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Technical Notes & Surgical Techniques

# A retrospective case series on the usefulness of fractionated stereotactic radiotherapy for benign intracranial tumors

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ABSTRACT

*Introduction:* Conventional radiation therapy has been progressively replaced by fractionated stereotactic radiotherapy (FSRT) and single fraction radiosurgery for dealing with benign intracranial lesions. Purpose of our study is to investigate the safety and efficacy of FSRT in a series of patients with benign intracranial tumors.
*Methods:* 31 patients with benign intracranial lesions treated with FSRT between 2006 and 2014 were retrospectively reviewed. Indications for treatment included post-operative residual tumor growth or symptomatic exacerbation in patients in whom surgery was not indicated. A clinical and radiological outcome evaluation was performed. Univariate analysis was executed to identify predictors for post-treatment neurological function and radiological tumor control.
*Results:* Median age was 62 years (range 22–82). The lesions treated included 20 meningiomas, 2 vestibular schwannomas, 7 pituitary adenomas, 1 craniopharyngioma, 1 jugular-tympanic paraganglioma. Median clinical target volume was 14.59 $cm^3$ (range 0.43–159.06) and median planning treatment volume was 18.16 $cm^3$ (range 0.81–217.24). Median total dose was 45 Gy (range 25–54), and median daily fraction 4 Gy (range 1.8–9). At a median follow-up of 78 and 50 months, respectively clinical and neuroradiological, no tumor had larger dimensions, and only one lesion changed in a way other than size determining a concomitant clinical worsening. Other three patients deteriorated without evidence of radiological progression. Conversely, 12 patients improved clinically. No significant predictor for post-treatment neurological function or radiological tumor control was found.
*Conclusion:* FSRT may represent, when indicated, a safe and effective treatment modality for benign intracranial tumors, especially for large/irregular lesions.

## 1. Introduction

Surgery is usually considered the treatment of choice for intracranial benign tumors as a gross total resection may assure long-term local control. However, the optimal management strategy has to be tailored on the basis of different factors such as the patients' preoperative clinical status, the size and location of the lesions, the vascular involvement as well as the surgeon's experience [1–10].

In symptomatic de novo or recurrent/residual patients in which surgery is not an option or in patients with documented neuroradiological residual tumor growth, radiation therapy is an option to control the disease. Although conventional fractionated radiation therapy has been historically effective in controlling these types of tumors [1–3], over the last 2 decades fractionated stereotactic radiotherapy (FSRT) and single fraction radiosurgery have progressively replaced conventional radiotherapy in these clinical situations. This change is due to technologic advances in both the precise delivery techniques and the accurate, rapid dose calculation methods. More focused techniques of irradiation have a steeper dose gradient between the tumor and the surrounding normal tissue [1,11–29]. The aim of this

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retrospective analysis is to evaluate the safety and efficacy of FSRT in a series of patients with benign intracranial tumors.

## 2. Materials and methods

A total of 36 patients with benign skull base lesions allocated to be treated with FSRT between 2006 and 2014 forms the subject of this retrospective case series. Five patients were excluded from the study: treatment could not be tolerated/completed (one patient); patient died of tumor unrelated cause before treatment could be completed (one patient); patient died of tumor unrelated cause before follow up MRI could be obtained (one patient); patients were lost to follow-up (two patients). Thus 31 patients could be evaluated.

IRB approval was obtained for this retrospective study.

Diagnosis was based on histological confirmation, or, for cases without surgery, on typical radiographic appearance. Indications for treatment included 1) post-operative residual tumor growth or 2) symptomatic exacerbation in patients in whom surgery was not indicated or could not be medically tolerated by the patient (age, comorbidities, etc.) either in an upfront setting or in a recurrent or residual tumor setting.

Of these 31, 30 patients were treated using serial Intensity-modulated radiation therapy (IMRT) using the Peacock System (NOMOS, Corp. Sewickley, PA). The remaining patient was treated using 7 static IMRT fields with True Beam (Varian Medical Systems, Inc. Palo Alto, CA.).

Gross target volume (GTV) was defined as the contrast enhancing tumor demonstrated on T1-weighted MRI fused with the simulation CT images with IV contrast. Clinical target volume (CTV) was considered the same as GTV. A 2–3 mm margin was added to define the planning target volume (PTV). The prescription dose to PTV ranged from 25 Gy in 5 fractions to 54 Gy in 28 fractions. The median prescription dose was 45 Gy. Dose constraints for adjacent normal structures were initially based on normal tissue tolerance tables of Emami et al. modified by alpha beta calculations of the hypofractionated regimens and later based on TG 101 [30,31].

