Gamma Knife Radiosurgery for Management of Peri-optic Meningiomas


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ABSTRACT

Received: 23 June 2015

Accepted: 24 October 2015

Key words: Radiosurgery, Gamma knife, Meningioma, Peri-optic

INTRODUCTION

Peri-optic meningiomas could refer to any intracranial meningiomas touching or in a close relation to the anterior visual pathway (AVP). The AVP is defined as the optic nerves, and chiasm. Visual symptoms result from direct compression or encasement of the optic apparatus. Visual disturbance is usually insidious or gradual. Other symptoms may include headache, mental changes, epilepsy, anosmia, or motor deficits.

Peri-optic meningiomas pose considerable therapeutic challenges because of their proximity to important cranial nerves, vasculature, and endocrine tissue at the anterior cranial base. Despite technical advances in open surgery, there are still potentially high risks of temporary or permanent neurological and endocrine dysfunction after surgical resection.

Gamma knife radiosurgery (GKS) could play an important role in the treatment strategy for meningiomas either as primary treatment or for patients with residual or recurrent meningiomas as a multimodality approach. The primary concern of single-fraction stereotactic radiosurgery (SRS) in the sellar and parasellar regions is the radiation tolerance of the anterior visual pathway (AVP). Currently, the tolerance dose of the anterior visual pathway in gamma knife radiosurgery is between 8 and 10 Gy in most of the studies.

PATIENTS AND METHODS

Patients population:

This is a retrospective analysis of a prospectively maintained study done in the Cairo Gamma Knife Centre in Nasser Institute. The study material included two hundred thirty three consecutive patients with benign skull base meningiomas in direct contact, displacing or within 3mm distance from the anterior visual pathway treated by single session gamma knife radiosurgery between July 2001 & July 2011 (10 years).
Exclusion criteria were; Atypical or malignant meningiomas, NF2 patients or multiple meningiomas, previous radiation therapy, staged volume GKRS for the same lesion, and follow-up less than 24 months. Every single patient had a pre-treatment whole brain MRI with contrast and a documented print out fresh visual field (VF) examination by perimeter. Regular follow-up was done by same investigations at regular intervals. (Fig. 3,4,5,6)

Radiosurgical Technique:

All patients underwent radiosurgical treatment with Leksell Gamma knife C- model (Elekta Instruments, Sweden, GA).

Immobilization was done using application of the stereotactic leksell frame G with the help of mild sedation and local anthesia. Stereotactic brain imaging using MRI doing a contrasted T1 weighted images 1.6mm or 2mm thickness, and zero spacing (in certain cases with intra orbital extension we may use fat suppression). Conformal dose planning by the radiosurgery team using the Gamma plan. Then Stereotactic radiation delivery to the target.

Tumour dosimetry:

The routine treatment strategy for benign meningiomas is to use 12 Gy prescription dose to the tumor margin with a desired tumor cover of 90% or more as previously reported. However, with meningiomas close to the visual pathway concessions to these requirements may have to be made. This can be done in one of two ways. Either the prescription dose is reduced from the desired 12 Gy or the percentage cover may be reduced to less than 90%. In the context of this material an arbitrary decision was taken to accept 80% instead of 90% tumor cover. This will be reflected in less than optimal conformity index & specificity. However, it has the advantage that enables the delivery of a greater total dose of radiation to the target than could be achieved by a reduction of the prescription dose to the whole tumor, with conventional acceptable cover and conformity measurements. (This is called suboptimal dose planning). (Table 1)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value (range)</th>
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<tbody>
<tr>
<td><strong>Male</strong></td>
<td>44(9%)</td>
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<tr>
<td><strong>Female</strong></td>
<td>96(51%)</td>
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<td><strong>Age (years)</strong></td>
<td>Median</td>
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<td><strong>Previous resection</strong>:</td>
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<td>Seno</td>
<td>166 (73%)</td>
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<td>more than one</td>
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<td><strong>Site</strong></td>
<td>Touching the AVP</td>
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<td><strong>Tumor vol (ml)</strong></td>
<td>Range</td>
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<tr>
<td><strong>Mean</strong></td>
<td></td>
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<tr>
<td><strong>Prescription dose (Gy)</strong></td>
<td>Range</td>
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<tr>
<td><strong>Mean</strong></td>
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<tr>
<td><strong>prescription isodose %</strong></td>
<td>Range</td>
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<td><strong>Mean</strong></td>
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<td><strong>percentage cover %</strong></td>
<td>Range</td>
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<td><strong>Mean</strong></td>
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<tr>
<td><strong>max. dose at AVP (Gy)</strong></td>
<td>Range</td>
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<td><strong>Mean</strong></td>
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<td><strong>Follow-up (months)</strong></td>
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RESULTS

