Long term experience of gamma knife radiosurgery for benign skull base meningiomas

W Kreil, J Luggin, I Fuchs, V Weigl, S Eustachio, G Papaefthymiou


PATIENTS AND METHODS

From April 1992 to June 1999, 237 patients with benign skull base meningiomas were treated with GKRS at our department. Five patients died of causes unrelated to GKRS or basal meningioma before the observation time reached 5 years, and 32 patients were lost to follow up. The remaining 200 patients were included in this study. None had received external beam radiotherapy in the past. The median age of the 40 men and 160 women was 57 years (range 10–81). The locations of the skull base meningiomas are listed in table 1.

Table 1 Distribution of tumour location in 200 patients with skull base meningiomas

<table>
<thead>
<tr>
<th>Location</th>
<th>No. of tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavernous sinus</td>
<td>69</td>
</tr>
<tr>
<td>Petroclival</td>
<td>44</td>
</tr>
<tr>
<td>Sphenoid wing</td>
<td>32</td>
</tr>
<tr>
<td>Cerebellopontine angle</td>
<td>21</td>
</tr>
<tr>
<td>Frontobasis</td>
<td>13</td>
</tr>
<tr>
<td>Orbita</td>
<td>10</td>
</tr>
<tr>
<td>Cranioceivalic</td>
<td>7</td>
</tr>
<tr>
<td>Sella</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
</tr>
</tbody>
</table>

In total, 99 patients, who had undergone between one and four microsurgical resections, received additional GKRS 0.2–195.1 months after their last craniotomy (median 3.1 months) to prevent a progressive growth of recurrent or residual basal meningiomas. All of these tumours were specified as grade 1 meningiomas according to the World Health Organization tumour classification. In total, 101 patients with typical findings on computerised tomography (CT) and/or magnetic resonance imaging (MRI) received GKRS as primary therapy because of medical infirmity, advanced age, or refusal of open surgery. None of the patients with primary GKRS suffered from increasing neurological deficit, especially progressive vision loss due to chiasmatic or optic nerve compression, as this is a clear indication for surgical treatment.

Abbreviations: CND, cranial nerve deficit; CT, computed tomography; GKRS, gamma knife radiosurgery; MRI, magnetic resonance imaging; PIV, prescription isodose volume

Advances in diagnostic and interventional radiology, improved microsurgical techniques, interdisciplinary skull base teamwork, and developments in anaesthesia and postoperative intensive care have expanded the scope and safety of the surgical treatment of basal meningiomas. However, microsurgical resection of these tumours is frequently associated with considerable aggravation or new onset of neurological impairment, and meningioma recurrences are observed even when complete removal has been accomplished. Therefore, surgery alone cannot be the ideal solution to treat all skull base meningiomas, and less invasive therapeutic options have to be considered not only as adjunctive but as alternative primary treatment.

The promising results following gamma knife radiosurgery (GKRS) for skull base meningiomas in earlier reports have to be interpreted with caution because most centres have related their early experience to short or mid-term observation periods. The purpose of this clinical study was to analyse retrospectively the toxicity and effectiveness of radiosurgical treatment in our patients with basal meningiomas with a follow up of 5–12 years to allow comparison with the risk–benefit ratio of other therapeutic methods.

Objectives: As most reports on the gamma knife have related only to short or mid-term results, we decided to evaluate the effectiveness and toxicity of radiosurgical treatment for benign skull base meningiomas in 200 patients with a follow up of 5–12 years to define the role of gamma knife radiosurgery (GKRS) for basal meningiomas and to provide further data for comparison with other treatment options.

Methods: In total, 99 patients were treated with a combination of microsurgical resection and GKRS. In 101 patients, GKRS was performed as the sole treatment option. Tumour volumes ranged from 0.38 to 89.8 cm³ (median 6.5 cm³), and doses of 7–25 Gy (median 12 Gy) were given to the tumour borders at covering isodose volume curves (range 20–80%, median 45%).

Results: The actual progression free survival rate was 98.5% at 5 years and 97.2% at 10 years. Passing radiation induced oedema occurred in two patients (1%). The neurological status improved in 83 cases (41.5%), remained unaltered in 108 (54%), and deteriorated in 9 (4.5%). Worsening was transient in seven patients (3.5%) and unrelated to tumour or treatment in one (0.5%). Repeated microsurgical resection was performed in five patients following GKRS (2.5%).

