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Tumor control and radiobiological fingerprint after Gamma Knife radiosurgery for posterior fossa meningiomas: A series of 46 consecutive cases

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ABSTRACT

Introduction: Gamma Knife radiosurgery (GKR) can be a valuable treatment option for posterior cranial fossa meningiomas (PCFM). We retrospectively analyzed outcomes of GKR for PCFM.
Methods: Were included forty-six patients with 47 PCFM. Primary endpoint was tumor control. Secondary endpoint was clinical improvement. Biologically effective dose (BED) was evaluated in relationship to primary and secondary outcomes. Mean marginal dose was 12.4 Gy (median 12, 12–14). Mean BED was 63.6 Gy (median 65, 49.1–88.3). Mean target volume (TV) was 2.21 cc (range 0.3–8.9 cc).
Results: Overall tumor control rate was 93.6% (44/47) after mean follow-up of 47.8 months ± 28.46 months (median 45.5, range 6–108). Radiological progression-free survival at 5 years was 94%. Higher pretherapeutic TVs were predictive for higher likelihood of tumor progression (Odds ratio, OR 1.448, 95% confidence interval - CI 1.001–2.093, $p = 0.049$). At last clinical follow-up, 28 patients (71.8%) remained stable, 10 (25.6%) improved and 1 patient (2.6%) worsened. Using logistic regression, the relationship between BED and clinical improvement was assessed (OR 0.903, standard error 0.59, coefficient 0.79–1.027, CI −0.10; 0.01; $p = 0.14$). The highest probability of clinical improvement corresponded to a range of BED values between 56 and 61 Gy.
Conclusion: Primary GKR for PCFM is safe and effective. Higher pretherapeutic TV was predictor of volumetric progression. Highest probability of clinical improvement might correspond to a range of BED values between 56 and 61 Gy, although this was not statistically significant. The importance of BED should be further validated in larger cohorts, other anatomical locations and other pathologies.

1. Introduction

Posterior cranial fossa meningiomas (PCFM) comprise approximately 9–10% of intracranial meningiomas[1,2]. Most of these tumors are often characterized by a close relationship to the critical vascular structures, cranial nerves and the brainstem[3,4]. As a consequence, gross total resection (GTR) with minimal morbidity and mortality is not always achievable[3,4].

Abbreviations: PCFM, Posterior cranial fossa meningiomas; GTR, gross total resection; SRS, stereotactic radiosurgery; GKR, Gamma Knife radiosurgery; BED, Biologically effective dose.

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Microsurgical resection is considered the mainstay treatment option in symptomatic meningiomas and/or in meningiomas displaying radiological progression [5]. The relationship between the extent of resection and recurrence rates, first advocated by Simpson in 1957[6], was consequently confirmed by multiple series[7–9]. In PCFM the reported rates of GTR varies from 57 up to 94%[1,2,4,5,10–12]. The recurrence rates and further disease progression is reported in 11.2–21% [1,2,4,12]. The reported rates of permanent neurological deficit ranges from 12.5% to 35% [1 4,12] and the operative mortality from 0 to 3.75% [1,2,4,12].

As a minimally invasive alternative, Gamma Knife radiosurgery (GKR) is considered a safe and effective upfront treatment for small to medium size meningiomas[13], particularly in critical locations[14-17]. Similarly, the GKR is an effective adjuvant treatment for residual or recurrent tumors[18,19].

Up-to-date, there are only few series reporting treatment outcomes of stereotactic radiosurgery (SRS) in PCFM[20,21]. Here, we report medium-term outcomes of GKR in PCFM. We analyze tumor control, as well as tumor volume variation after GKR. Moreover, we evaluate symptom improvement after such an approach. We further assess whether the biologically effective dose (BED) could be related to clinical outcomes[22,23].

2. Methods

2.1. Study design and patient selection

A total of forty-six consecutive patients with 47 PCFM were treated with primary GKR at Lausanne University Hospital, Switzerland, between the moment of the opening of our Gamma Knife center in June 2010 and November 2016. All patients signed written informed consent for the procedure. The number of treated patients by GKR, with PCFM, as per total of meningiomas (all locations included) in the same period was 18.1%.

Retrospective clinical and radiological analysis was performed in this historical cohort.

Inclusion criteria were: clinical and neuroimaging finding compatible with a benign PCFM, minimum 6 months of neuroimaging follow-up after GKR, capacity to give written informed consent and primary malignancy. An exclusion criterion was previous surgical resection.

Four patients with clinical follow-up of less than 6 months, two with prior fractionated radiation therapy and 1 with prior GKR (a total of 7/46) were excluded from the analysis related to clinical improvement. All cases had radiological follow-up and were included in the analysis related to progression free survival (please see below).