Outcome evaluation was performed both from a radiological and a clinical standpoint. For the radiological evaluation, the pretreatment and most recent post treatment scan were carefully evaluated independently by two board certified neuroradiologists and described according to an author developed four point scale (Table 1). The tumor size and response was calculated according to a modified Mc Donald's criteria [32]. Tumor control was defined as the absence of radiological tumor progression.

Clinical evaluation was determined considering both subjective and objective criteria. The subjective criteria consisted of the patients' own evaluation of the evolution of their symptomatology. This information was gathered through patient interviews at follow up appointments or over the telephone. The objective criteria relied on the treating team's clinical evaluation at follow up appointments, including assessment of the Karnofsky performance status (KPS). Improvement in neurological symptoms was defined as a resolution or improvement in neurological deficit or tumor related symptoms.

Pre-treatment KPS was determined at the initial presentation of the patient by our treating team clinician and post-treatment KPS was determined at every follow up visit of the patient, and the latest score was utilized for this study.

**Table 1**
Radiological scoring.

| Score | Determination |
|---|---|
| 1 | Smaller |
| 2 | Unchanged |
| 3 | Larger |
| 4 | Change other than size (aggressivity, contrast enhancement, parenchymal invasion, bleeding) |

Statistical analysis was performed using SPSS software (version 20; SPSS Inc., Chicago, IL). Univariate analysis (Pearson Chi-square test for discrete variables, paired *t*-test for the continuous ones) was used to evaluate the presence of significant predictors for post-treatment neurological function as well as for radiological tumor control. Statistical significance was set at $p < 0.05$.

## 3. Results

### 3.1. Population

Of the 31 patients included in the study, there were 21 Female patients and 10 male patients, yielding a 2.1:1 ratio Female to Male. The age ranged from 22 to 82 years with a median age of 62 years.

The initial clinical presentation included only focal neurological deficits in two cases, and cranial nerve deficits in 23. Two patients presented with both seizures and hemiparesis. One patient suffered from epilepsy and multiple cranial nerve deficits. Chronic headaches represented the only clinical symptoms in three patients.

Regarding the cranial nerve deficits, in detail, visual field defects were present in 16 cases, an impaired ocular motility in five, trigeminal dysaesthesia in one, cranial nerve VII palsy in three, vestibulocochlear nerve dysfunction in eight, and lower cranial nerves deficit in two. Ten patients had multiple cranial nerve deficits at presentation. Endocrine deficits were present in seven patients.

### 3.2. Lesions treated

The types of lesions treated included 20 meningiomas, two vestibular schwannomas, seven pituitary adenomas, one craniopharyngioma, and one jugular-tympanic paraganglioma.

Meningiomas presented in the following locations: optic canal in three cases, sphenoid wing in five, falx cerebri in two, tentorium cerebelli in two, cerebellopontine angle in two, petroclival region in three, cavernous sinus in two. One patient harbored a sphenopetroclival meningioma involving the cavernous sinus.

One of the patients with a sphenoid wing meningioma suffered from neurofibromatosis type II, and underwent bilateral vestibular schwannomas microsurgical removal.

Prior to FSRT, 10 patients underwent one surgical intervention (biopsy in three cases, and surgical removal in seven cases), and nine patients underwent two surgical resections. In 12 patients, the radiological characteristics of the lesion were consistent with the diagnosis of benign tumor [vestibular schwannoma in 2 cases and meningioma in 10 cases (2 in the sphenoid wing, 2 in the optic canal, 2 in the cerebellopontine angle, 2 in the petroclival region, one in the tentorium cerebelli, one in the cavernous sinus)] and surgery was not indicated.

The CTV ranged from 0.43 to 159.06 $cm^3$ with a median volume of 14.59 $cm^3$. The PTV ranged from 0.81 to 217.24 $cm^3$ with a median volume of 18.16 $cm^3$ (Table 2).

The median total dose was 45 Gy (range, 25–54 Gy), with a median daily fraction of 4 Gy (range, 1.8–9 Gy). The fractionation ranged from 5 to 28 fractions (median, 10 fractions) (Table 2).

In a patient with a petroclival meningioma, in order to protect the optic apparatus and the brainstem, the target was separated in two smaller ones that respectively received 20 and 25 Gy in 5 fractions.

