Radiotherapy for atypical meningiomas

Clinical article


1 Department of Neurosurgery, Sheffield Teaching Hospitals NHS Foundation Trust, Royal Hallamshire Hospital, Sheffield; and Departments of 2 Neurosurgery and 3 Neuropathology, Hull and East Yorkshire NHS Trust, Hull Royal Infirmary, Hull, United Kingdom

Object. The role of postoperative radiotherapy in patients undergoing first-time resection of WHO Grade II meningioma remains unclear as reflected by varied practices in published clinical studies and national professional surveys. Much of the relevant literature is based on pre-2000 WHO grading criteria for atypical meningiomas. Authors in this study set out to explore the role of postoperative radiotherapy in patients undergoing first-time surgery for WHO Grade II meningiomas diagnosed using revised WHO 2000 criteria, against a background of otherwise limited published literature on this issue.

Methods. The authors retrospectively collected data on 114 consecutive patients who underwent first-time resection of WHO Grade II atypical meningiomas diagnosed using 2000 WHO criteria, and who variably underwent postoperative radiotherapy according to individual surgeon practices. Outcomes, including radiological recurrence, were submitted to Kaplan-Meier and Cox regression analyses.

Results. Postoperative radiotherapy demonstrated a significant benefit only when patients who had undergone gross-total tumor resection and those who had undergone subtotal resection along with postoperative radiosurgery to the tumor remnant were excluded from analysis.

Conclusions. The authors have performed the largest study in the literature to examine the use of radiotherapy for WHO Grade II, atypical, meningiomas following a first-time resection. They suggest that radiotherapy is not appropriate after first-time resection of those lesions in which a gross-total resection (Simpson Grade 1 or 2) has been achieved. They also advise that any tumor remnant radiologically demonstrated on postoperative imaging should be treated with radiosurgery and that postoperative radiotherapy after a first-time resection should be reserved for tumor remnants too large for radiosurgery and for which a second staged operation is not planned.

(DOI: 10.3171/2011.5.JNS111112)

Key Words • atypical meningioma • radiotherapy • radiosurgery • oncology • stereotactic radiosurgery

Meningiomas account for 13%–34% of all surgically removed primary brain tumors. 22 An established and prognostically significant histological classification of these tumors was originally described by the WHO in 1993, with a significant subsequent revision in 2000 and further codification in 2007. 12 The majority of meningiomas are histologically classified as benign, or WHO Grade I, having a more indolent course and a lower rate of local recurrence. A minority of CNS meningiomas are WHO Grade II histologically, the most common variant being the atypical form; rarer variants are chordoid and clear cell. These tumors have a higher incidence of disease progression. A smaller proportion is identified as WHO Grade III, or the anaplastic type, and is considered to be predictive of a more malignant course. The year 2000 changes to the WHO grading system for meningiomas have significantly improved the correlation between histological grade and subsequent tumor behavior. 34

The 2000 changes to the grading criteria have also led to a significant increase in the proportion of meningiomas diagnosed as WHO Grade II (or atypical) as compared with the pre-2000 criteria. For example, Pearson et al. 25 described an increase from 4.4% to 35.5% and Smith et al. 29 showed an increase from 18.3% to 23%, with the introduction of the 2000 WHO criteria.

Abbreviations used in this paper: GTR = gross-total resection; STR = subtotal resection.
Prior to the 2000 WHO classification scheme, several subjective classification systems existed. As a result much of the early data regarding atypical meningiomas has suffered from a lack of comparability. The 2000 WHO grading system reclassified meningiomas, creating a standardizable set of diagnostic criteria, including for the first time that for WHO Grade II (atypical) meningiomas, that is, ≥ 4 mitotic cells per 10 hpf and/or 3 or more of the following: increased cellularity, small cells, necrosis, prominent nucleoli, and sheeting. A further revision in 2007 included brain invasion in an otherwise Grade I tumor as an additional criterion for a WHO Grade II lesion. The 2000 WHO grading system has enabled a more objective comparison—of published outcomes, for example—and also permits pooling of data between neuroscience centers.