2.2. Patient population

There were 46 patients with 47 PCFM in this cohort (Table 1). No patient died during the study. The mean follow-up period was 47.81 ± 28.46 months (median 45.5, range 6–108 months). The median patient age was 59.9 years (range 31–82 years). There was a clear female predominance, with 37 (80.4%) females and 9 males (19.6%). Prior fractionated radiation therapy (FRT) was performed in 2 patients (4.3%) and one patient (2.2%) underwent previous GKR. The two patients with previous FRT underwent such therapy 10 years before GKR, using 30 fractions and 1.8 Gy per fraction (for a total of 50 Gy). Eight patients (8/39, 20.5%) presented with clinical symptoms: dizziness in 5 cases (12.8%), headache in 2 cases (5.1%) and ipsilateral facial paresthesias in one case (2.6%). Prior neurological signs and symptoms were present in 22 patients (56.4%), as follows trigeminal hypoesthesia in 5 (12.8%), trigeminal neuralgia in 8 (20.5%), VI^{-th} nerve palsy in 6 (15.4%), vestibular deficit in 2 (5.1%), VII^{-th} nerve palsy, hemifacial spasm, hypoacusia, vocal cord paralysis with 1 in each (2.6% each; Table 1). PCFM localizations were as follows: 11 (23.4%) petrous, 11 (23.4%) petroclival, 11 (23.4%) cerebellopontine angle, 5 (10.6%) foramen magnum, 3 (6.4%) tentorial, 2 (4.3%) petrocavernous, 2 (4.3%) clival, 1 (2.1%) petrotentorial, 1 (2.1%) jugular foramen.

Table 1
Demographic data and tumor characteristics.

		n	%
Median age ± SD (range)		59.7 ± 14.4 (31–82)	
Sex		37F: 9 M	
Previous irradiation			
	Fractionated radiotherapy	2	4.3%
	Stereotactic radiosurgery	1	2.2%
Presenting symptoms		8	20.5%
	Dizziness	5	12.8%
	Headache	2	5.1%
	Facial paresthesias	1	2.6%
Neurologic deficits or symptoms prior to GKR		22	56.4%
	Trigeminal hypoesthesia	5	12.8%
	Trigeminal neuralgia	8	20.5%
	Abduces nerve palsy	6	13.0%
	Facial nerve palsy	1	2.6%
	Hemifacial spasm	1	2.6%
	Vestibular deficit	2	5.1%
	Hypoacusia	1	2.6%
	Tinnitus	1	2.6%
	Vocal cord paralysis	1	2.6%
PCFMs localization			
	Petrous	11	23.4%
	Petroclival	11	23.4%
	Cerebellopontine angle	11	23.4%
	Foramen magnum	5	10.6%
	Tentorial	3	6.4%
	Petrocavernous	2	4.3%
	Petrotentorial	1	2.1%
	Clival	2	4.1%
	Jugular foramen	1	2.1%

*SD = standard deviation; F = female; M = male; GKR = Gamma Knife radiosurgery; PCFM = posterior cerebral fossa meningiomas.

2.3. Primary and secondary endpoints

Primary endpoint was tumor control. Secondary endpoint was symptom improvement. We further defined overall outcome as favorable (tumor control along with neurological stability or improvement) or unfavorable (tumor progression and new or worsening neurological deficit).

2.4. Radiological considerations

Concerning the radiological appearance, the probability of an inappropriate diagnosis based only upon neuroimaging definitions in the lack of histology had been beforehand evaluated by Flickinger et al. at 1.4%[24]. All patients analyzed here had typical imaging features of meningiomas. There was no patient with previous surgery and/or microscopic diagnosis other than suspected WHO grade I meningioma.

Of note, benign intracranial meningiomas exhibit neuroimaging features[25,26], which permit the right diagnosis with high diagnostic accuracy. The MRI remains the gold standard. Typical meningioma features include extra-axial dural-based lesions, hypo- to isointense on T1- weighted sequences and variable T2-weighted sequences, with further homogenous Gadolinium enhancement[27]. There is also a characteristic dural tails, which is usually related to the dural reactive changes. There might be some degree of vasogenic oedema in surrounding brain tissue in about half of the cases (which might also sometimes be a sign of atypical features). Additional sequences with diffusions weighted imaging (DWI) might depict higher-grade meningiomas, with increased cellularity, which further shows reduced values on corresponding apparent diffusion coefficient (ADC) maps, which

remains however controversial[28]. Atypical features might include undefined brain-tumor interface, intra-tumoral necrosis and cyst or absence of calcifications[29].

2.5. Radiosurgical technique

We always apply the Leksell model G stereotactic frame (Elekta Instruments AB, Sweden) under local anesthesia. All patients undergo stereotactic imaging on the day of GKR. In our center, we use multimodal imaging for target definition: magnetic resonance imaging (MRI, including T1 MPR without and with contrast enhancement- 1-mm slice, T2 SPACE-0.6 mm slice, T2 TSE coronal- 1 mm slice) and computer tomography (CT- 0.5 mm slice).

All patients were treated with Leksell Gamma Knife Perfexion TM and ICON TM (Elekta Instruments, AB, Sweden) by the same operators (ML, CT), during the specified timeframe. Dosimetry planning was performed using Leksell Gamma Plan (LGP version 10.0 and further 11.0, Elekta Instruments AB, Sweden).

The TVs are always drawn during the GKR day by the neurosurgeons (ML, CT). Follow-up imaging was imported for each patient within the LGP. Moreover, tumor was drawn by the same operators (ML, CT) at each follow-up time-points. Using the *"Volume"* module from LGP, both pretherapeutic and follow-up values were calculated in an uniform way.

The mean target volume (TV) at the time of GKR was 2.21 cm^3 (range 0.26–8.90 cm^3). Mean prescription dose to the tumor margin was 12.4 Gy (median12, range 12–14 Gy, Table 2), prescribed at the 50% prescription isodose line in all the patients; 38 patients (82.6%) received 12 Gy marginal dose. Mean treatment time was 66.2 min (median 71.7, range 32.2–130.8).

