Long-term Outcome After Radiotherapy in Patients with Atypical and Malignant Meningiomas—Clinical Results in 85 Patients Treated in a Single Institution Leading to Optimized Guidelines for Early Radiation Therapy

Sebastian Adeberg,* Christian Hartmann, M.D.,† Thomas Welzel, M.D.,* Stefan Rieken, M.D.,* Daniel Habermehl, M.D.,* Andreas von Deimling, M.D.,† Jürgen Debus, M.D., Ph.D.,* and Stephanie E. Combs, M.D.*

From the Departments of *Radiation Oncology and †Neuropathology, Institute for Pathology, University Hospital of Heidelberg, Heidelberg, Germany; and ‡German Cancer Research Center, Clinical Cooperation Unit Neuropathology, Heidelberg, Germany

Received Mar 26, 2011, and in revised form May 26, 2011. Accepted for publication Aug 10, 2011

Summary

This study evaluated the long-term results for atypical and malignant meningioma patients diagnosed according to the most recent WHO categorization system and receiving radiation after surgery. Histologic grade had a significant impact on overall and progression-free survival for both kinds of forms of meningioma. Overall survival at 5 years was 81% for atypical and 50% for malignant. RT also improved pre-existing clinical symptoms. Radiation therapy appears to be an

Purpose: Previously, we could show that the new World Health Organization (WHO) classification of meningiomas significantly correlated with outcome in patients with atypical and anaplastic histology. In the present work, we analyzed our long-term experience in radiotherapy for atypical and malignant meningioma diagnosed according to the most recent WHO categorization system.

Patients and Methods: Sixty-two patients with atypical and 23 patients with malignant meningioma have been treated with radiotherapy. Sixty percent of all patients received radiotherapy (RT) after surgical resection, 19% at disease progression and 8.3% as a primary treatment. Radiation was applied using different techniques including fractionated stereotactic RT (FSRT), intensity-modulated RT, and combination treatment with carbon ions. The median PTV was 156.0 mL. An average dose of 57.6 Gy (range, 30–68.4 Gy) in 1.8–3 Gy fractions was applied.

Results: Overall survival was impacted significantly by histological grade, with 81% and 53% at 5 years for atypical or anaplastic meningiomas, respectively. This difference was significant at \( p = 0.022 \). Eighteen patients died of tumor progression during follow-up. Progression-free survival was 95% and 50% for atypical, and 63% and 13% for anaplastic histology at 2 and 5 years. This difference was significant at \( p = 0.017 \). Despite histology, we could not observe any prognostic factors including age, resection status, or Karnofsky performance score. However, pre-existing clinical symptoms observed in 63 patients improved in 29.3% of these patients.

Conclusion: RT resulted in improvement of preexisting clinical symptoms; outcome is comparable to other series reported in the literature. RT should be offered after surgical resection after
Introduction

Meningiomas account approximately for 15−20% of all primary brain tumors in adults with an annual incidence of about 6 in 100,000 (1). Only a minority of around 10% are graded as high-risk tumors: Atypical and malignant meningiomas account for approximately 5−7% and 1−3% of all meningiomas (2−4). These meningiomas are associated with aggressive growth patterns reflecting their clinical and histopathological features of malignancy.

Although high-risk meningiomas can be considered a rare disease, diagnosis can be associated with severe debilitating and life-threatening signs and symptoms, and optimal diagnosis and management of these fast-growing lesions is necessary. Exact classification of these tumors is of high importance, because early radiotherapy (RT) can be withheld in low-grade tumors, whereas higher-grade meningiomas benefit from immediate RT (5). Therefore, over the years, the World Health Organization (WHO) Classification System for Meningiomas has been optimized to optimally correlate with clinical behavior. Only recently, we could show that the new and improved classification system reflects the biological behavior as measured by patients’ outcome significantly better than the previous categorization systems (6).

In our institution, early RT has been favored in high-risk meningiomas directly after diagnosis. Emphasis was put on optimized treatment techniques in meningioma patients, including fractionated stereotactic RT (FSRT), intensity-modulated RT (IMRT), or particle therapy, aiming at an increase in local control and survival, as well as a reduction of treatment-associated side effects (6, 10−16). In the present work, we analyzed the outcome in one of the largest populations of atypical and anaplastic meningiomas patients treated with RT in a single institution with special focus side effects, prognostic factors as well as the impact of novel radiation techniques on outcome.

Patients and Methods

Between June 1985 and October 2009, 62 patients with atypical and 23 patients with malignant meningiomas have been treated with RT at the Department of Radiation Oncology at the University Hospital Heidelberg, Germany. Our study included 37 men and 48 women with an average age of 55 years. Patients’ characteristics Patient characteristics are shown in Table 1.