Conclusions: GKRS has proved to be an effective alternative to microsurgical resection, radiotherapy, and LINAC based radiosurgery for adjunction and primary treatment of selected patients with basal meningiomas. Because of the excellent long term tumour control rate and low morbidity associated with GKRS, this treatment option should be used more frequently in the therapeutic management of benign skull base meningiomas.
prior radiosurgical series 19–27–29 and our previous experi-
planning was performed using the Kula or GammaPlan
ranged from 4.6 to 6.2 months (median 6). Treatment
went the third radiosurgical partial volume treatment after
avoid adverse radiation related tissue effects.
ment in seven patients and three stage GKRS in another to
GKRS is summarised in table 2.
tion of presenting clinical symptoms and signs at the time of
surgical resection of skull base meningiomas. The distribu-
dimensions and tumour progression or involution was
GKRS, calibre measurements were made in three separate
treatment. Except for a 10 year old patient who was treated
required to treat the mostly irregularly shaped meningiomas.
low doses were applied because of large tumour volume,
(20 Gy (median 12) were delivered to the tumour borders,
marginal doses of 7, 8, and 25 Gy respectively, doses of 10–
biological risk of adjacent neural structures. Apart from three
marginal doses of 7, 8, and 25 Gy respectively, doses of 10–
that the plan offers. Since
well the created radiation field conforms to the size and
shape of the target and attests that an undertreatment is as
bad as an overtreatment. The theoretically perfect score of
1.00 lowers the smaller conformity the plan offers. Since
October 2000, we have routinely applied the conformity index:

\[
\text{Conformity Index} = \frac{TV_{\text{ref}}}{TV} \times \frac{TV_{\text{ref}}}{PIV} = \frac{TV_{\text{ref}}^2}{TV \times PIV}
\]

where \( TV \) = target volume, \( PIV \) = prescription isodose volume,
and \( TV_{\text{ref}} \) = prescription target volume.

All patients were discharged within 24 hours following
GKRS and were able to resume their preradiosurgical
functional level within 3 to 5 days. Postradiosurgical imaging
and clinical controls were conducted after 6 months,
12 months, and then once a year for the first 3 years,
and if the tumour showed no growth, follow up was performed
biennially thereafter. Tumour progression was defined as
radiologically proven enlargement or need for additional
surgical resection because of neurological deterioration
despite an unchanged tumour volume. Rates of total tumour
control were generated, and actuarial tumour control rates
were calculated by the Kaplan-Meier method.34

RESULTS
Radiological changes
During the observation period of 5–12 years (median 7.9),
the tumour volume remained stable in 83 patients (41.5%) and
decreased in 113 (56.5%). Tumour enlargement was
observed in four patients (2%), 17, 25, 74, and 77 months,
respectively, after combined surgical and radiosurgical treat-
ment. In 39 patients (19.5%), reduced central contrast
enhancement indicating marked tumour necrosis was
demonstrated in the follow up studies. Temporarily increased
peritumoural oedema, detected 3.6 and 6 months following
secondary GKRS in two patients (1%) with extensive
meningiomas mostly located in the region of the cavernous
sinus completely subsided after oral administration of
dexamethasone.

Clinical outcome
The neurological examinations revealed stable clinical status
in 108 patients (54%) and improved neurological disorders in
83 cases (41.5%). Of the patients with clinical amelioration,
21 (10.5%) showed complete relief of neurological impair-
ment, while transient (seven patients) or permanent (two
cases) clinical deterioration was found in nine cases (4.5%)
However, the permanent clinical worsening (new ipsilateral hemiparesis at 24 months following primary GKRS of a cavernous sinus meningioma) was not related to GKRS or tumour, but caused by stroke in a 68 year old patient. The distribution of preradiosurgical and postradiosurgical cranial nerve deficits and neurological disorders are listed in table 2.

**Salvage surgical procedures**

Five patients required repeated microsurgical resection after GKRS. In three patients, further debulking of the meningioma was necessary due to radiologically proven enlargement combined with neurological deterioration. Postoperatively, the impaired vision and oculomotor nerve dysfunction returned to normal in two patients respectively and the temporarily worsened hemiparesis in the third patient improved. Another patient with unaltered excellent clinical status underwent a second (conventional) surgery because the follow up scans displayed tumour progression. The remaining patient, harbouring a partially resected cavernous sinus meningioma with neuroradiologically unchanged extension, experienced progressive deterioration of a pre-existing visual field defect 5.5 months after radiosurgical treatment. The patient underwent microsurgical reoperation with further decompression of the optic chiasm and the optic nerve, but vision did not return to the same level as prior to GKRS.