2.6. BED calculation

The BED was calculated using the basic model, which considers the prescribed dose and the time. For single fraction GKR, time was classically in the basic BED model with beam-on time, which was used in our formula[22,23,30-32]. The unit for BED is classically considered Gy (as for the prescribed dose).

BED[22] was analyzed in relationship to primary and secondary outcomes.

The mean BED received by the tumor was 63.6 Gy (median 65, range 49.14–88.29).

2.7. Clinical and radiological follow-up

Follow-up MRI and clinical outpatients visit were performed at 6, 12, 24, 36, 60, 84 and 120 months for all patients, with the exception of those having had only MRI assessment and not a clinical one (as previously detailed).

All patients with clinical follow-up as presented here have been seen in person by our neurosurgical team (MD, ML, CT). Moreover, for patients presenting with pretherapeutic diplopia, a neuroophtalmological exam was performed. Likewise, patients with pretherapeutic vocal cord palsy or vestibular symptoms benefitted from an ENT evaluation. The time to clinical improvement was also reported for each individual case.

Table 2
Gamma Knife radiosurgery treatment parameters.

Characteristic	Value
Mean margin dose in Gy ± SD (range)	12.4 ± 0.8 (12–14)
Mean isodose line % ± SD (range)	50.0 ± 0 (50–50)
Mean TV in cm^3 ± SD (range)	2.2 ± 2.0 (0.3–8.9)
Mean PIV in cm3 ± SD (range)	2.9 ± 2.5 (0.4–11.9)
Median BED ± SD (range)	60.1 ± 10.0 (49.1–88.3)

*Gy = Gray; SD = standard deviation; TV = target volume; PIV = prescription isodose volume; BED = biologically effective dose.

The tumor volumes were estimated for every control MRI using the co-registration and manual contouring instruments available in LGP.

Tumor decrease was characterized as a follow-up tumor volume of less than 85% of initial TV, the tumor stability as 85–115% of TV and tumor progression as tumor volume exceeding 115% of TV, as previously suggested by other studies[33-36].

2.8. Statistical analysis

Statistical analysis was performed using Stata 14 (StataCorp, College 109 Station, Texas). Descriptive statistics were related as proportion/frequency for categorical data and mean, median and range for continuous variables.

Tumor control and symptomatic improvement are both two binary outcomes. To assess the association between each predictor and the outcome we performed a univariate logistic regression analysis. The strength and the significance of the association were measured using the OR (Odds-Ratio) and the calculated p-value. Fractional polynomial analysis was used to check for the functional relationship between each continuous predictor and the outcome.

Additionally, for local progression free survival after GKR, survival over time was examined using the Kaplan-Meier method. Patient censoring occurred at the moment of failure, or at last follow-up, otherwise.

Given the insufficient number of patients with tumor progression, no univariate analysis has been carried out for this outcome. However, we have displayed the longitudinal volume analysis (in terms of volumetric changes) during follow-up course after GKR.

Because of the limited sample size (n = 10) and the number of variables, a multivariate analysis was difficult to perform for clinical improvement.

The Area Under the Receiver Operating Characteristics (ROC) Curves (AUC) and its 95% confidence interval were calculated to assess the discriminative performance of the final model.

3. Results

3.1. 1. Local progression free survival (n = 46 cases, n = 47 meningiomas)

Kaplan-Meier analysis showed that actuarial progression-free survival (PFS) rates at 1, 3 and 5 years were 98%, 98% and 94% (see Fig. 1, A).

At last follow-up, 3 meningiomas (6.4%) increased in volume (without any further therapy up-to-date), 32 (68.1%) decreased, and 12 (27.3%) remained unchanged. The overall tumor control rate was 44/47 (93.6%).

According to univariate analysis, the only statistically significant factor, predictive of tumor progression was higher initial pretherapeutic TV (hazard ratio (HR) 1.448, 95% CI 1.001–2.093, p = 0.04; Table 3).

In cases with tumor progression, the BED values corresponded to 60.5, 62.8 and 55.3 Gy, respectively. BED has no incidence on tumor control in this small series (area under the ROC curve 0.57; figure not illustrated).

3.2. Tumor volume changes after GKR as continuous values (n = 46 cases, n = 47 meningiomas)

The mean initial TV was 2.21 cm^3 (range 0.26–8.90 cm^3). Tumor volume decreased by a mean of 0.35 cm^3 to a mean posttreatment volume of 1.86 ± 2.2 cm^3 (range 0.14 – 11.89 cm^3). Moreover, tumor volume at last follow-up corresponded to mean 77.56 ± 26.41% of TV (median 78, range 18.54 – 150.79% of TV; Fig. 1, B).