Radiological outcome:

Tumor volume after GK treatment was stable in one hundred thirty eight cases (59%), decreased in eighty three cases (36%), and increased in twelve cases (5%), that gives overall growth control rate 95%. (mean FU 4 years)

It was apparent that the prescription dose did not affect the radiological outcome "P=0.72". There was also no correlation between the radiological outcome and the Prescription isodose "P=0.17", cover percentage "p=0.82" or the target volume "p=0.17". It seemed that with increasing the duration of follow-up, more cases show radiological changes either enlargement or shrinkage "P=0.00"; and that indicates that longer follow-up is advisable.
There was also no relation between the tumor control and history of previous surgical resection "P=0.8", although the percentage of tumor enlargement was more in patients had more than one surgical resection "P=0.00". The control rate of cases that were histopathological diagnosed was 95.1%, while the control rate for cases that were diagnosed radiologically was 94.8%. That means that method of diagnosis did not affect the outcome (p=0.8). The actuarial progression free survival was found to be 99% at 3 years, 94% at 5 years, 87% at 8 years, and 62% at 10 years. (Fig. 1)

Visual outcome:

The visual outcome for each case depended on the last visual field exam at the time of data analysis compared to the visual field done before treatment. (Fig. 3-6). The visual field improved in ninety nine patients (42%), remained stable in one hundred nineteen (52%) and worsened in fifteen (6%). It is worth mentioning that out of cases that had pre-treatment VF deficit or blindness after exclusion of the normal cases the actual rate of VF improvement would be 58.5%.

Reviewing these 15 cases that had worse vision after treatment we found:

- Eight cases were accompanied with tumor growth,
- One case was accompanied with peri-tumoral oedema,
- Three cases were reported by the ophthalmologists to have glaucomatous field defect, (max. radiation dose to AVP in such cases were 7.7, 7.5 & 8.7 Gy)
- Three cases had mild deterioration in VF without apparent cause other than radiation (max. radiation dose to AVP in such cases were 9.5, 8.5 & 7.9 Gy)

The duration of pre-treatment VF affection also did not seem to affect the outcome (P=0.28). The closer relation between the lesion & AVP dose not seem to negatively affect the visual outcome comparing the visual outcome in patients having lesions touching and not touching the AVP. (P=0.7). There was no correlation between visual outcome and the domestic treatment parameters; prescription dose (P=0.8), isodose (P=0.93), percentage cover (P=0.83), target volume (P=0.55) or even the Max dose of radiation to the AVP (P=0.24). Although visual impairment was related to tumor enlargement (P=0.00). There was no relation between visual improvement & tumor shrinkage; (P=0.75). (Fig. 2)

There was an improvement in twenty nine patients out of fifty six patients that had pre-treatment ocular nerve palsy (51.8%). There was no correlation between improvement and duration of nerve palsy (P=0.23), or relation to tumor shrinkage (P=0.97).

Out of eighteen cases with pre-treatment proptosis, only six cases (33.3%) showed mild improvement, four patients of them had shown apparent tumor shrinkage in the follow-up MRI (P=0.37).