**Complications following GKRS**

Five patients developed treatment related complications following GKRS, accounting for a complication rate of 2.5% (2% transient and 0.5% permanent complications). Increased seizure activity and aggravation of headache subsided completely in the two patients with temporarily increased peritumoral oedema. Two patients complained of new appearance of trigeminal neuralgia 12 and 16 months after secondary GKRS, respectively. No evidence of tumour progression was found on the imaging controls, and during the course of the following months, the trigeminal neuralgia resolved in both patients. The permanent visual deterioration in the patient with unchanged tumour volume that did not resolve after repeated microsurgery was considered as radiosurgically induced damage of the optic apparatus.

**Impact of conformity index on tumour control and complications**

We found 50 patients to have values below 0.7, 107 with scores between 0.7 and 0.9, 35 between 0.9 and 0.95, and 9 >0.95. Of the four patients with tumour progression after GKRS, only one patient with a conformity index of 0.62 and treatment involvement of 85% of the meningioma had obviously received suboptimal treatment. In the remaining three patients, with scores of 0.83, 0.85, and 0.89, progressive tumour growth was not caused by inadequate conformity.

The low index of 0.66 in our patient with permanent visual disturbance but radiologically stable tumour volume was caused by the attempt to shift the radiation dose away from the optic apparatus. The good conformity indices of 0.79 and 0.8 with the tumours totally covered by the prescription isodose volume do not explain the development of temporarily increased peritumoral oedema in two patients. The scores of 0.46 and 0.68 indicate undertreatment, but do not explain the occurrence of transient trigeminal neuralgia in two patients, as the radiosensitive structures of the cavernous sinus and the posterior fossa were deliberately excluded from radiosurgical treatment.

**Actuarial control rates**

Two patients with radiologically decreased tumour volume and improved neurological status died at 96 and 71 months following GKRS, due to unrelated intercurrent disease (lymphoblastic cancer and pneumonia), aged 72 and 82 years, respectively. Applying Kaplan-Meier method,34 progression free survival rate was 98.5% at 3 years' and 97.2% at 10 years' follow-up (fig 2).

**DISCUSSION**

The aim of microsurgery, which is considered the treatment of choice for skull base meningiomas, is complete excision with minimal morbidity and mortality.1–5 7 15 19 35 36 39 40 In more recent series, total removal of basal meningiomas was achieved in 60–87.5% of the patients. Between 30% and 56% of the patients suffered postoperative complications,1 4 9 10 but many authors mentioned only the percentage for specific complications and did not detail the absolute complication rate.5 6 10–12 The most common surgical sequelae were new or deteriorated pre-existing cranial nerve deficit (CND), occurring temporarily in 20–44% and permanently in 16–56% of the patients. The postoperative mortality rate ranges from 0% to 9% (median 3.6%).1–12 Furthermore, the recurrence/progression rates increase with the duration of follow up, and also seem to be influenced by tumour site and specific histopathological factors.1 6 11 15 35 39 Application of more sophisticated analysis, eventually including life table or Kaplan-Meier44 studies, proved that the long term recurrence rates of microsurgically treated meningiomas are often underestimated. The risk of meningioma recurrence following total removal ranges from 3.5% to 19% at 5 years, whereas the 5 year progression rate of partially resected meningiomas varies between 25% and 60%.3 15 35 38 39 At 10 years, recurrence free rates range from 10% to 33% following radical resection, while tumour progression counts for 35–73% after partial meningioma removal.35 38 39

As microsurgery alone still leaves us with a substantial recurrence or residual rate, considerable morbidity, and occasional mortality, less invasive alternative strategies have to be considered for the therapeutic management of basal meningiomas.2 5 6 10 14 15 30 20 29 In elderly or medically infirm patients particularly, it must be considered whether the meningioma will be likely to cause serious problems in the natural course of the remaining years and if the risks of surgery will exceed the potential benefits offered. Conventional radiation therapy for the management of recurrent, partially removed, or unresectable benign meningiomas seems to prevent or delay progressive tumour growth with local control rates of 76–92% at 5 years and 77–82% at
10 years.\textsuperscript{13, 34–42} Complications following irradiation developed in 3.6–19% of the cases.\textsuperscript{36–42} One series reported that 9.4% of the patients with benign meningiomas died due to uncontrolled tumour growth following radiotherapy.\textsuperscript{42}

Comparisons, especially with Linac accelerator based series, are of interest (table 3), but it is difficult to compare among series with missing variables (such as tumour volume and marginal dose).\textsuperscript{43, 44}

