Radiotherapy in the treatment of benign meningioma of the skull base


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Object. This study was undertaken to assess the long-term efficacy and toxicity of conventional fractionated external-beam radiation in the treatment of benign skull base meningioma.

Methods. This is a retrospective study of 82 patients with histologically verified benign skull base meningioma treated by surgery followed by fractionated external-beam radiation at the Royal Marsden Hospital between 1962 and 1992. The 5- and 10-year progression-free survival (PFS) rates were 92% and 83%, respectively, with the site of disease being the only independent prognostic factor for tumor control according to multivariate analysis. The 10-year PFS rate for patients with sphenoid ridge meningiomas was 69% compared with 90% for those with tumors in the paraseptal region. The overall 10-year survival rate was 71%, with performance status and patient age found to be significant independent prognostic factors. Six patients had worsening vision, which was due to cataract in five cases and retinopathy in one. There were no recorded cases of cranial nerve neuropathy.

Conclusions. The excellent long-term tumor control and length of survival with minimal toxicity associated with conventional external-beam radiation should serve as a baseline for evaluation of new treatment strategies such as radiosurgery and skull base surgery.

KEY WORDS • meningioma • skull base • radiotherapy • radiosurgery

MENINGIOMAS account for 20% of primary intracranial tumors,22 and 90% of these are benign. They may occur at any meningeal site, with approximately one half of benign intracranial meningiomas arising in the skull base.22 Complete surgical excision is undoubtedly the treatment of choice for benign meningioma at an accessible site.

There is no uniform agreement on the indications for radiotherapy in cases of benign meningioma because there have been no randomized clinical trials testing its efficacy. Nevertheless, radiotherapy is usually given after incomplete resection of primary or recurrent tumors, with a suggestion of improved tumor control compared with outcomes in patients treated by surgery alone.2,7,9,17,26 Following apparently complete excision of benign meningiomas, the 5-year control rate is 72 to 100%, 2,7,8,17,18,26 The 5-year control rate after subtotal surgical resection is 31 to 70%, 2,17,18,26,28 With the addition of postoperative radiotherapy, the control rate at 5 years has been reported to be 80 to 85%, 2,3,7,9,17,26

The surgical approach used to excise skull base meningiomas is more technically challenging than that used to treat convexity tumors18,19 and, in the past, many benign meningiomas at this site were incompletely excised. Radiotherapy was therefore used more frequently in cases in which the tumor was located at the skull base than in cases in which the tumor was found at another more accessible location.

New techniques of surgery and radiotherapy have been developed that are considered of value in the treatment of skull base meningioma. These include skull base surgery, radiosurgery, and stereotactically guided conformal radiotherapy,7,15 which is a high-precision technique involving the use of stereotactically guided irradiation. We assessed the long-term results of conventional treatment with surgery and radiotherapy, which should serve as a baseline to compare the potential advantages of new treatment approaches.

Clinical Material and Methods

Patient Population

Between 1962 and 1992, 82 patients with benign menin-
skull base meningioma. Sixty-two patients underwent surgery followed by radiotherapy as part of their primary therapy. Nine patients had apparent macroscopic excision, 45 subtotal excision, and six underwent a biopsy alone. In the two remaining patients, the extent of surgery could not be determined. Twenty patients were treated with radiotherapy following tumor recurrence and a second surgical resection. At the time of recurrence, 10 patients underwent partial excision and 10 underwent a biopsy procedure or no further surgery. Patients with primary or recurrent disease were treated with the same radiotherapy protocol. Three-field treatment was delivered by a 6- or 8-MV linear accelerator. All fields were treated daily up to a dose of 55 to 60 Gy in 33 fractions. The dose planning target volume was defined as the preoperative tumor volume observed on the patient’s computerized tomography (CT) scan (35 patients) or magnetic resonance (MR) image (four patients) plus a 2-cm margin. Prior to the CT scanning era (pre-1973), planning volume was defined in 43 patients on the basis of surgical information, anatomical landmarks, and plain radiographs; in these cases a 2- to 3-cm margin was added.

The patients were assessed clinically every 3 to 6 months by using CT or MR images obtained at the time of suspected disease progression. Clinical suspicion was based on the progression of neurological deficit relating to the site of the meningioma and features of raised intracranial pressure. Before the CT scanning era, the diagnosis of progressive disease was made in six patients based on symptoms and clinical signs and confirmed by surgical findings. Toxicity was assessed retrospectively as a change in the patient’s neurological or clinical status during follow-up examination in comparison with status before the start of radiotherapy. The median follow-up period was 9 years (range 1 month–27 years).