Complications:

Twenty-five patients (10.7%) developed post treatment focal brain oedema, thirteen of them were symptomatic (5.6%) (headache, fits, visual deterioration, or temporary cranial nerve palsy). Twenty-three patients out of them showed gradual improvement (oedema resolved) either spontaneously or after medical treatment (steroids, or dehydrating measures). Correlating the post-treatment oedema with treatment parameters. We found that it could be related to larger tumor vol (p=0.019).

Other complications included; ocular nerve palsy occurred in four patients (two cases were temporary, and two were permanent) (1.7%), facial pain occurred in seven patients (4%), fits occurred in three patients. Most of these complications were related to post-operative brain oedema; and improved with medical treatment.

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**Fig. 1:** Kaplan-Meire curve illustrating progression free survival

**Fig. 2:** Relation between the visual and radiological outcome
Fig. 3a&b: Female patient 60 years old, presented with left diminished vision since one year. a: MRI shows a left medial sphenoid wing meningioma. This 9.5 cc tumor was treated with 12 Gy to the 50% isodose with 85% cover, the maximum dose to the visual pathway was 9 Gy. b: A supervised MRI in 2013 (5 years FU) shows smaller tumor (the red margin represent the old target at the treatment day, notice it is larger than the current tumor size).

Fig. 4a&b: a: Visual field of the same patient before treatment in 2008. b: Visual field in 2013 follow-up (5 years).

Fig. 5a&b: a: MRI of a female patient 56 years old operated twice for an olfactory groove meningioma. b: MRI shows a large residual shifting the optic chiasm posteriorly. This 5.6 cc tumor was treated with 10 Gy to the 50% isodose with 85% cover. The maximum dose to the visual pathway was 8.5 Gy.
DISCUSSION

Definition of tumor location is not simple with meningiomas adjacent to the AVP. There are variations between definitions of various tumor locations defined by different authors with larger tumors near the cavernous sinus precise definition of the site of origin may not be possible. Because definitions of the location of meningiomas varies even between experts. In the current study, we defined peri optic meningiomas as meningiomas that are indirect contact, displacing, abutting or less than 3 mm away from the AVP (optic nerves & chiasm) regardless their origin whether; sphenoid wing, planum, clinoidal, tuberculum sellae, or cavernous sinus. (Fig 3, Fig 5)

In the current study, there was no statistical difference in tumor control or visual outcome in patients who had a histologically confirmed diagnosis of a WHO Grade I meningiomas as compared to patients diagnosed via neuroimaging and clinical features alone. Our study indicated that an appropriate clinical history coupled with modern neuroimaging studies yields an accurate rate of diagnosis for benign peri optic meningiomas, and that coincided with other studies.4

Parasellar tumors pose considerable therapeutic challenges because of their proximity to important cranial nerves, vasculature, and endocrine tissue at the anterior cranial base. Despite technical advances in open surgery, there are still potentially high risks of temporary or permanent neurological and endocrine dysfunction after surgical resection. Standard fractionated radiotherapy has also been used. In recent years, radiosurgery has been advocated as an adjunct to surgery for control of postoperative tumor residual, recurrence or as a primary treatment modality. The assessment of any form of treatment will depend on its efficacy (tumor control, visual outcome) and complication incidence.

In one study over 119 patients with skull base meningiomas treated surgically at the University of Pittsburgh, gross total resection was achieved in (61%) patients. The 5-year local control rate was 81% after complete resection compared with 62% after subtotal resection (The mean follow-up was 34 months) control rates which are much lower than after GKS in our series.

Standard fractionated radiotherapy has also been used in such cases. Control rates for skull base meningiomas after conventional radiation therapy delivering 50–55 Gy in 30–33 fractions vary from 75% to 95%, 10 years progression free survival were 75-90% results that do not appear to be better than radiosurgery in the current series (95%), regardless the higher complication incidence with conventional radiation. Fractionated stereotactic conformal radiotherapy in which a lesser volume of normal brain is irradiated with high doses; had reported tumor control rates also of >90%. Large series and long-term results for radiosurgical treatment using GKS for meningiomas are available. Results were very near in most of them; with an overall control rate > 90%, and progression free survival more that 98%, 95%, at 3 and 5 years respectively.