Clinically, 64.7–91% of the patients remained unchanged or experienced improvement of neurological disorders. Permanent or transient CND were found in 3.6–22% of cases, parenchymal radiation necrosis developed in 3.6–11.8%, and radiation induced oedema in 3.6–23.5%.\textsuperscript{43–45} Engenhart et al observed treatment related mortality in one patient (5.9%) of their series.\textsuperscript{45}

Within the past few years, GKRS has begun to play an increasingly important role as a non-invasive alternative therapeutic modality for patients with skull base meningiomas.\textsuperscript{17, 18, 20–22, 24, 31, 46, 48, 51, 52} The aim of GKRS is to achieve long term tumour control with maintenance of the patient’s clinical status and prevention of new treatment related morbidity.\textsuperscript{14} Excellent results were related in the early to intermediate gamma knife series (table 4), but the follow up intervals of these reports are too short to ensure that the biological behaviour of basal meningiomas has been altered.\textsuperscript{14, 17, 18, 20–25} Only very limited data concerning the long term effectiveness in the use of GKRS for meningiomas are available.\textsuperscript{15, 16, 47} In our current series with 5–12 years’ follow up, local control of skull base meningiomas could be obtained in 97.5%. The 5 year and 10 year progression free survival rates of 98.5% and 97.2%, respectively, compare favourably with the results of other treatment methods. Most of the patients (95.5%) had ameliorated or stable neurological status. Permanent clinical worsening was caused by unrelated intercurrent disease (stroke) in one patient. Transient deterioration in three patients with tumour progression was a result of tumour compression and cannot be considered a radiation induced complication. The permanently deteriorated vision in one patient, the temporary appearance of a trigeminal neuralgia in two patients, and the passing worsening in two patients with presence of transient radiation induced oedema were the only treatment related complications following GKRS, accounting for a complication rate of 2.5% (2% transient and 0.5% permanent complications). Similar results were reported by Kondziolka et al\textsuperscript{46} and Kobayashi et al.\textsuperscript{47} In all of the series, no death resulted from the radiosurgical treatment of basal meningiomas with GKRS. Only one early report\textsuperscript{48} described neuroradiological changes in one of 50 patients (2%) that could be attributed to radionecrosis of brain parenchyma.

Concerning the role of GKRS for primary treatment, an open microsurgical approach is recommended to establish tissue diagnosis if the findings on preradiosurgical MRI/CT scans do not clearly display the typical radiological features of benign meningioma, so that the possibility of other lesions can be ruled out.\textsuperscript{49}

Comparison of the radiosurgical series of basal meningiomas shows a trend towards lower treatment doses over the years associated with unchanged excellent tumour control rates but reduced incidence of radiation induced adverse side effects.\textsuperscript{17, 18, 20–22, 24, 31, 46, 48, 51, 52} Currently, we advocate that benign meningiomas should be treated with margin doses of 12 Gy, but the radiosensitivity of juxtaposed cranial nerves or the brainstem sometimes necessitates an application of lower doses to the small portion of the meningioma borders directly in contact with the structures at risk. The anterior visual pathways seem to be less radio-resistant than the other cranial nerves. Although no clear threshold doses have been found for the optic nerve, chiasm, and tract,\textsuperscript{50} we keep maximum irradiation exposure of these structures below 10 Gy. Nevertheless, one patient of our current series experienced permanent deterioration of vision without

### Table 3
Summary of Linac based radiosurgical series for meningioma treatment

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Follow up range (median)</th>
<th>Tumour volume $\text{cm}^3$ (range)</th>
<th>Marginal dose (Gy) (range)</th>
<th>Tumour control rate (%)</th>
<th>Comp (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engenhart</td>
<td>17</td>
<td>1 to 60 (40)</td>
<td>N/A</td>
<td>N/A</td>
<td>94 to 95 (7.33)</td>
<td>10.1</td>
</tr>
<tr>
<td>Chang</td>
<td>55</td>
<td>17 to 81 (48.8)</td>
<td>0.45 to 27.65 (7.33)</td>
<td>12 to 25 (18.3)</td>
<td>98 to 24 (15.0)</td>
<td>10.1</td>
</tr>
<tr>
<td>Villacencio</td>
<td>56</td>
<td>6 to 66 (26)</td>
<td>N/A</td>
<td>12 to 18.5 (15.0)</td>
<td>93 to 9 (6.5)</td>
<td>10.1</td>
</tr>
</tbody>
</table>