Postoperative radiotherapy is frequently given for WHO Grade II meningiomas. However, there is no professional consensus on the indications for such treatment. More particularly, there is debate on whether all WHO Grade II meningiomas should receive radiotherapy or whether the treatment should be limited to subtotally resected tumors or should be given only after revisional surgery. This lack of consensus was highlighted following the introduction of the 2000 WHO definition of Grade II meningiomas, as most of the literature was derived from pre-2000 diagnostic criteria. Consequently, the validity of postoperative radiotherapy for WHO Grade II tumors must be readdressed, especially in view of the increasing frequency of the tumor’s diagnosis.

The indications for postoperative radiotherapy in WHO Grade II meningiomas are also worth reevaluating within the wider context of increased access to MR imaging for surveillance imaging, the availability of stereotactic radiosurgery for the treatment of postoperative remnants and small recurrences, the development of skull base and neurooncological clinical services, and safer surgical interventions facilitated by the widespread adoption of neuronavigation and minimal brain retraction techniques. The use of radiotherapy following a first surgery must also be seen in the context of WHO Grade II meningioma as a chronic and potentially lifelong condition in which there is now the possibility in most Western health care systems of repeated radiosurgical interventions. Moreover, in cases in which prior radiotherapy has been given, any subsequent operations are likely to carry a higher risk of morbidity (for example, postoperative infection or reconstruction issues). There are also increasing patient and societal expectations for maintaining quality of life even with multiple interventions, in both the short term (minimizing the number of hospital admissions) and the long term (cognitive concerns). The historical literature implies that radiotherapy continues to have value in the management of these tumors. In the present study we have attempted to define this value, and we believe that it is particularly relevant given that modern health care practice involves presenting patients with management choices, in most circumstances leading to an ensuing discussion concerning the evidence of efficacy. In addition, with increasing demands on health care commissioning, there is a responsibility to present evidence to justify patient treatment funding streams.

We specifically set out to explore the benefit of postoperative radiotherapy in patients undergoing first-time surgery for WHO Grade II atypical meningiomas. We exploited the variable referral patterns for radiotherapy during the individual consultant neurosurgeons in two teaching hospitals to determine the extent of any benefit. A benefit was judged based on the extent of radiologically demonstrated tumor recurrence or remnant progression on interval imaging following first-time surgery. Neither the outcome following a second intervention for tumor recurrence or remnant progression nor the sequelae of radiotherapy were examined. We considered that such questions would be unanswerable in our cohort over the relatively short period since the introduction of the revised 2000 WHO meningioma grading criteria.

Methods

We retrospectively reviewed the records of consecutive patients with diagnosed WHO Grade II meningiomas between December 2001 and August 2010 at a large teaching hospital and between January 2007 and August 2010 at a second large teaching hospital in a service evaluation context. The diagnosis of atypical meningioma was made according to 2000 WHO criteria. Patient sex, age at the time of surgery, tumor location, the extent of resection, the use of postoperative radiotherapy, the duration of follow-up, and recurrence were recorded for each patient. The location of the tumor was categorized as convexity, parasagittal/parafalcine, skull base, or other. The degree of tumor resection was recorded as either GTR, in which all tumor was removed with dural excision or coagulation (Simpson Grade 1 or 2), or STR, in which some tumor remnant was left (Simpson Grade 4), as implied by the surgeon and as shown subsequently on postoperative imaging.

A recurrence was the development of new tumor in patients who had undergone a GTR or the progression of a tumor remnant in patients who had undergone a STR, on the basis of surveillance imaging.

Radiotherapy was given using an average dose of 51.8 Gy in 28 fractions over 6 weeks.

The data were submitted to first a Kaplan-Meier analysis and then a Cox regression analysis, thus taking into account multiple possible covariates contributing to the recurrence “hazard” and addressing censored data, that is, no recurrence or follow-up ends before the recurrence “event.”

