were conducted at 6th month, with annual follow-up after that. Tumor volume was measured on contrast enhanced T1W MR images using Elements™ SmartBrush (BrainLAB AG). The volume of TSM at the latest follow-up was compared with pre-GKRS imaging data and was classified as stable (change within 20%), partial volumetric response (> 20% decrease), or progressive disease ($\geq$ 20% increase) [2]. A partial volumetric response and stable disease were indicative of local control (LC). The LC was assessed throughout the study until local failure or death. Progression-free survival (PFS) was described as the time from the GKRS until the time of documented progression or death. Visual follow-up was performed with visual field and acuity examinations. The visual status change was categorized as not changed, improved, or declined. GKRS-related adverse events were categorized according to the Common Terminology Criteria for Adverse Events version 5 [37].

Statistical Analysis

All analyses were performed using SPSS 21.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA). The study cohort's demographic, clinical, radiological, and radiosurgical characteristics were summed by standard descriptive statistics (median, range, mean, and standard deviation). Kaplan–Meier method was used to evaluate LC, PFS, and toxicity. The log-rank test was used to assess predictive factors on these outcomes. All tests were two-sided, and $p < 0.05$ was regarded as statistically significant.

Results

Patient demographic data are reviewed in Table 1. The median age was 50.5 years (range, 16-80 years), and 80.8% of patients were female. The median KPS score was 90 (range, 70-90). There was at least one neurological symptom, sign, or cranial nerve deficit in all patients before GKRS, including headache (65.4%) and impaired vision (60.3%). The median duration of visual impairment before GKRS was 35 months (range, 11-206). Regarding impaired vision, total vision loss was observed in 2.6% of patients with unresected tumors. This rate was significantly higher in patients with residual (57.1%) and recurrent (57.9%) tumors ($p<0.001$). The median number of previous surgeries was 1 (range, 1-2). Post-operative worsening in vision was seen in 81% of subjects with subtotal resection (STR) and 57.9% of subjects with GTR.

Table 1
Baseline and treatment features of 78 patients with tuberculum sella meningiomas

Parameters	Value
Female: Male	63/15
Median age, (range), years	50.5 (16-80)
Median KPS (range)	90 (70-90)
Presenting signs, %	
Headache	65.4
Visual impairment	60.3
Dizziness	5.1
Other	7.7
Previous surgical resection, n (%)	40 (51.3)
Median number of surgeries, (range)	1 (1-2)
Extent of surgeries, n (%)	
Gross-total resection	19 (47.5)
Subtotal resection	21 (52.5)
Median interval between diagnosis/surgery to GKRS (range), months	
Unresected tumors	3 (1-132)
Residual tumors	10 (1-61)
Recurrent tumors	96 (12-360)
Median target volume (range), cm ³	1.7 (0.1-14.6)
Fractionation scheme, n (%)	
Single fraction	66 (84.6)
Hypofractionated	12 (15.4)
Median isodose line, (range), %	50 (40-60)
Median dose to the margin (range), Gy	
Single fraction	11 (10-15)
Hypofractionated	20 (16.5-25)
Median follow-up time (range), months	78.5 (6-192)

Parameters	Value
Radiologic outcome, n (%)	
Stable disease	63 (80.8)
Partial volumetric response	13 (16.7)
Progressive disease	2 (2.6)
Visual outcome in patients with impaired vision, n (%)	
Improved	26 (55.3)
Unchanged	20 (42.6)
Deteriorated	1 (2.1)

The median target volume was 1.7 cm³ (range, 0.1-14.6 cm³), and it was not statistically different between patients with unresected tumors and patients with a previous history of surgery (1.3 vs. 2.1 cm³, respectively, p=0.279). Thirty-eight patients (48.7%) underwent GKRS as initial treatment, and 40 (51.3%) underwent GKRS for residual (n=21) or recurrent tumor (n=19). The median interval between diagnosis and GKRS was three months (range, 1-132) for unresected tumors. On the other hand, the mean interval between surgery and GKRS was ten months (range, 1-61) for residual tumors and 96 months (range, 12-360) for recurrent tumors. GKRS was performed as sfGKRS in 84.6% of patients. Three patients were treated in three daily fractions (margin dose 6 Gy/fraction), and nine patients were treated with five daily fractions (margin dose 4 Gy/fraction in eight patients and 5 Gy/fraction in one patient). A median margin dose of 11 Gy (range, 10–15) was prescribed to a median isodose line of 50% (range, 40–55) for sfGKRS. For hfGKRS, the median margin dose, maximum dose, and the isodose line were 20 Gy in 5 fractions, 40 Gy (range, 33.3-50 Gy), and 50% (range, 45-60). Median maximal radiation dose to any portion of the optic apparatus was 6.7 Gy (2.4-11.6).