The tumor was localized at the convexity in 31 patients (37%), parasagittally or along the falx in 13 patients (15%), at the skull base in 29 patients (34%), and in other locations including the orbit, intraventricular regions, or along the cervical spine in 12 patients (14%). Tumor localization was right-sided in 29.3%, left-sided in 58.6%, and 12.1% bilateral. Of the 85 patients, 53 (62%) presented with clinical symptoms before treatment. They included mostly headaches, visual deficits, uncertain gait, and dizziness. No patient had a history of neurofibromatosis.

In all patients at least one neurosurgical intervention had been performed: A total of 60% of all patients received RT after surgical resection, which was complete in 55% and subtotal in 45% of these patients. In 32% of the patients, RT was performed for disease progression and in 8% as a primary treatment after biopsy. Neuropathological diagnosis was performed according to the most recent WHO classification system; reanalysis and reclassification of patients treated before the optimized WHO classification had been performed and published in detail previously (6).

Over the years, patients were treated with different radiation techniques including three-dimensional conformal RT, fractionated stereotactic RT (FSRT), intensity-modulated RT (IMRT), and combination treatments with precision photon RT and carbon ion RT in 5 patients as published previously (10, 12, 15).

For treatment planning, patients were fixed with a custom-made mask fixation, and computed tomography as well as magnetic resonance imaging were used for treatment planning when available. We defined the macroscopic lesion visible on contrast-enhanced imaging and/or the resection cavity as the gross tumor volume (GTV) adding 1−2 cm margin for the clinical target volume (CTV) adhering to anatomical borders. To account for setup inaccuracy, a PTV was added between 1 and 5 mm depending on technique used for treatment. The median PTV was 156.0 mL (range, 26−387 mL).

| Table 1 | Patients’ characteristics of 85 patients with high-grade meningiomas treated with radiation therapy |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Characteristic | Number (%)      | Number (%)      | Number (%)      | Number (%)      | Number (%)      | Number (%)      | Number (%)      |
| Histology       | Atypical        | 62 (73)         | Anaplastic      | 23 (27)         | Gender          | Male            | Female          |
|                 |                 |                 |                 |                 |                 | 37 (44)         | 48 (56)         |
| Location        | Skull base      | 29 (34)         | Parasagittal/falcial | 13 (15)         | Karnofsky performance score | ≥80 | 61 (72) |
|                 |                 |                 | Convexity       | 31 (37)         |                  | <80             | 24 (2)          |
|                 |                 |                 | Other           | 12 (14)         | Resection status | Complete        | 35 (41)         |
|                 |                 |                 |                 |                 |                  | Subtotal        | 50 (59)         |

Keywords: High-risk meningiomas, Radiation therapy, Outcome, Prognostic factors
For patients treated with photon RT, we applied a median dose of 59.4 Gy (range, 41.4–68.4 Gy); patients treated with carbon ion RT received a dose of 50.4 Gy to the CTV and a carbon ion boost to the macroscopic tumor (GTV), with $6 \times 3$ Gy E delivered by the intensity-modulated raster scanning technique as published previously (10).

Patients were followed prospectively at the center for follow-up examinations, which were scheduled initially 6 weeks after completion of RT, and thereafter in 3-month intervals. No patient was lost to follow-up. They included a thorough clinical-neurological assessments as well as contrast-enhanced imaging. The median follow-up time was 73 months (range, 3–243 months). To complete data acquisition, assessments by a questionnaire sent to the patients asking about recent neurological status including cranial nerve deficits, side effects after treatment during follow-up, additional treatments for the meningioma, quality of life before and after RT as well as any improvement in preexisting sequelae; 73% percent of the patients answered the questionnaire. Cases were included in the study if adequate documentation could be provided by these sources.

Survival statistics were based on overall survival (OS) and progression-free survival (PFS). OS being measured from the day of the first diagnosis to the date of last follow-up/death. PFS was measured from the date of beginning of RT to the date of last follow-up/progression/death, whichever occurred first. Both were calculated using the Kaplan-Meier method. Influence on prognostic factors on outcome was assessed using the univariate Cox proportional regression model. Patterns of failure analysis were performed by correlating the imaging at recurrence with the treatment plan dividing patients into three categories: In-field recurrences developing within the 90% isodose of the irradiation field, out-field recurrences diagnosed at distant sites from the RT field, and marginal recurrences were adjacent to the RT-field but outside the 90%-isodose.

Statistical analyses were performed with the software program Statistica 6.0 (StatSoft, Hamburg, Germany).

**Results**

**Side effects**

In all patients, RT could be completed without interruptions ≥ 4 days. No treatment discontinuations because of side effects had to be undertaken. Transient mild side effects including skin irritation, alopecia, fatigue, edema, dizziness headache, mucositis, or dry eyes could be observed in most patients. No acute severe side effects could be seen. During follow-up, 1 patient suffered from an acute hemorrhage into the tumor, 1 patient with a skull base meningioma with severe visual deficits before RT developed amaurosis, and in 1 patient magnetic resonance examinations showed an asymptomatic temporal gliosis.