There was no statistically significant relationship between the tumor volume changes (as compared to baseline) and BED values. At 6, 12, 24, 36, 60 months and at last follow-up the corresponding p values were

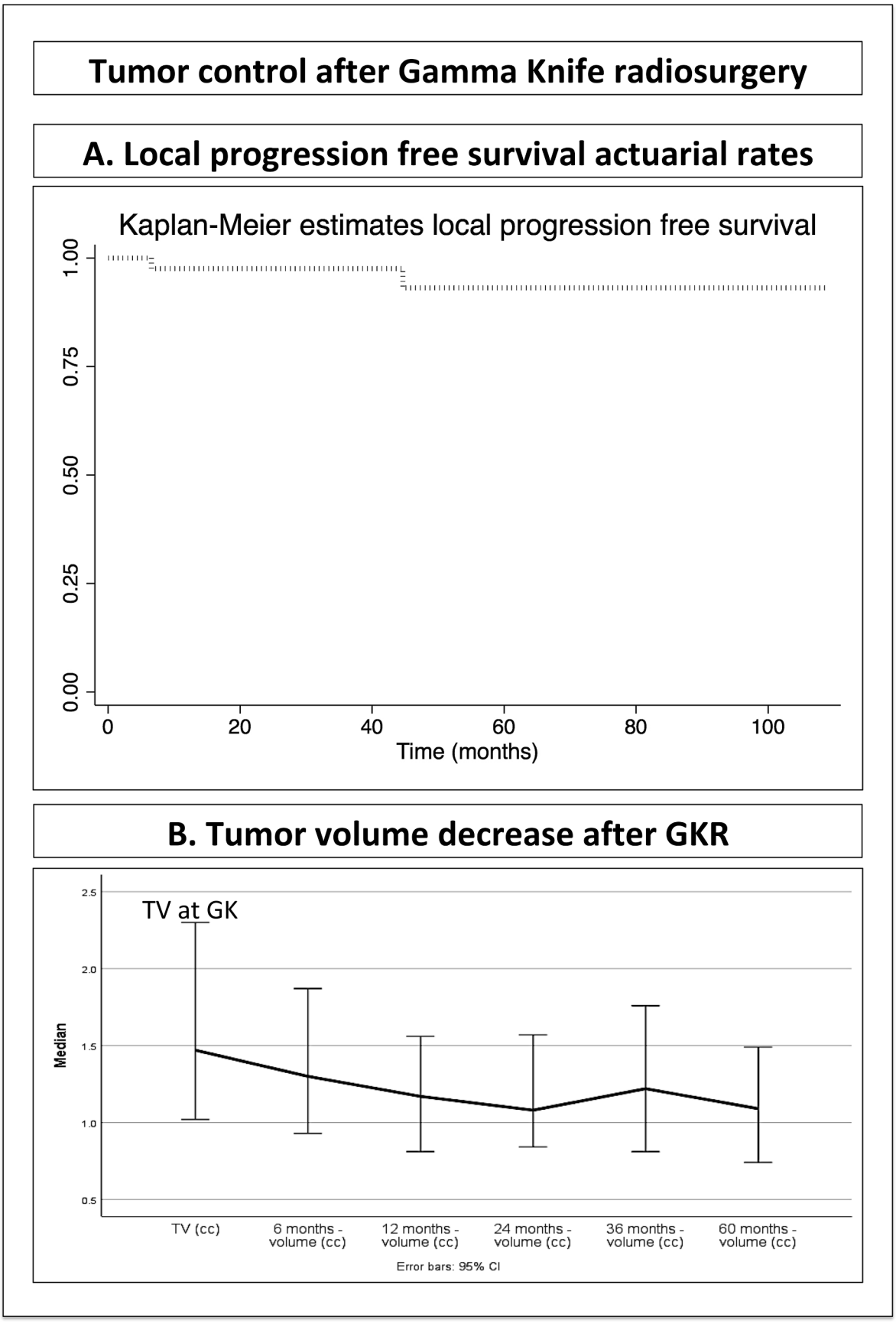

Fig. 1. A: PFS actuarial rates, B: tumor volume decreases after GKR.

Table 3
Statistical analysis (univariate).

Radiological outcome Pre-GKR Variables	**OR (95% CI)**	**p Value**
TV	**1.448 (1.001–2.093)**	**0.04**
Age ≥ 65	7.262 (0.563–93.684)	0.129
Presence of symptoms	3.383 (0.303–37.772)	0.322
Age	1.031 (0.947–1.121)	0.482
Presence of signs	2.240 (0.201–25.025)	0.512
Volumetric progression	0.500 (0.044–5.670)	0.576
Sex	1.586 (0.142–17.734)	0.708
Previous irradiation	0.045 (0.000-NA)	0.821
BED	0.980 (0.822–1.169)	0.821
Clinical outcome Pre-GKR Variables	***OR (95% CI)**	**p Value**
BED	**0.903 (0.79–1.027,**	
***coefficient using fractional polynomial)**		
CI −0.10; 0.01	**0.14**	
Volumetric progression	0.266 (0.049–1.444)	0.125
Age	0.976 (0.927–1.027)	0.342
Sex	1.929 (0.383–9.707)	0.426
Age ≥ 65	0.582 (0.127–2.655)	0.484
TV	0.872 (0.576–1.322)	0.520
Presence of symptoms	0.622 (0.064–6.050)	0.683
Previous irradiation	1.111 (0.103–12.037)	0.931
Presence of signs	NA	0.998
Overall outcome Pre-GKR Variables	**OR (95% CI)**	**p Value**
TV	1.612 (1.076–2.414)	**0.02**
Presence of signs	3.882 (0.370–40.709)	0.258
BED	0.926 (0.779–1.101)	0.383
Volumetric progression	0.431 (0.041–4.523)	0.483
Presence of symptoms	2.267 (0.196–26.271)	0.513
Age ≥ 65	1.600 (0.203–12.596)	0.655
Age	0.989 (0.920–1.063)	0.766
Sex	1.292 (0.118–14.138)	0.834
Previous irradiation	NA	0.999

* GKR = Gamma Knife radiosurgery; OR = Odds ratio; CI = confidence intervals; TV = target volume; BED = biologically effective dose; TV = target volume; NA = not applicable.