During a median follow-up of 78.5 months (range, 6–192), the radiologic outcome was stable disease in 63 patients (80.8%), partial volumetric response in 13 patients (16.7%), and progressive disease in 2 patients (2.6%) (Figure 1). The median recurrence time from GKRS was 74 months (range, 50-98) in patients with progressive disease. Both patients with progressive disease underwent cranial surgery for the second and third times, respectively, and they were deceased following surgeries. Logistic regression analysis for univariate associations between recurrence and specific patient, tumor-related, and GKRS-related characteristics was insignificant. Due to the limited absolute numbers of events, multivariate logistic regression analysis was not feasible. The cumulative PFS rates of the study cohort at 1, 5, and 10 years were 100%, 97.9%, and 94.5%, respectively (Figure 2). Although both cases with recurrence were in the group of patients with previous surgery, the PFS distributions for unresected and resected groups were not statistically significantly different, $\chi^2(2) = 1.526$, p=0.217 (Figure 3).

Forty-seven patients (60.3%) had impaired vision prior to GKRS. Thirty-six of these 47 patients had a history of previous surgery for TSM. Of these 47 patients, vision improved in 26 patients (55.3%),

unchanged in 20 patients (42.6%), and declined in one patient (2.1%). No statistical difference was found between patients with improved and unchanged vision regarding patient, tumor-related and GKRS-related characteristics. The patient with visual deterioration also had radiographic evidence of tumor progression, and a further craniotomy was performed. Logistic regression analysis for univariate associations between visual deterioration and specific patient, tumor-related, and GKRS-related characteristics was insignificant. Due to the limited absolute numbers of events, multivariate logistic regression analysis was not feasible. None of the patients had hormonal impairment before or after GKRS. No adverse radiation effects were observed. At the last follow-up, three patients (3.9%) had died. Causes of death included post-surgical mortality in two patients (2.6%) and leukemia in one patient (1.3%).

Discussion

Until recently, TSMs were frequently included in radiosurgical studies as parasellar or anterior skull base meningiomas. This study is the first to report the radiological and clinical outcomes in 78 consecutive TSM patients treated with GKRS as primary or adjuvant therapy. The study demonstrated that GKRS is a feasible option with favorable tumor control and low complication rate.

TSMs account for approximately 10% of all intracranial meningiomas and typically originate from the dura mater of tuberculum sellae, chiasmatic sulcus, and limbus sphenoidale [25]. Due to the close anatomical relationship between tuberculum sellae and the optic apparatus, up to 80% of patients present with visual deterioration, as demonstrated by Schick et al [36]. Other well-known manifestations include headache, anosmia, seizures, cranial nerve deficits, and pituitary dysfunction [18]. In our study, the most common symptoms included visual disturbance (60.3%) and headache (65.4%). The visual disturbance was significantly higher in patients with prior surgery than patients with unresected tumors (69.2% vs. 26.9%, $p < 0.001$).

The natural history of TSMs is not well described. However, researches have demonstrated that an untreated skull base meningioma tends to grow. Bindal et al. [4] reported that only 42% of skull base meningiomas were essentially unchanged on imaging studies during a mean radiographic follow-up of 76 months. In a study by Sughrue et al. [41], linear diameter growth rates up to 93% were demonstrated in 675 patients with untreated meningiomas. Therefore, once the diagnosis is definitive, treatment should be carried out as early as possible as it is probably best to avoid significant size increases in more surgically challenging regions. Transcranial approaches have been conventional techniques in surgery, and less-invasive techniques have been introduced recently. However, despite recent advances, documented rates of subtotal resection and adverse events have been reported up to 60% [7, 8, 29, 42]. In a recent study by Troude et al. [44], STR rate was 26% in 94 patients with TSM, and it was reported to be due to severe adhesion to optic nerve or ICA (75%), or extension to the cavernous sinus (25%). Regarding the patients with prior surgery in the present study, 82.5% underwent STR. Cranial nerve deficits are significant drawbacks, with up to 41% reported post-operative rates in parasellar meningiomas [8, 20, 23, 39]. Although improved vision was observed in 50–66%, it remained unchanged in up to 28%, and

deterioration was noted in almost 25% of patients [26, 31, 33]. Long-term post-operative aggravated visual disturbance was stated in 9% of 94 surgically treated TSM patients [44]. In the present study, post-surgical worsening in vision was observed in 65% of patients with a previous history of surgery. On the other hand, following GKRS, vision improved in 26 patients (55.3%) and remained unchanged in 20 patients (42.6%). Post-operative, usually transient, diabetes insipidus has been described in up to 26% of patients [14]. In a review by Bassiouni et al. [3], preoperative hypopituitarism ranged up to 42%. Regarding the review by Dusick et al. [11], hypopituitarism was also noted in up to 14.5% of patients. Post-surgical hypopituitarism prior to GKRS was observed in only one patient (2.5%) in our cohort. Another surgical complication is CSF leak, and it has been reported as high as 62% [13, 15]. Regarding recurrence following surgical resection of TSMs, reports have indicated a mean recurrence rate of 5.5-24.2% [1, 3, 6, 12, 16, 31, 32, 34, 45]. Similarly, the post-surgical recurrence rate was 47.5% in our study. Domingues et al. reported that anterior cranial base meningiomas were linked to shorter relapse-free survival (RFS) than other meningiomas, and 15-year RFS was reported as 52% [10]. In our study, the Kaplan-Meier estimate of the median PFS was 49 months (95% CI 15.7-82.3) in subjects with unresected tumors and patients with a prior GTR.