Tumor control rates In the current study, did not differ much from these studies (overall growth control rate 95%). only 12 cases (5%) showed tumor enlargement (mean FU: 4 years); PFS found to be 99%, 94%, 87% and 62% at 3, 5, 8 and 10 years respectively.

Variations in patient population, tumor volume, treatment characteristics, and duration of follow-up are all potential explanations for the minor different outcomes among these studies. In most of the studies longer follow-up duration was associated with either a decrease or increase in tumor volume. This emphasizes the necessity for long-term follow-up for such cases.

Using same prescription dose & isodose in almost all patients in this current study made them statistically insignificant factors in predicting tumor enlargement. This was consistent with other studies like Iwai et al who used prescription dose (8-12) Gy. He found also that patient age, sex, prior surgery status, and radiation dose to the tumor margin were not statistically significant factors in predicting tumor enlargement. It was not consistent with others who found that a decreasing tumor margin dose (p =0.017) and decreasing maximum dose (p=0.087) were predictive of tumor progression. It worth to mention that these both studies used a wider range of prescription dose (5-30) Gy, which may explain that difference.

Patients who underwent more than 1 prior surgery were significantly more likely to have tumor progression despite radiosurgery (p= 0.004), which were consistent with others. That raises the suspicion...
that lesions that had more than one surgery may have more aggressive nature and higher grades.

Complication rates for gross-total resection of meningiomas in the parasellar region vary widely, and adverse events have been reported to occur in between 0% and 60% of patients. In the review of Chen et al; the incidence of perioperative morbidity in Tuberculum sellae meningiomas, Medial sphenoid ridge, Clinoidal and Cavernous sinus were (25-45%), (6-13%), (4-29%) and (8-15%) respectively. 1

Complication rates associated with external beam radiation therapy range from 0% to 24%. The risk of radiation-associated injury to the optic apparatus varies between 0% and 3%; other cranial nerve deficits reported in less than 1-3%, hypopituitarism were reported in <5% of irradiated patients with skull base meningiomas. 21 Neurocognitive dysfunctions were recognized with large volume RT, specially short term memory impairment. 621 Fractionated stereotactic conformal radiotherapy had a late significant toxicity was reported in less than 5%. 9,10

In the current study among fifteen cases (6%) that had visual deterioration after treatment. Only three cases (13%) had mild visual deterioration without apparent cause other than radiation (max. radiation dose to AVP in these cases were 9.5, 8.5 &7.9 Gy). Stafford et al; reported rate of 1.9% for radiation induced optic neuropathy in their study on of 218 gamma knife procedures for treatment of benign tumors of the sellar and parasellar region. 28

The actual rate of visual field improvement after GKS in the current study was about 58% which is very satisfactory and convenient after a treatment modality that does not include surgical decompression. It was also not related to tumor shrinkage which raises the idea of other causes of improvement.

The rate of developed of new ocular nerve palsy or trigeminal pain was (5%) that gives incidence of cranial nerve toxicity of 6.3% (including the optic). Sheehan et al; reported new or worsening cranial nerve deficits in 9.6%, with cranial nerve (CN) V being the most adversely affected nerve. Williams et al; reported 10% incidence, in their large studies on GKS for parasellar meningiomas. (31),(35) In their study on fractionated stereotactic conformal radiotherapy for large benign skull base meningiomas Minniti et al, found clinically significant late neurological toxicity was observed in 3 (5.5%) patients consisting of worsening of pre-existing cranial nerve deficits consistent with our result of single session gamma knife treatment (6.3%) 22.

The percentage of improvement in patients already had pretreatment ocular nerve palsy in the current study (51%) was higher than previous studies (32-34 %) 28,5. It was also not related to tumor shrinkage. It is worth mentioning that these last two studies included the trigeminal nerve in this percentage which differs from ours.