**Statistical Analysis**

Rates of survival and progression-free survival (PFS) were calculated using the Kaplan–Meier method. Survival and PFS rates were measured from the date the patient began receiving radiotherapy. The survival and PFS rates were compared using log-rank analysis. Multivariate analysis was performed using Cox’s proportional hazard model.

**Results**

**Tumor Control**

The PFS rate for the 82 patients with benign skull base meningioma treated by surgery and radiotherapy was 92% at 5 years and 83% at 10 years (Fig. 1). The patient’s age, gender, and performance status; the tumor site; extent of surgery; treatment era; use of diagnostic imaging; and radiotherapy timing (primary tumor as opposed to recurrence) were tested for prognostic significance. Only tumor site was a significant prognostic factor for PFS on univariate and multivariate analysis (Table 1). The 10-year PFS rate was 69% in patients with tumors arising from the sphenoid ridge compared with 90% in patients with parasellar region tumors (suprasellar, parasellar, and cavernous sinus) (Fig. 2). The relative risk of progression for tumors arising from the sphenoid ridge was 5.2 (95% confidence interval [CI] 1.7–16.5) compared with other sites. There was no significant difference in tumor control between patients who received radiotherapy following primary surgery and those treated after tumor recurrence.

**Survival Rates**

The actuarial survival rate was 83% at 5 years and 71% at 10 years. The patient’s age, gender, and performance status; extent of surgery; time of radiotherapy (primary tumor or tumor at recurrence); tumor site; treatment era; and use of CT or MR imaging were assessed for their effect on survival time by using univariate analysis. Patient age older than 50 years and KPS score less than 70 were significant adverse prognostic factors according to univariate and multivariate analyses (Table 1). Patients older than 50 years had a relative risk of death of 4.5 (95% CI 1.8–11.7), and those with a KPS score less than 70 had a relative risk of death of 4.6 (95% CI 2–10.4). The extent of surgery and the timing of radiotherapy had no prognostic significance.

**Toxicity of the Treatment**

Sixty-one of 82 patients were assessable for late toxicity. Visual impairment was noted in six patients; in five of these it was due to cataract and in one it was a result of...
presumed radiation retinopathy, leading to hemorrhage and blindness in one eye. There were no recorded cases of posttreatment optic nerve chiasm or other cranial nerve neuropathy. Three patients developed hypopituitarism that required hormone replacement therapy. Four patients (aged 59–71 years) were noted to have impairment of short-term memory 6, 10, 15, and 23 years, respectively, after treatment. There were no cases of second brain tumor, although one patient developed chronic lymphatic leukemia. Four patients aged 67 to 75 years experienced a cerebrovascular accident.

**Discussion**

The 5- and 10-year local tumor control rates of 92% and 83%, respectively, found in this study are comparable with data from other studies in which meningiomas were treated with surgery and radiotherapy (Table 2). Tumor site was the only significant predictor of local control. Patients with sphenoid ridge tumors had worse local control, and this was independent of the extent of surgery. It is not clear whether the difference in local control of tumors at different sites represents different biological behaviors of the disease. It seems more likely that the seemingly better tumor control is the consequence of the size of the lesion, with parasellar tumors presenting earlier because of their proximity to eloquent structures and the earlier appearance of neurological deficit. Length bias may also play a role because smaller tumors may represent more indolent meningiomas. Local control and survival rates from radiotherapy were similar, whether the patients were treated with radiotherapy as part of their primary treatment or at

**TABLE 1**

*Predictors of local tumor control and overall survival in 82 patients with benign skull base meningioma*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Local Tumor Control</th>
<th>Overall Survival</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>PFS Rate (%)</td>
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<tr>
<td></td>
<td></td>
<td>5 Yr</td>
</tr>
<tr>
<td>all patients</td>
<td>82</td>
<td>92</td>
</tr>
<tr>
<td>age (yrs)</td>
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<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>38</td>
<td>90</td>
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<tr>
<td>≥50</td>
<td>44</td>
<td>94</td>
</tr>
<tr>
<td>KPS score*</td>
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<td></td>
</tr>
<tr>
<td>&gt;70</td>
<td>62</td>
<td>92</td>
</tr>
<tr>
<td>≤70</td>
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<tr>
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</tr>
<tr>
<td>total</td>
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<td>100</td>
</tr>
<tr>
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<td>94</td>
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<td>83</td>
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<tr>
<td>time of radiotherapy</td>
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<td>after first therapy</td>
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<td>92</td>
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<tr>
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<td>94</td>
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<td>pre-1970</td>
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<td>89</td>
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<tr>
<td>1970 &amp; after</td>
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<tr>
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<td>43</td>
<td>94</td>
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<tr>
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<td>100</td>
</tr>
<tr>
<td>other</td>
<td>12</td>
<td>100</td>
</tr>
</tbody>
</table>

*In some cases there were insufficient data with which to calculate a KPS score.*
the time of recurrence; this finding has been reported previously.