N/A, data not available in the publication. Comp, complications.
tumour progression, although all parts of the optic pathways received less than 10 Gy. The encouraging preliminary results after fractionated stereotactic radiotherapy for lesions directly abutting the critical structures of the optic apparatus, combining the advantages of physical dose localisation of stereotactic radiotherapy with the radiobiological benefits of dose fractionation, require studies with longer follow up periods to determine the value of this therapeutic approach.13 15 18 21 29 30 In our patient, passing oculomotor nerve palsy developed, although no part of the third cranial nerve received more than 10–20 Gy. Consistent with our experience, Morita et al found one patient to have permanent new oculomotor palsy following application of 10 Gy to the cavernous sinus.10

Prevailing reports stated that the fifth cranial nerve seems to tolerate doses of up to 20 Gy,15 17 19 30 50 but the new onset of transient trigeminal neuralgia (meningioma volume 7.4 cm3, margin dose 12 Gy at the 40% isodose curve) gave no explanation for the temporary appearance of radiation induced oedema in another patient.40% isodose curve) gave no explanation for the temporary appearance of radiation induced oedema in another patient. In fact, the passing peritumoral oedema, occurring in one patient very early in our study after a tumour volume of 23 cm3 had received 12 Gy at the 40% covering isodose line, seemingly resulted from inadequate dose-volume relation. Owing to this experience, we developed our proposed strategy of performing staged radiosurgical treatment for larger meningiomas to maximise potential benefits, which has been rarely described in adequate literature.17 18 22 23 31 As we obtained local tumour control and clinical amelioration in all cases following staged GKRS, we assume that this strategy may expand the indication for radiosurgical treatment in benign, slowly growing lesions with diameters larger than 3 cm.12 21 29 However, careful analysis of the treatment parameters (meningioma volume 7.4 cm3, margin dose 12 Gy at the 40% isodose curve) gave no explanation for the temporary appearance of radiation induced oedema in another patient. The application of the aforementioned conformity index showed that tumour progression in one patient of our current series was due to undertreatment. Further data will be necessary to establish its final role in the treatment planning of GKRS.

Some authors have mentioned that surgical resection following GKRS becomes extremely difficult due to post-irradiation changes in the tumour, such as formation of adherent scar tissue or loss of defining arachnoidal planes of dissection.24 This is in contrast to our own experience in the two patients who underwent further, conventional surgery at our department after a combined surgical and radiosurgical treatment. During the operation, we found highly avascular tumour tissue, as we had expected, following endovascular occlusion of feeding vessels without any adherence to the juxtaposed neurovascular structures.

Aside from other considerations, appealing aspects of GKRS are the short duration of hospitalisation (less than 48 hours) and the quick return to normal daily life activities (3–5 days following GKRS) on the same level as prior to radiosurgery, thus favourably contributing to the cost effectiveness of this minimally invasive treatment method.21 29

CONCLUSION

In our 5–12 year experience, GKRS provided an excellent long term tumour control rate associated with maintenance of neurological function and low treatment related morbidity for selected patients with benign skull base meningiomas. The long term outcome following GKRS for skull base meningiomas treatment favourably compares with the results obtained by microsurgery, conventional radiotherapy, and Linac based radiosurgery either in combination or on its own. The apparently better results of GKRS in the treatment for skull base meningiomas should provide the impetus for even more aggressive application of this approach in the management of basal meningiomas.

Nevertheless, increasing neurological deficit, especially rapidly progressive vision loss due to chiasmatic or optic nerve compression, is a clear indication for surgical resection. With regard to the possibility of an additional radiosurgical approach to residual tumours and the excellent results, following combined microsurgical–radiosurgical treatment, the objective of surgical treatment of basal meningiomas should be preservation of function and of as much normal tissue as possible, rather than radical resection. Patients harbouring recurrences of skull base meningiomas should receive GKRS rather than undergo repeated open resection.

In patients with advanced age, significant concomitant medical problems, high risk tumour location or patients who are not willing to undergo an open microsurgical procedure, we would recommend performing GKRS as a safe and effective alternative primary treatment modality, with close and frequent clinical and neuroradiological follow up. However, the long natural history of skull base meningiomas necessitates observation periods of at least 10–20 years before any final conclusion regarding the various treatment options can be expected.

Authors’ affiliations

W Kreil, J Luggin, I Fuchs, V Weigi, S Eustachio, G Papaefthymiou, Department of Neurosurgery, Medical University, Graz, Austria

Competing interests: none declared

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Cusimano MD, Mirimanoff RO


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