Post treatment edema is the most common complication in different type of radiation therapy. In the current study; twenty five patients (10.7%) developed post treatment focal brain edema (only half of them were symptomatic). In their study on GKS for 34 cases of skull base meningiomas; Davidson et al; found only one case developed oedema (3%).2 Franzin et al; reported an incidence of (4.1%) in their study on GKS for 123 patent with cavernous sinus meningioma. In our study; Post GKS brain edema was related to larger tumor volumes (p=0.019). The much larger mean volume in our series that others’ may explain this higher rate of post-treatment edema in our cases. Regarding that larger tumors usually means a wider contact area with the brain parenchyma and more radiation exposure to the surrounding brain.

Recommendations on safe dose to the AVP In literature are varied. The commonest recommended safe doses to the AVP are <8Gy 23,24,26, <9 Gy (18) or <10 Gy 21,25. Among this latter group, there are patients reported without ill effects from doses noticeably higher than 10 Gy. In all these papers reporting a higher tolerated dose, the measurement of radiation exposure to the AVP was the maximum dose in the AVP volume. This is the same measurement used in the current study. It is suggested this could the standard way to record this parameter. In the current series; Excluding the 6 bilaterally blind patients The Maximum dose reached the AVP in our series was 11.5 Gy, the Minimum was 5.4 Gy (mean : 8.7Gy). Only twenty three patients received > 10 Gy Max dose to the AVP; amonu these 23, no patient has suffered from deterioration in vision (mean FU: 66 months). In cases where the visual pathway maximum dose exceeded the dose desired, a dose volume histogram was performed. The results suggest the doses given were tolerated.

Kondziolka et al insisted that only a 1 mm gap between tumour margin and the chiasm might be necessary for GK treatment, as verified with current high resolution MRI techniques. 23 In the current study; The closer relation between the lesion & AVP dose not seem to negatively affect the visual outcome comparing the visual outcome in patients having lesions touching and not touching the AVP. (P= 0.7). The findings of this paper and the studies of other workers suggest that such a distance is not necessary. 25

It is postulated that there are two basic possible ways of protecting the visual pathway. One is to underdose the entire tumour. The other is to underdose that part of the tumour which is adjacent or close to the visual pathway. This leads inevitably to poorer dosimetry statistics with a lower cover and a higher conformity index. However, it has the advantage of delivering a potentially adequate dose to the majority of the tumour. It is suggested that this is theoretically preferable, even if dosimetrically less elegant. It is emphasized that a key principle is the notion that if an
adequate treatment can place the visual pathway at risk then suboptimal treatment is sacrificed in favour of preserving vision.

It is suggested that the possibility of rapid loss of vision from radiation damage is less acceptable than the postulated slower more gradual loss from tumour growth. If unfortunate cases had lost vision at a later date, a second more effective GKs treatment can be given. Thus, in conclusion the dose or cover or both were reduced in a number of patients to protect visual function.

Despite earlier work which suggested that 12 Gy is required for tumour control\textsuperscript{15}, other authors have achieved tumour control with grade 1 basal meningiomas with lower doses\textsuperscript{12}. Our earlier experience with 97 large meningiomas (min vol 10 cc) and mean follow-up 54 months, using the Gamma Plan software suggests that 12 Gy is an adequate dose to the tumour margin.\textsuperscript{6}

**CONCLUSION**

Single session Stereotactic radiosurgery with the Gamma Knife is an effective and minimally invasive option for the treatment of perioptic meningiomas. It offers a reasonable rate of tumor control (95%) with a considerable rate of tumor shrinkage (36%), and a low incidence of new neurological complications.

Vision could be improved after GKs in spite of exposing the visual pathway to doses higher than usually accepted as safe. The maximum dose to the visual pathway would seem today to be at least 10 Gy. There is no need to have a distance between the tumour and the AVP increasing the number of suitable cases which may be treated with GKs. Improvement in vision is not necessarily a consequence of tumor shrinkage.

**REFERENCES**