Results

Between December 2001 and August 2010, 129 consecutive patients underwent one or more operations for a WHO Grade II meningioma at our institutions (Sheffield Teaching Hospitals NHS Foundation Trust and Hull and East Yorkshire Hospitals NHS Trust), that is, 19% of all patients undergoing surgery for CNS meningiomas over this period. All meningiomas were diagnosed using the updated 2000 WHO criteria. Of these patients, 114
Radiotherapy for atypical meningiomas

underwent a first-time operation for these meningiomas during the period concerned. Subsequent analysis was restricted to this first-time operation patient group.

Of these 114 patients, 55 (48%) were male (Fig. 1A). Tumors were located at the cerebral convexity in 39 patients (34%), in a parasagittal/parafalcine location in 33 (29%), arising from the skull base in 38 (33%), and at other sites, for example, an intraventricular region (Fig. 1B), in 4 (4%).

Sixty-six patients (58%) underwent GTR (Simpson Grade 1 or 2) with the remaining 48 (42%) undergoing STR (Simpson Grade 4; Fig. 1C). Gross-total resection was achieved in 91% of the convexity tumors, 55% of those in a parasagittal/parafalcine location, and in 37% arising from the skull base. Subtotal resection was judged on the basis of the initial baseline postoperative scan or the surgeon’s written comment in the operative notes in the absence of a postoperative scan. We did not attempt to analyze the size of the tumor remnant or its location (such as in the cavernous sinus or within a venous sinus). Postoperative imaging was performed in 104 patients (91%), with the initial baseline scan obtained an average of 5.7 ± 3.8 months (mean ± SD, range 0.5–18 months) after the date of surgery. The imaging modality on follow-up was CT in 11 patients (11%) and MR imaging in 93 (89%) patients. Ten patients did not have postoperative imaging: imaging pending at the time of data collection (2 patients), postoperative death (2 patients), death from unrelated causes prior to interval imaging (4 patients), circumstances that were considered palliative (1 patient), and poor postoperative neurological status persisting (1 patient).

Two patients suffered from neurofibromatosis Type 2. Another patient had undergone radiotherapy for unilateral retinoblastoma as a child. Two patients had previous-ly undergone the removal of WHO Grade I meningiomas around the site of the resected WHO Grade II meningiomas. Three patients had WHO Grade II meningiomas of the clear cell type; lesions in the remainder were atypical. Two patients who underwent subsequent surgeries for recurrence had these tumors identified as WHO Grade III anaplastic lesions.

Thirty patients (26%) were given postoperative radiotherapy (Fig. 1D), reflecting the practice of each patient’s treating surgeon as well as each patient’s preference. The demographics of the radiotherapy group were similar overall in age, sex, and tumor location as compared with the nonradiotherapy group (Table 1).

The mean age at the time of surgery was 57 ± 18 years (range 17–85 years; Fig. 2).

Tumor recurrence or remnant progression was determined on the basis of any changing appearance on inter-vals. The median time to radiological tumor recurrence or remnant progression was 54 months (Fig. 3). The overall tumor recurrence rate at 6 years postsurgery was 60%, with the Kaplan-Meier curve plateauing beyond this time point.

Individual Kaplan-Meier curves for the time to radiologically demonstrated tumor recurrence or remnant progression were plotted for each of the following factors: patient sex, tumor location, degree of tumor resection, and use of postoperative radiotherapy (Fig. 4). The mean times to radiological tumor recurrence or remnant progression with confidence intervals are shown in Table 2.

On the basis of the Kaplan-Meier curves, a Cox regression was limited to assessing the degree of tumor resection and the use of postoperative radiotherapy as predictors of radiological tumor recurrence or progression (Table 3). Postoperative radiotherapy did not provide a statistically

![Fig. 1.](image-url) Graphic representation of sex profile (A), tumor location (B), extent of resection (C), and postoperative radiotherapy (D) in 114 patients undergoing first-time resection for WHO Grade II meningiomas.
significant benefit. However, the degree of tumor resection did significantly impact radiological tumor recurrence or progression on excluding 5 patients who underwent postoperative radiosurgery for a tumor remnant.