### 3.3. Treatment evaluation

Clinical follow-up time after FSRT ranged from 8 to 109 months with a median of 78 months. Median radiological follow-up was 50 months (range 7–102).

Six patients died during the follow-up period. The cause of death was a systemic malignancy in two patients, dementia in two cases, respiratory in one, and tumor progression in one case. This patient

**Table 2**
Average tumor volumes and radiation dosage for the different type of tumors.

| Diagnosis | Median CTV (range) ($cm^3$) | Median PTV (range) ($cm^3$) | Median total dose (range) (Gy) | Median daily fraction (range) (Gy) | Median number of fractions (range) |
|---|---|---|---|---|---|
| Meningioma (20 cases) | 13.44 (2.94–159.06) | 17.02 (5.78–217.24) | 42.5 (25–54) | 4 (1.8–9) | 10 (5–28) |
| Vestibular schwannoma (2 cases) | 0.43 | 0.81 | 26.25 (25–27.5) | 5.25 (5–5.5) | 5 in both the cases |
| Pituitary adenoma (7 cases) | 15.65 (4.26–31.05) | 19.55 (6.27–37.47) | 45 (25–50.4) | 1.8 (1.8–5) | 25 (5–28) |
| Craniopharyngioma (1 case) | 28.86 | 54.48 | 50.4 | 1.8 | 28 |
| Jugular-tympanic paraganglioma (1 case) | – | – | 25 | 5 | 5 |
| Entire series (31 cases) | 14.59 (0.43–159.06) | 18.16 (0.81–217.24) | 45 (25–54) | 4 (1.8–9) | 10 (5–28) |

CTV, Clinical Target volume; PTV, planning treatment volume.

presented a progressive worsening of his neurological status from brainstem compression due to his cerebellopontine angle meningioma whose size remained unchanged. Hydroxyurea and rapamycin chemotherapy produced only a temporary improvement of his symptoms.

Radiological evaluation revealed no changes in 10 (32.26%), and a reduction in tumor size in 20 patients (64.52%). One lesion changed in a way other than size.

After FSRT, 12 patients had a clinical improvement in one or more neurological deficits. On the other hand, three patients deteriorated without evidence of tumor progression on imaging (2 had a stable tumor and 1 had a smaller tumor on follow-up MRI).

In detail, a patient with an optic nerve sheath meningioma, one with a cerebellopontine meningioma, and one with a pituitary adenoma worsened, respectively, after 14, 23, and 32 months. The patient with cerebellopontine meningioma was the one who died. Two of these patients underwent a reoperation. Surgery was not indicated in the patient harboring a cerebellopontine angle meningioma due to his poor clinical conditions.

Gamma knife radiosurgery has a reported accuracy of $< 1$ mm while fractionated stereotactic methods, as utilized in the above patients, have a setup accuracy of approximately $< 2$ mm. However, gamma knife radiosurgery with the fixed head frame, typically is completed in one fraction. The late effects of radiation, i.e. normal tissue complications, are highly dependent on the dose per fraction and treatment volume. Thus, when critical structures are encompassed by the tumor, such as the optic nerve sheath meningioma encompassing the optic nerve, or immediately adjacent to the tumor, such as the chiasm in pituitary adenomas, it typically is safer to fractionate the patient's treatment unless there is adequate distance ($> 5$ mm from the normal structure and the tumor). Also, when tailoring treatments for patients with larger tumors ($> 10\ cm^3$), fractionated stereotactic radiotherapy is preferred over 1 fraction radiosurgery.

A female with a right sphenoid wing meningioma that changed in a way other than size also presented a worsening of her clinical symptoms 55 months after FSRT, when she was 83 years old. She experienced a progressive loss of vision in her right eye, and developed numbness of right cheek. At the time of analysis, her KPS was 80, unchanged if compared with the pre-treatment one.

Neurological status did not change after FSRT in 15 patients. No significant difference was found between pre-treatment and post-treatment KPS ($p = 0.359$, paired *t*-test). No change was observed in 17 cases (54.84%), an improvement in 10 patients (32.26%), and a decrease in 4 (12.9%). Overall, pre- and post-treatment KPS were found to be $\geq 70$ in 21 and 22 patients, respectively.

When considering the two clinical determining factors jointly, of 31 patients, seven improved radiologically (smaller) and clinically, 12 improved radiologically (smaller) but were unchanged clinically (stable), five were found to be unchanged radiologically (stable) but improved clinically, three were unchanged (stable) both radiologically and clinically, two were radiologically unchanged (stable) but clinically worse, one was found to be radiologically improved (smaller) but clinically worse, and one was radiologically changed in a way other than size while clinically worsened.