RT has also been applied in selected patients with recurrence or those unfit for surgery. Mendenhall et al. [27] reported 92% control rate at 15 years after conventional RT in 101 patients with skull base meningiomas. Neurological deficits have also improved or remained stable in 69–100% of patients following fractionated RT. Complication rates have ranged from 0–24%, and the risk of injury to the optic apparatus and other cranial nerves has varied between 0% and 3% [28]. With the advent of SRS, management options have shifted to initial SRS for small tumors or surgery accompanied by SRS for larger tumors. GKRS has turned into an acceptable alternative for intracranial meningiomas. There are many GKRS-treated large intracranial meningioma series in the literature that reported favorable long-term results. Lee et al. [24] reported tumor shrinkage in 34% and stable tumor volume in 60% of 159 patients with cavernous sinus meningiomas. The tumor control rate was 96.9% at five years in whom GKRS was used as a primary option. Similarly, 5-year local control rates of up to 98.5% have been reported in several skull base meningioma series [9, 17, 19, 21, 22, 30, 40, 43]. Santacrose et al. [35] performed a retrospective, observational analysis of 5300 benign meningiomas and reported a control rate of 92.5% and a 5-year PFS of 95.2%. Eighty of these meningiomas were intrasellar, and 2073 were parasellar overall. O.Cohen-Inbar et al. [5] reported 48.1% post-GKRS tumor shrinkage in patients with parasellar meningiomas. Sheehan et al. [38] published 44.1% tumor shrinkage following GKRS of 763 patients for parasellar and sellar meningiomas. A 91.5% tumor volume control was demonstrated in 189 GKRS-treated parasellar meningiomas. In our series, during a median follow-up of 78.5 months, LC was obtained in 97.5% of patients. The cumulative PFS rates of the study cohort at 1, 5, and 10 years were 100%, 97.9%, and 94.5%, respectively.

The available literature provides less clarity regarding complications after SRS for sellar and parasellar meningiomas. Cranial nerve dysfunction and neurological deficits caused by adverse radiation effects are among the long-term complications. Regarding studies involving ≥ 100 patients, long-term complications varied from 0–16% [38]. An analysis of 2065 cavernous sinus meningiomas showed a

pooled cranial neuropathy rate of 59.6% for subjects undergoing surgery, compared with 25.7% for those undergoing SRS alone ($p < 0.05$) [42]. Cohen et al. [5] reported new or worsening deficits in 54 parasellar meningioma cases, including 19 trigeminal nerve dysfunction and 18 optic nerve dysfunction. They reported that only 9.3% of these were attributable to SRS. In the current study, vision improved in 26 patients (55.3%) and unchanged in 20 patients (42.6%) and declined only in one patient (2.1%). The patient with visual deterioration also had radiographic evidence of tumor progression. So, this deterioration might be due to tumor growth rather than the adverse radiation effect of SRS. We also did not observe any delayed endocrinopathy, radiation-related tumors, or stroke.

This study has some limitations due to retrospective nature of the study; however, all consecutive patients were included and exclusion criteria were minimized to overcome bias as much as possible. Although the present study has a limited sample size, it is the largest dedicated study reporting clinical, radiological and long-term outcome characteristics of patients with TSMs.

Conclusion

TSMs are challenging tumors that cause severe morbidity for patients, mainly by compression to optic nerves. Surgical resection remains the primary treatment; however, GKRS can serve as an effective and safe treatment option in selected patients.

Declarations

Funding: None

Conflicts of interest: The authors declare that they have no conflict of interest.

Ethics approval: This study was approved by the Ethics Committee of Koç University (2020.190.IRB1.058).

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: Patients signed informed consent regarding publishing their data.

Availability of data and material: Not applicable

Code availability: Not applicable

Authors' contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Yavuz SAMANCI, Gokce Deniz ARDOR and Selcuk PEKER. The first draft of the manuscript was written by Yavuz SAMANCI and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

An illustrative case of tuberculum sellae meningioma (TSM) treated with hypofractionated Gamma Knife radiosurgery. (a) A 68-year-old male patient was examined for visual loss and diagnosed with a TSM. He underwent surgery and subtotal resection was performed. The residual lesion was irradiated with a marginal dose of 25 Gy in 5 fractions (targeted to 50% isodose line) (The treatment plan is given on the

upper part). (b) A follow-up imaging scan and ophthalmological examination, obtained 6 months after radiosurgery, showed that a partial volumetric response and improved vision were achieved.

Figure 2

The Kaplan Meier survival analysis showing cumulative progression-free survival rates of the whole cohort.

Figure 3

The Kaplan Meier survival analysis showing progression-free survival distributions for unresected and resected groups ($\chi^2(2) = 1.526$, $p=0.217$).