We attempted to further explore the impact of postoperative radiotherapy on patients who had undergone STR by completing a Kaplan-Meier analysis (Fig. 5 left). Although there appeared to be a trend toward postoperative radiotherapy having some impact on reducing the chances of tumor recurrence or progression, a log-rank test failed to demonstrate a statistically significant difference. However, when excluding the 5 patients who had undergone postoperative radiosurgery for a tumor remnant but no radiotherapy, a p value of 0.043 was obtained using a log-rank test.

Thirteen of 31 patients with radiological tumor recurrence or progression underwent further surgery. Among these 13 patients, 3 also underwent radiosurgery and another 6 had radiotherapy after the revision operations. The indication for surgery was a tumor size or conformation not suitable for radiosurgery or a situation in which a smaller recurrence was compressing the optic nerve or chiasm. Seven of the remaining patients were treated with stereotactic radiosurgery alone. A Kaplan-Meier analysis did not show the extent of tumor resection or the use of postoperative radiotherapy as significant contributing factors predictive of revisional surgery (Fig. 6). Similarly, a specific Kaplan-Meier analysis of patients who underwent STR at the time of the first surgery did not show any significant benefit from postoperative radiotherapy in reducing the chances of a further operation (Fig. 5 right).

**Discussion**

The 2000 revision for classifying WHO tumors of the CNS led to regrading of many meningiomas, and thus a greater proportion of surgically treated CNS meningiomas have been identified as WHO Grade II atypical lesions. Consequently, much of the original published material supporting postoperative radiotherapy for WHO Grade II meningiomas, a subject area that has historically attracted some professional controversy, is subject to question. We are the first group to explore the impact of postoperative radiotherapy in patients following first-time resection of WHO Grade II meningiomas in the post-2000 era. We believe this makes our data more relevant to current clinical practice. We also present the largest dataset in the literature on WHO Grade II meningiomas treated with postoperative radiotherapy.

Our results failed to demonstrate a significant overall difference with respect to postoperative radiotherapy reducing tumor recurrence following first-time surgery.
Radiotherapy for atypical meningiomas

Unfortunately, the published literature dealing with the issue of radiotherapy for WHO Grade II meningiomas is based on small patient numbers, with WHO Grade II and Grade III (anaplastic) tumors often grouped together. It is limited further in any time-to-event comparative analysis and fails to separately consider GTR and STR without distinguishing between first-time resection and surgery for recurrence.1,3,4,6,9–11,13,14,21,23,24,30,35 Many of the publications predate the 2000 WHO grading change, and all include patients prior to this time point. In addition, authors of many of the papers attempt to present a time-to-event analysis based on radiological recurrences in which imaging has been performed only on the basis of symptom development and in which follow-up within patient cohorts is otherwise clinical rather than via interval imaging.

Most patients undergoing tumor treatment increasingly access information sources other than their treating clinician, particularly the Internet and relevant patient support groups.31 Wikipedia has the highest average search engine position and the most frequently viewed pages compared with other Internet medical information sources such as MedlinePlus, NHS Direct, emedicine, Patient.co.uk, or .gov domains.15 At the time this paper was going to press, Wikipedia indicated that “in the case

Fig. 4. Kaplan-Meier curves showing the time to radiologically demonstrated tumor recurrence or remnant progression plotted for each of the factors patient sex (A), tumor location (B), degree of tumor resection (C), and use of postoperative radiotherapy (D).
of a Grade II meningioma, the current standard of care involves postoperative radiation treatment regardless of the degree of surgical resection.” Similarly, on the British national patient support group website MeningiomaUK (http://www.meningiomauk.org), an expert opinion is presented with the view that “all patients with a Grade 2 meningioma should have radiotherapy.”

The potential side effects associated with radiotherapy are not trivial. They include radiation necrosis, leukoencephalopathy, cognitive decline, visual impairment, hypopituitarism, and postradiation tumor formation that can develop many years after the original treatment and can affect up to half of the patients subjected to cranial radiation. Radiotherapy can also present issues with respect to any subsequent surgery: poorer wound healing, increased infection risk, and greater complexity for any reconstructive aspects (particularly for skull base operations in which interval progression is demonstrated). However, these sequelae may become less problematic with the introduction of more modern methods of radiation delivery, such as intensity-modulated radiotherapy and CyberKnife, and their reduced exposure to adjacent brain/neural structures.