0.17, 0.18, 0.2, 0.19, 0.4 and 0.17, respectively.

3.3. Clinical outcome (n = 39, 7/46 excluded- as described in methods section)

The mean clinical follow-up duration was 43.76 ± 28.44 months (range 6–108 months).

The mean time to improvement was 12.7 months (range 6–48).

At last clinical follow-up, 28 patients (71.8%) remained stable, 10 (25.6%) improved and 1 patient (2.6%) worsened. Among 10 patients, which presented improvement, 3 had previous trigeminal neuralgia (37.5%, 3 out of 8), 6 had VIth nerve palsy (100% improvement) and 1 had trigeminal hypoesthesia (20%, 1 out of 5). The patient with pre-existing vocal cord palsy worsened. This was associated with an increase in the tumor volume up to 141.3% at last follow-up.

The actuarial probability of clinical improvement was 17.2% at 12 months, 20.1% at 25 months, 25.1% at 48 months and 30.4% at 51 months further remaining stable until last follow-up (Fig. 2, A).

Fig. 2 illustrates the correlation between BED and clinical improvement (standard error 0.59, confidence coefficient 0.79–1.027, CI −0.10; 0.01; p = 0.14; Fig. 2, B; Table 3). Highest probability of clinical improvement corresponded to a range of BED values between 56 and 61 Gy (Fig. 2, B), although this was not statistically significant.

The area under the ROC curve for BED and clinical improvement was 0.69 (Fig. 2, C) while for the dose and clinical improvement was 0.56 (figure for dose-clinical improvement relationship not illustrated). The exact relationship between dose, beam on time and BED is shown in Fig. 3.

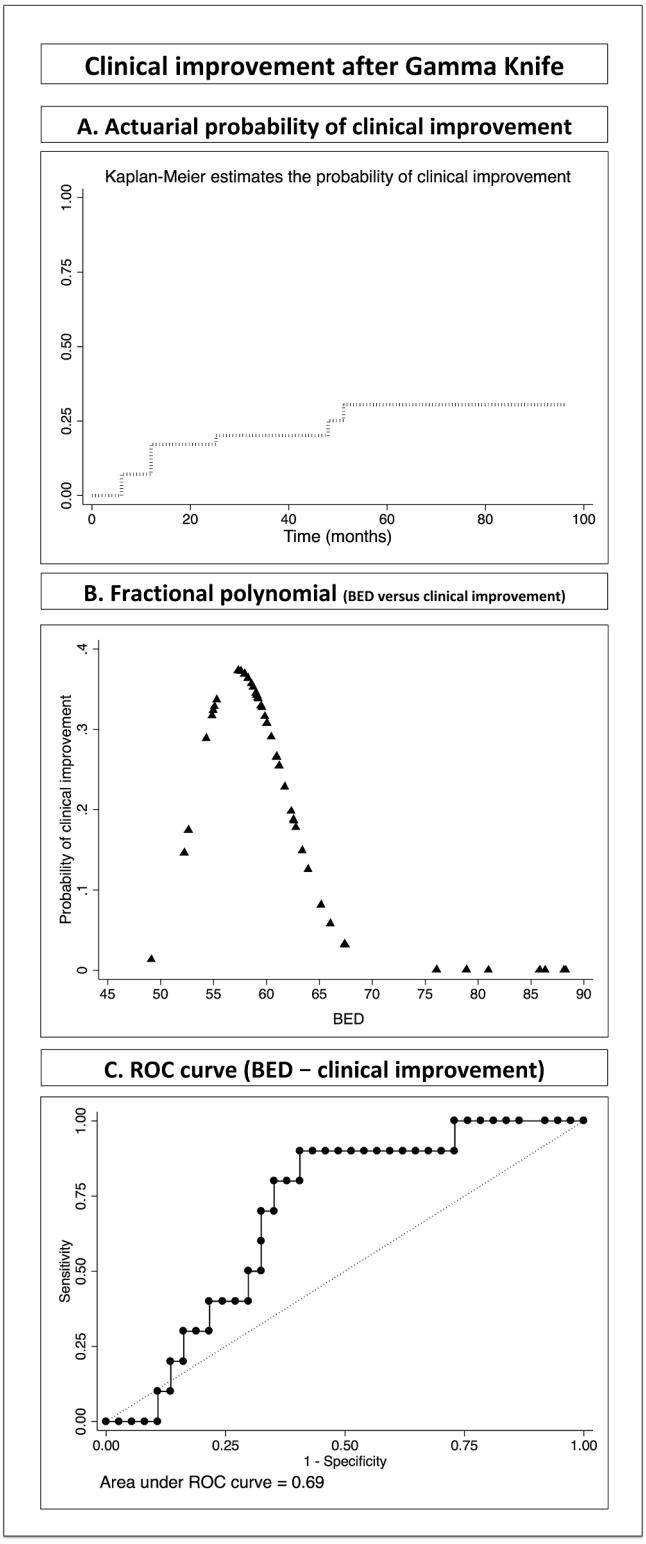

Fig. 2. A: actuarial probability of clinical improvement; B: fractional polynomial of BED in clinical improvement; C: ROC curve for BED-clinical improvement.