No obvious adverse effects were reported by the study team clinicians nor the patients. One patient had severe back pain from pre-existent pathology and could not tolerate lying still on the treatment table for the duration of the fractions and therefore was excluded from the study.

On univariate analysis, gender, age, radiation doses (total dose as well as daily fraction), PTV, lesion type, lesion location, and previous surgery were not correlated with post-treatment neurological function nor with changes at radiological evaluation.

## 4. Discussion

Overall, based on the data in this study, the conclusion can be made that Intensity Modulated FSRT can successfully be used to treat benign intracranial lesions under the aforementioned indications.

At a median follow-up of 78 and 50 months, respectively clinical and neuroradiological, no tumor had larger dimensions, and only one lesion changed in a way other than size determining a concomitant worsening of the clinical conditions of the patient. Other three patients deteriorated without evidence of tumor progression on imaging. On the other hand, after FSRT, 12 patients had a clinical improvement in one or more neurological deficits.

Even if the comparison among different series may be difficult due to different criteria in defining tumor control as well as to various follow-up duration, our results seem to be in line with those of recently published studies. Indeed, FSRT has been reported as a valuable option for the management of several intracranial benign tumors with 5 year tumor control rates of 88–98% for meningiomas [11,33–38], 86–97.9% for acoustic neuromas [24,39–44], 93–99% for pituitary adenomas [37,45–50], and 81.3–100% for craniopharyngiomas [25,26,51–53].

The tumor location has been reported by some authors as a predictor of local control. For example, a recent study showed an excellent local control (100% at 5 and 10 years) in patients with optic nerve sheath, suprasellar/parasellar/cavernous meningiomas if compared with falx meningiomas (54% at 5 years), and with those in other skull base sites (88% at 5 and 81% at 10 years). These results entailed the more indolent disease characteristics of the first group with little justification for more invasive treatment methods [33].

However, some studies showed a worse local control of the patients receiving FSRT after previous surgery than patients who received FSRT as the initial treatment. This may represent a selection bias underlining the more aggressive features of grade I meningiomas requiring post-operative radiotherapy [12,33,54].

Our findings and data from literature support the role of FSRT as an effective treatment modality for large recurrent or enlarging intracranial benign lesions with a 5-year tumor control comparable or even superior to conventional radiotherapy/single fraction radiosurgery [1,11–26].

Furthermore, from a radiobiologic standpoint, dose fractionation has known advantages compared with a single fraction dose. These include reoxygenation of the tumor cells leading to greater