Our results suggested that radiotherapy should not be given to patients who have undergone GTR (Simpson Grade 1/2) of a WHO Grade II meningioma. We showed that radiotherapy only had a significant benefit on radio logical recurrence when the gross totally resected tumor group (as well as the subtotally resected tumors undergoing postoperative radiosurgery) was removed from analysis. Yang et al. also failed to demonstrate a significant beneficial effect from radiotherapy on disease-free survival for WHO Grade II meningiomas as a whole. Approximately 50% of patients who undergo GTR will ultimately remain free of recurrent disease, a group that would, in the context of a policy of routine postoperative radiotherapy, otherwise receive unnecessary radiation. We suggest that most recurrent disease, with regular interval MR imaging, would be amenable to treatment with stereotactic radiosurgery.

Our data support the value of giving radiotherapy for WHO Grade II meningiomas in which there is a postoperative tumor remnant. However, in considering radiotherapy for such a group, other factors must be considered such as overall functional status, periradiation discomfort, potential long-term side effects, impact on the quality of life during repeated attendances over weeks of a treatment course, and increased access to MR imaging surveillance and stereotactic radiosurgery. An alternative approach for patients who have undergone first-time STR of a WHO Grade II meningioma, justifiable on the basis of our results, would be to undergo stereotactic radiosurgery for the tumor remnant if it has a size and appearance appropriate for radiosurgery. Early treatment of a postsurgical remnant rather than waiting for the remnant to progress is justifiable based on the analysis of Harris et al., who showed a highly significant survival advantage with early radiosurgery.

In addition, in patients who have undergone either GTR or STR along with postoperative stereotactic radiosurgery to the tumor remnant, any subsequent small single or multiple local tumor recurrences demonstrated on interval imaging should be subjected to repeated radiosurgical treatments in a “spot-welding” manner. This strategy is in concordance with the current standard of care for small incidental nonsurgically treated meningiomas in which interval imaging progression is demonstrated.

We suggest that postoperative radiotherapy should only be considered following first-time STR in patients with good functional status in whom the morphology (for example, en plaque) or larger size of the tumor remnant precludes radiosurgery and a further staged operation is not being planned.

The Kaplan-Meier curves in Figs. 3 and 4 provide a visual representation of the risk of recurrence and also assist in clarifying the extent of the imaging follow-up required. The Kaplan-Meier curves appear to plateau after 6 years of follow-up. It would seem appropriate that

---

Here is the table for the mean times to radiological tumor recurrence or remnant progression:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Time (mos)*</th>
<th>95% CI (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>58 ± 6</td>
<td>47–70</td>
</tr>
<tr>
<td>F</td>
<td>57 ± 6</td>
<td>44–69</td>
</tr>
<tr>
<td>location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>convexity</td>
<td>53 ± 5</td>
<td>44–62</td>
</tr>
<tr>
<td>parasinus</td>
<td>56 ± 8</td>
<td>41–72</td>
</tr>
<tr>
<td>skull base</td>
<td>61 ± 7</td>
<td>37–65</td>
</tr>
<tr>
<td>resection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STR</td>
<td>42 ± 4</td>
<td>35–49</td>
</tr>
<tr>
<td>GTR</td>
<td>67 ± 6</td>
<td>55–79</td>
</tr>
<tr>
<td>radiotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>58 ± 6</td>
<td>47–68</td>
</tr>
<tr>
<td>yes</td>
<td>60 ± 6</td>
<td>47–72</td>
</tr>
</tbody>
</table>

* Values expressed as the means ± standard error.
Radiotherapy for atypical meningiomas

alongside a baseline postoperative MR image, annual interval imaging, ideally MR, should be performed in all patients, including those with tumors that have undergone GTR and those of the convexity, for a period of at least 7 years, although 10 years would be a reasonable cutoff.