There was no statistically significant relationship between clinical improvement and volumetric changes after GKR at 6 months (p = 0.052), 12 months (p = 0.43), 24 months (p = 0.292), 36 months (p = 0.27), 60 months (0.93) and last follow-up (p = 0.66).

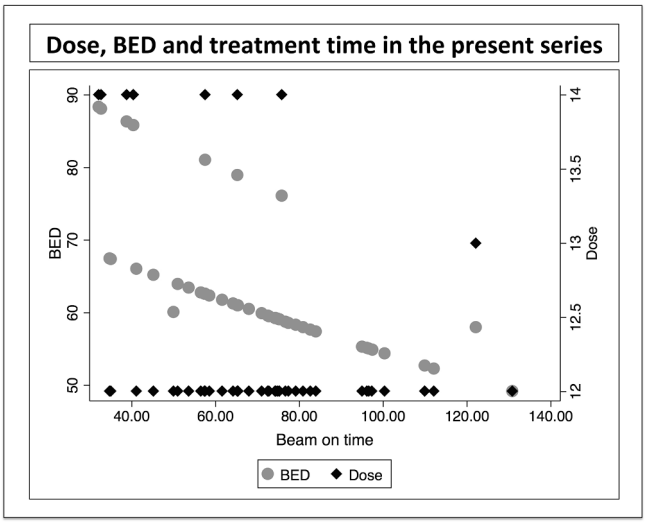

Fig. 3. A graphic illustration of the distribution of BED, dose and treatment time in the present series.

3.4. Overall outcome (42 patients included, 4 excluded)

Four patients (8.7%) were excluded from this analysis because of short clinical follow-up, which was less than 6 months (as per inclusion criteria).

Favorable overall outcome was documented in 39 patients (92.9%).

An unfavorable outcome was documented in 3 patients (7.1%). The first patient had an asymptomatic and the second patient had symptomatic tumor progression. In the third case, there was asymptomatic pseudoprogression 6 months after GKR. This case presented with further tumor decrease during follow-up course, in absence of any symptoms.

The only predictor of unfavorable overall outcome according to univariate analyses was the higher pretherapeutic TV (HR 1.612, 95% CI 1.076–2.414, p = 0.021).

3.5. Adverse radiation effects

In the present study there were no serious adverse radiation effects. In two patients, the follow-up MRI performed at 6 months following GKR revealed peritumoral edema, which was asymptomatic and transient in both cases.

4. Discussion

Here, we report the outcomes of GKR as first intention treatment for PCFM. The overall tumor control rate was 93.6% after a mean follow-up of 47.8 ± 28.46 months. Radiological progression-free survival at 1, 3 and 5 years were 98%, 98% and 94%. Higher pretherapeutic tumor volumes were predictive for higher likelihood of tumor progression. Clinically, 10 patients (23.8%) improved and only 1 patient (2.4%) worsened. Highest probability of clinical improvement corresponded to a range of BED values between 56 and 61 Gy, although this was not statistically significant. However, the correlation BED and symptom improvement was higher as compared with the prescribed dose and symptom improvement. There were no serious adverse radiation effects.

There are few series evaluating the role of stereotactic radiosurgery in PCFM. In recent GKR series, the tumor control ranges from 87 to 100 % (follow-up range: 29–84 months) and neurologic preservation ranges from 85 to 100 %[20,21,33,36-39]. Pollock et al.[40] compared the surgical resection with the GKR. The overall recurrence rate was significantly higher in the resection group (12 versus 2%; p = 0.04) while GKR ensured longer control after Simpson grade II resection (P = 0.05) or grades III to IV resections (P = 0.001)[40]. Thus, GKR was suggested as equal or better than surgical resection in small to medium size tumors, upon the degree of resection expected[40].

Previously, limited number of series analyzed the predictive factors of PCFM progression. According to Nicolato et al., the only significant factor was meningioma's biological aggressiveness of the meningioma (grade II or III versus I)[38]. Flannery et al. reported that meningioma volume ≥ 8 cm^3 (p = 0.001) and male sex (p = 0.02) were predictive of petroclival meningioma progression[33]. Muticentric study by Sheehan et al. revealed that age > 65 years, prior history of irradiation and higher pretherapeutic meningioma tumor volume are associated the tumor progression[20]. In the present series, there was no statistically significant relationship between the tumor volume changes (as compared to baseline) and BED values. This raises the question whether such volumetric changes would be pathology dependent. Alternatively, the low number of cases included here might be responsible for such findings. With the state-of-art of the current literature, further analysis on larger cohorts and various anatomical locations are necessary before drawing further conclusions.

The novelty of the present study is mainly related to the evaluation of the BED and further involvement in tumor control or clinical improvement. Here, in the present manuscript, the number of failures with regards to PFS were too small to be able to perform a correct analysis as related to this parameter. In the case of the patients reported here, there were no gaps in treatment delivery. However, calculation of BED for multi isocentric plans remains a complicated process. It would require a detailed knowledge of dose contribution from each isocenter, in each voxel in the region of interest in a given treatment plan. This information is currently not available from the current commercial version of the LGP. As a recall, the efficacy of a radiation treatment for neoplastic entities is related to producing double-strand DNA breaks in the target tissue while engendering cell death and apoptosis. For many years, it has been considered that dose rate or the radiation dose itself are relevant for outcomes after GKR. However, treatment time has emerged as more relevant[41]. In fact, with longer treatment time, there is a greater possibility for DNA to repair, and thus this might decrease the biological effectiveness of a given dose, as compared with shorter treatment times.