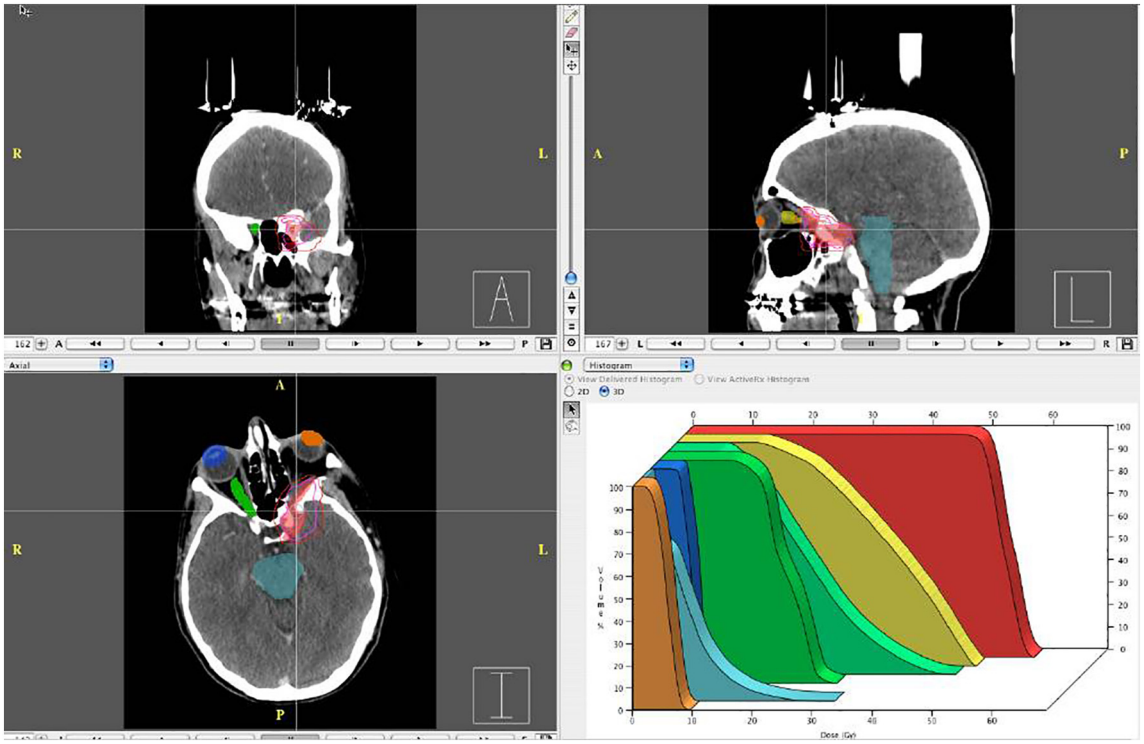


**Fig. 1.** Optic nerve meningioma treated with 50 Gy/25 tx/6 MV. Pink isodose line = 100% of prescribed dose; red isodose line = 90% of prescribed dose; solid red = target volume.
Dose volume histogram. Red = planning target volume; aqua = brainstem; orange = left lens; blue = right lens; light green = optic chiasm; yellow = left optic nerve; dark green = right optic nerve. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

radiosensitivity, cycling thru the cell cycle to a more radiosensitive phase, and more repair of the adjacent normal tissue (with a lower dose per fraction) (Fig. 1). This becomes even more relevant with larger tumors ($> 10\,cm^3$) or tumors with close proximity to critical structures (orbits, brainstem, cranial nerves, cochlea, normal brain parenchyma). Radiosurgery simply cannot effectively treat these type of tumors with reasonable toxicity. In summary, dose fractionation customization allows an optimal delivery of therapeutic radiation to the lesion maximizing the dose to the target while simultaneously minimizing the dose to the surrounding structures. This technique may decrease acute and late toxicity [4,55–58].

In our study, a variety of fractionation regimens were utilized varying from 5 to a more conventional 28 fractions. This underlines that the optimal dose fractionation schedule for stereotactic radiotherapy has to be tailored on a case-by-case basis depending on the specific lesion characteristics. The most common fractionation dose was 25 Gy/in 5 fraction that was utilized in 10 patients. Dose calculations were performed with the alpha/beta formula, assuming an alpha/beta ratio of 10 for acute (tumor) effects and 2 for late (normal tissue) effects. The calculated acute effects for this regimen was 31.25 Gy, and the calculate late effects was 43.75 Gy, when compared to conventionally fractionated radiotherapy with a fraction size of 2 Gy. The investigators felt comfortable with this dose regimen since these calculated doses did not exceed the tolerance of the adjacent normal tissues (brain, brainstem, and optic apparatus). For the smaller tumors, away from critical structures, either FSRT or SRS were excellent treatment options. Patient choice played an important role in the decision process (i.e. some patients refused the gamma knife headframe placement).

It is worth mentioning that neuroradiological tumor control does not always goes hand in hand with clinical control, as demonstrated by the fact that about 10% of our patients had tumor control from a neuroradiological standpoint but were worse clinically, with one of them dying of tumor related cause.

There was independent interpretation by 2 board certified neuroradiologists who were not involved in the care of the patients. This objective reading helped to disencumber the potential error inherent in radiologic interpretation. Of note, there were 2 patients with differing interpretations by the neuroradiologists. For these two patients, the 2 neuroradiologists convened to discuss and after further review, agreed upon a single conclusion. We feel that this feature of our study helped reducing bias in images evaluation. Clinical and contextual information associated with images may influence surgeons' and even radiologists' evaluation, thus hindering an objective assessment. On the other hand, once again, we believe that the external review by two neuroradiologists who were not involved in patients' care provided an unbiased and accurate analysis of radiological data.

The major limitation of our study rests on its retrospective nature.

In conclusion, FSRT represents a safe and effective treatment modality when utilized under appropriate indications for diverse benign brain tumors. In particular, FSRT occupies an important place in the radiotherapy armamentarium for the management of large and irregular lesions because it permits, thanks to modern imaging and focused treatment, achievement of excellent tumor control with low morbidity.

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## Declarations of interest

None.

## 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 and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

For this type of study formal consent is not required.

## Informed consent

Informed consent was obtained from all individual participants included in the study.

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