Our study is limited by its retrospective nature, the small number of patients undergoing postoperative radiotherapy (although still the largest of any published series to date), and the variation in the follow-up among the study cohort (reflected by censoring on the Kaplan-Meier curves). We also assumed that patient selection for radiotherapy was based on individual surgeon practices (that is, some favored radiotherapy, whereas others did not) rather than, for example, the extent of disease. In addition, MR imaging follow-up, although performed in the majority of cases, was not universal, with disease progression being a subjective assertion made by a neuroradiologist rather than a calculation based on radiological tumor volume analysis. Note that MR imaging within 24 hours of meningioma resection was not routinely performed at either of the two institutions involved in the study over the period concerned.

There are significant unanswered questions that our study has not addressed. We did not explore the issue of postoperative radiotherapy following a second or subsequent operations. Neither did we explore the timing of postoperative radiotherapy. For example, are better outcomes achieved following early postoperative radiotherapy as is the case for malignancy, or is there anything to be lost by waiting for imaging-demonstrated remnant progression? In more refractive recurrent tumors, is there a synergistic benefit in taking advantage of both spot-welding effect stereotactic radiosurgery and the fractionated nature of radiotherapy, as has been demonstrated for brain metastases?

Two phase II clinical trials are currently underway (RTOG-0539 and EORTC 22042–26042; Clinicaltrials.gov), examining the effects of radiotherapy on both gross totally and subtotally resected atypical meningiomas as well as the impact of radiosurgery on postoperative tu-

![Fig. 5. Kaplan-Meier curves for subtotally resected meningiomas showing the relationship between postoperative radiotherapy and radiological tumor recurrence/remnant progression (left) and revision surgery (right). Note that 5 patients who had postoperative radiosurgery but not radiotherapy and who did not, at the time of data collection, show radiological tumor progression, were excluded from analysis.](image)

![Fig. 6. Kaplan-Meier curves showing the time from the first-time surgery to revisional surgery of all WHO Grade II meningiomas, plotted for the degree of tumor resection (left) and the use of postoperative radiotherapy (right).](image)
The results of these studies are eagerly anticipated; however, their prospective nature and the duration of follow-up required when dealing with meningioma recurrence will mean that the data will not soon be available to the clinician. Such is especially the case in documenting the extent of any adverse effects from radiotherapy. The value of our paper lies in providing some clarification on this issue in the interim. Remaining unanswered questions concerning the role of radiotherapy in WHO Grade II meningiomas will likely be answerable only with much larger patient numbers via either multidpartmental, cooperatively collected data or national sustained data collections such as the Central Brain Tumor Registry of the United States (http://www.cbtrus.org) or the National Brain Tumour Registry (http://www.nbtr.nhs.uk) in the United Kingdom.

Conclusions

We provide the largest study in the literature thus far to examine the use of postoperative radiotherapy for WHO Grade II atypical meningiomas following first-time resection. We suggest that radiotherapy is not appropriate after first-time surgery for WHO Grade II meningiomas during which GTR (Simpson Grade 1/2) has been achieved. For subtotaly resected WHO Grade II meningiomas (Simpson Grade 3), we suggest that factors, such as access to interval MR imaging, suitability of remnant for radiosurgery as per postoperative MR imaging, patient age and comorbidity, and implications with respect to any future surgical treatment, should be considered before a decision is made to proceed with radiotherapy. In particular, we advise that any postoperative, radiologically demonstrated tumor remnant should be treated with radiosurgery and that radiotherapy be reserved for tumor remnants deemed too large for radiosurgery in which a second operation is inappropriate.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Carroll, Mair. Acquisition of data: Mair, Morris, Scott. Analysis and interpretation of data: Carroll, Mair. Drafting the article: Mair. Critically revising the article: all authors. Statistical analysis: Carroll, Mair.

Administrative/technical/material support: Carroll, Mair. Study supervision: Carroll.

References

Radiotherapy for atypical meningiomas