In the present report, BED values between 56 and 61 Gy were suggestive for better clinical outcomes, although not statistically significant. One explanation would be that BED might affect in a differential manner the tumor control and symptomatic improvement, causing several radiobiological cascades while sparing others. The interesting fact is that for a narrow range of doses (12 to 14 Gy, 2 units difference), the variation of BED was much larger (49.1–88.3 Gy, 39.2 units) in the current analysis. As a comparison with other pathologies, prescribed radiation doses and the corresponding BED as function of beam-on treatment time values would be of interest. Recently, a study on the effect of BED on the SRS treatment outcomes of trigeminal neuralgia was published[22]. In that report, although the targeting philosophy differs (not an irradiated volume, as here, but a dose on a point on the trigeminal nerve), there was also a narrow prescription dose, ranging between 75 and 97.9 Gy, delivered in a radiation time between 25 and 135 min. The corresponding variation in BED ranged between 1550 and 2600 Gy. Interestingly, the authors stated that "pain free" status developed more slowly at lowed BED values. In the current study, such BED values favoring therapeutic improvement, within a particular range of 56 to 61 Gy (as reflected by Fig. 2) for a narrow range of physical dose (12 to 14 Gy), might represent a similar therapeutic window to what is considered the one related to the physical dose in the context of tumor control after radiosurgery for meningiomas. In fact, it is now well acknowledged that the marginal dose prescription for presumed WHO grade I meningiomas is between 12 and 15 Gy depending on centers and risk structures (brainstem or optic pathways) constraints. Such physical dose therapeutic window might further apply to BED both in terms of tumor control and clinical alleviation. Although our series is small to raise potential BED values related to radiological failure, we tried to provide the reader such preliminary findings for clinical improvement.

However, such findings should be replicated in larger cohort.

Our study has the inherent limitations of any cohort study, with potential selection bias, residual confounds, retrospective analysis of prospectively collected data etc. The calculation of the BED was made, as already stated, by the basic BED approach as previously described in the literature and not by the voxel-to-voxel approach, which is a method rather complicated and not currently available on accurate basis. In this sense, some approximations might exist. Another limitation is the small number of subjects in this cohort. However, they benefitted from a rigorous follow-up, at precise time-points. A third limitation is that posterior fossa meningiomas can cause a variety of different symptoms depending on location. Here, we have included all patients with clinical improvement due to the limited sample size, rather than focusing on one anatomical location. Further studies on larger cohorts would be able to clarify such aspect using the specific individual anatomical location.

5. Conclusions

Our results confirm that primary GKR for PCFM is safe and effective. Higher pretherapeutic tumor volume was predictor of volumetric progression and of overall outcome. Highest probability of clinical improvement could potentially correspond to a range of BED values between 56 and 61 Gy, although this was not statistically significant. However, our series is small and such findings should be validated in larger cohorts, other anatomical locations, as well as other pathologies treated by GKR. The importance of BED in such approach should be further validated in larger cohorts and with further evaluating its effect on other benign tumors treated with SRS.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name of institute/committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained prior to the procedure.