It is difficult retrospectively to ascribe late effects to radiotherapy, surgery, or the tumor itself and to distinguish these from the consequences of the normal aging process, particularly in older patients with meningiomas. Nevertheless, the frequency of severe late complications was low. There were no recorded cases of radiation-induced neuropathy; this is consistent with the dose-fractionation parameters, which were kept below the known radiation tolerance of the normal central nervous system. Visual impairment due to a cataract could have been caused by radiotherapy in three patients in whom the lens was known to have received significant doses of irradiation. Age-related lens changes are also likely to have played a role in this patient population. Retinopathy with hemorrhage (one case) and hypopituitarism (three cases) were likely to have been related to irradiation because in these cases the structures were adjacent to the tumor and, therefore, received high doses of radiation. The association of short-term memory loss and stroke with radiotherapy is not clear. High-dose irradiation of large portions of normal brain may lead to cognitive impairment, but this is confounded by age. Irradiation of pituitary adenoma at similar doses and similar volumes has not been shown to cause late cognitive deficit.\textsuperscript{10,20} Similarly, the development of stroke in the elderly population may be accompanied by predisposing risk factors, such as dysrhythmia noted in one patient (atrial fibrillation) and cannot currently be ascribed to radiotherapy alone.

On the basis of the available data, it is possible to conclude that a conservative approach to the management of benign skull base meningioma leads to reasonable long-term disease control with minimum incidences of morbidity. It is not possible to claim that the tumor control achieved in this study was the result of radiotherapy because there was no comparative group of patients treated by surgery alone. The results are those of a management policy that serves as a baseline for future comparison with other treatment policies, rather than evidence for the efficacy of conservative surgery and radiotherapy. The best results are seen in patients with parasellar tumors, which have a 10-year control rate of 90%. Despite such excellent results, it is not possible to prove that the favorable tumor control was the result of the treatment approach rather than a reflection of the indolent natural history of a benign meningioma. Nevertheless, because the majority of patients had either residual or recurrent tumors at the time of radiotherapy, the lack of progression at 10 years in 83% of all patients, and in 90% of those who had parasellar tumors, suggests that fractionated irradiation may have produced at least a temporary growth arrest.

With the advent of innovative skull base surgical approaches and the use of modern three-dimensional imaging and image-guided surgery, a higher proportion of patients undergo a radical surgical procedure.\textsuperscript{5,23,25} Nevertheless, the curative value of radical surgery in long-term disease control is not clear. The tumor control rate reported at 15 years was as low as 68% in patients with skull base meningiomas treated by surgery alone.\textsuperscript{12,16,24} Aggressive surgical approaches should be compared with conservative surgery and radiotherapy with respect to early and late toxicity, including incidences of treatment-related mortality and morbidity and long-term disease control.

The same comparison should be the basis of evaluation of new radiotherapy procedures. Radiosurgery has been reported as a potentially effective treatment for small cavernous sinus\textsuperscript{14} and other skull base meningiomas. Stereotactic radiotherapy or radiosurgery in which a conventional apparatus (gamma knife or a linear accelerator multiple-arc stereotactic system) is used produces small spherical dose distributions with considerable dose homogeneity in meningiomas that are mostly nonspherical. The success of radiosurgery has so far been measured with surrogate endpoints as a reduction in the size of the treated lesion. Data on long-term tumor control\textsuperscript{11} do not indicate any clear benefit compared with results in patients treated with conservative surgery and radiotherapy. Radiosurgery has been associated with considerable incidences of morbidity,\textsuperscript{5,11} even with incidences of treatment-related mortality not seen with fractionated irradiation. We have to await full peer-reviewed reports of long-term results to judge the value of single-fraction radiosurgery in comparison with fractionated irradiation. However, the toxicity of single-fraction radiosurgery to the optic apparatus\textsuperscript{22} and the nerves of the cavernous sinus would make the widespread use of this technique in larger meningiomas, particularly those involving sensitive structures, unwise.

Assuming that fractionated radiotherapy is of value in achieving tumor control in patients with residual and recurrent benign skull base meningioma, we have developed a technique of stereotactically guided conformal radiotherapy, which combines the safety and efficacy of fractionated irradiation with the high-precision technology of stereotaxy and localized dose delivery with conformal techniques.\textsuperscript{1} This should lead to a reduction in the volume of normal brain that is irradiated without compromising tumor control. This study will serve as a baseline against which to judge the value of single-fraction radiosurgery.
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for the evaluation of all new treatment strategies, including stereotactically guided conformal radiotherapy.

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References


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