References

[1] Cudlip SA, et al. Posterior fossa meningiomas: surgical experience in 52 cases. Acta Neurochir (Wien) 1998;140(10):1007–12.
[2] Roberti F, et al. Posterior fossa meningiomas: surgical experience in 161 cases. Surg Neurol 2001;56(1):8–20.
[3] Markham JW, et al. Meningiomas of the posterior fossa; their diagnosis, clinical features, and surgical treatment. AMA Arch Neurol Psychiatry 1955;74(2):163–70.
[4] Lobato RD, et al. Meningiomas of the basal posterior fossa. Surgical experience in 80 cases. Neurocirugia (Astur) 2004;15(6):525–42.
[5] Corniola MV, et al. Posterior fossa meningiomas: perioperative predictors of extent of resection, overall survival and progression-free survival. Acta Neurochir (Wien) 2019;161(5):1003–11.
[6] Simpson D. The recurrence of intracranial meningiomas after surgical treatment. J Neurol Neurosurg Psychiatry 1957;20(1):22–39.
[7] Gousias K, Schramm J, Simon M. The Simpson grading revisited: aggressive surgery and its place in modern meningioma management. J Neurosurg 2016;125(3):551–60.
[8] Hasseleid BF, et al. Surgery for convexity meningioma: Simpson Grade I resection as the goal: clinical article. J Neurosurg 2012;117(6):999–1006.
[9] McGovern SL, et al. A comparison of World Health Organization tumor grades at recurrence in patients with non-skull base and skull base meningiomas. J Neurosurg 2010;112(5):925–33.
[10] Shen T, Friedman RA, Brackmann DE, Slattery WH, Hitselberger WE, Schwartz MS, et al. The evolution of surgical approaches for posterior fossa meningiomas. Otol Neurotol 2004;25(3):394–7.
[11] Saleh EA, et al. Posterior fossa meningioma: surgical strategy. Skull Base Surg 1994;4(04):202–12.
[12] Javalkar V, Banerjee AD, Nanda A. Posterior cranial fossa meningiomas. J Neurol Surg B Skull Base 2012;73(1):1–10.
[13] Santacroce A, et al., Long-term tumor control of benign intracranial meningiomas after radiosurgery in a series of 4565 patients. Neurosurgery, 2012. 70(1): p. 32-9; discussion 39.
[14] Kollová A, et al. Gamma Knife surgery for benign meningioma. J Neurosurg 2007;107(2):325–36.
[15] Chang JH, et al. Complications after gamma knife radiosurgery for benign meningiomas. J Neurol Neurosurg Psychiatry 2003;74(2):226–30.
[16] Kondziolka D, et al. Long-term Outcomes After Gamma Knife Radiosurgery for Meningiomas. Am J Clin Oncol 2016;39(5):453–7.
[17] Kondziolka D, Flickinger JC, Perez B. Judicious resection and/or radiosurgery for parasagittal meningiomas: outcomes from a multicenter review. Gamma Knife Meningioma Study Group. Neurosurgery 1998;43(3):405–13.
[18] Kondziolka D, Levy EI, Niranjan A, Flickinger JC, Lunsford LD. Long-term outcomes after meningioma radiosurgery: physician and patient perspectives. J Neurosurg 1999;91(1):44–50.
[19] Kondziolka D, et al., Radiosurgery as definitive management of intracranial meningiomas. Neurosurgery, 2008. 62(1): p. 53-8; discussion 58-60.
[20] Sheehan JP, et al. Gamma Knife radiosurgery for posterior fossa meningiomas: a multicenter study. J Neurosurg 2015;122(6):1479–89.
[21] Starke RM, et al. Gamma knife radiosurgery of meningiomas involving the foramen magnum. J Craniovertebr Junction Spine 2010;1(1):23.
[22] Tuleasca C, et al. Establishment of a Therapeutic Ratio for Gamma Knife Radiosurgery of Trigeminal Neuralgia: The Critical Importance of Biologically Effective Dose Versus Physical Dose. World Neurosurg 2020;134:e204–13.
[23] Tuleasca C, et al. Biologically effective dose and prediction of obliteration of unruptured arteriovenous malformations treated by upfront Gamma Knife radiosurgery: a series of 149 consecutive cases. J Neurosurg 2021;134(6):1901–11.
[24] Flickinger JC, et al. Gamma knife radiosurgery of imaging-diagnosed intracranial meningioma. Int J Radiat Oncol Biol Phys 2003;56(3):801–6.
[25] Lyndon D, et al. Dural masses: meningiomas and their mimics. Insights Imaging 2019;10(1).
[26] Watts J, et al. Magnetic resonance imaging of meningiomas: a pictorial review. Insights Imaging 2014;5(1):113–22.
[27] Ly KI, Wen PY, Huang RY. Imaging of central nervous system tumors based on the 2016 World Health Organization Classification. Neurol Clin 2020;38(1):95–113.
[28] Sanverdi SE, et al. Is diffusion-weighted imaging useful in grading and differentiating histopathological subtypes of meningiomas? Eur J Radiol 2012;81(9):2389–95.
[29] Lee EJ, et al. A novel weighted scoring system for estimating the risk of rapid growth in untreated intracranial meningiomas. J Neurosurg 2017;127(5):971–80.
[30] Hall EJ, Brenner DJ. The radiobiology of radiosurgery: rationale for different treatment regimes for AVMs and malignancies. Int J Radiat Oncol Biol Phys 1993;25(2):381–5.
[31] Jones B, et al. The role of biologically effective dose (BED) in clinical oncology. Clin Oncol (R Coll Radiol) 2001;13(2):71–81.
[32] Jones B, Hopewell JW. Modelling the influence of treatment time on the biological effectiveness of single radiosurgery treatments: derivation of “protective” dose modification factors. Br J Radiol 2018:20180111.
[33] Flannery TJ, et al. Long-term control of petroclival meningiomas through radiosurgery. J Neurosurg 2010;112(5):957–64.
[34] Kim KH, et al. Clinical and radiological outcomes of proactive Gamma Knife surgery for asymptomatic meningiomas compared with the natural course without intervention. J Neurosurg 2018:1–10.
[35] Snell JW, et al. Assessment of imaging studies used with radiosurgery: a volumetric algorithm and an estimation of its error. *Technical note* J Neurosurg 2006;104(1):157–62.
[36] Starke RM, et al. Gamma Knife surgery of meningiomas located in the posterior fossa: factors predictive of outcome and remission. J Neurosurg 2011;114(5):1399–409.
[37] Subach BR. et al., Management of petroclival meningiomas by stereotactic radiosurgery. Neurosurgery, 1998. 42(3): p. 437-43; discussion 443-5.
[38] Nicolato A, et al. Gamma knife radiosurgery in meningiomas of the posterior fossa. Experience with 62 treated lesions. Minim Invasive Neurosurg 2001;44(4):211–7.

[39] Zenonos G, et al. Gamma Knife surgery in the treatment paradigm for foramen magnum meningiomas. J Neurosurg 2012;117(5):864–73.
[40] Pollock BE, et al. Stereotactic radiosurgery provides equivalent tumor control to Simpson Grade 1 resection for patients with small- to medium-size meningiomas. Int J Radiat Oncol Biol Phys 2003;55(4):1000–5.
[41] Hopewell JW, et al. Application of the concept of biologically effective dose (BED) to patients with Vestibular Schwannomas treated by radiosurgery. J Radiosurg SBRT 2013;2(4):257–71.