**Improvement of symptoms**

Preexisting clinical symptoms were observed in 63 patients. These included headaches, visual deficits, sensorial and motor deficits, uncertain gain, and seizures. The majority of patients presented with multiple symptoms. After RT, symptoms improved in 29% of these patients.

New symptoms were observed in 13 patients. Four patients with skull base tumors showed slight visual impairment, 2 sensory deficits, 2 complained of localized pain in the irradiated area, and 1 patient each complained of aggravation of headaches, change in character, increased lacrimation of the eyes, hearing loss, and dizziness.

**Survival**

Overall survival was impacted significantly by histological grade, with 81% and 53% at 5 years for atypical or anaplastic meningiomas respectively (Fig. 1). This difference was significant at $p = 0.022$. Other factors including resection status, Karnofsky performance score, and age (<60 vs. ≥60 years) did not influence OS (Table 2).

**PFS**

Eighteen patients died of tumor progression during follow-up. PFS was 95% and 50% for atypical, and 63% and 13% for anaplastic histology at 2 and 5 years. This difference was significant at $p = 0.017$ (Fig. 2). Of all recurrences, 85% were localized within the former high-dose RT field, and 7% were localized at the field border. In 7% distant recurrences along the spine were observed, which was combined with a local recurrence in 1 patient.

Despite histology, we could not observe any prognostic factors including age, resection status or Karnofsky performance score (Table 2).

**Discussion**

The aim of the present work was the analysis of long-term outcome in a large group of patients with high-grade meningiomas treated with RT in a single institution. Our intention was to focus on the influence of prognostic factors on local recurrence and survival rates. Results show long-term local progression-free rates as well as overall survival, which are comparable to data found in the literature, with no severe treatment-related side effects. Only
histological grade could be identified as a prognostic factor supporting the high importance of exact neuropathological diagnosis in these tumors.

Recently, we could show that the controversially discussed modification of grading criteria for malignant meningiomas in the WHO 2000/2007 classification of brain tumors correlated significantly better with outcome than the older version. In that study, we regraded all cases that had been treated at that time according to the new and revised WHO grading system. Analysis of the relationship of the new and old grading criteria with outcome showed a significantly better correlation between the new version than the old version of the WHO grading system and outcome (6). Other groups have also shown that exact neuropathological categorization has a strong impact on tumor control and survival, because the decision for adjuvant RT is based on the neuropathological grading. Smith and colleagues could show that using the different WHO classification systems, the numbers of patients identified as high-grade tumors may increase, and because these patients are typically selected for RT, clinical impact is high (17). Similar data were reported by Willis et al., also showing an increase in atypical histology using the new grading system (18). However, Simon et al. showed a decrease in high-grade tumors, which could be similarly shown in our previous work (6, 19). In total, these studies show that correlation with outcome using the new grading systems correlated much better, stressing the importance of exact neuropathological grading. Moreover, not only the indication for RT is influenced by histology, but also target volume definition as well as RT dose. For high-grade tumors, larger safety margins are required than for WHO Grade I tumors, and we would recommend higher doses ideally up to 60–66 Gy for long-term tumor control (5, 20, 21).

Keeping in mind that most older data reported in the literature were based on the previous neuropathological classifications, it seems warranted to reanalyze clinical data using the most recent and refined neuropathological definition criteria. Naturally, there is a transition period in diagnostics when new guidelines are established. This has been shown nicely by Pearson and colleagues: A reanalysis of 471 meningioma specimens collected between 1994 and 2006 revealed an increase in the annual percentage of diagnosed atypical meningiomas after 2002 up to 32.7% and 35.5% between 2004 and 2006 (22). However, this study only shows statistics of meningioma grading, but no reclassification of older tumors to determine “real” outcome with respect to the new grading system had been performed. Therefore, the present study evaluated a large group of 85 patients treated in a single institution from 1985 and October 2009. All early patients treated until 2004 were reclassified according to the new WHO classification system as published previously (6). Subsequent patients had been diagnosed later and neuropathological guidelines for diagnosis were already based on the new WHO grading system. As opposed to the previous work mainly focusing on the differences within the grading systems, the present study is focused on treatment outcome and prognostic factors in high-grade meningiomas.

The data show good efficacy and low rates of side effects in patients with meningiomas, and overall survival times are relatively high compared with histological data. However, compared with patient groups with low-grade meningiomas, local control and survival rates are significantly lower supporting the rationale for adjuvant RT. In Table 3, publications of radiation therapy for high-risk meningiomas have been summarized. However, a clear clinical dataset supporting up-to-date RT recommendations can only be generated using the new and improved WHO grading system. Therefore, the data of the present manuscript present a useful basis for argumentation and treatment decision, because the work is based on one of the largest groups of patients with atypical and anaplastic meningiomas treated in a single institution with homogeneous guidelines for treatment decision and treatment planning, including target volume definition. In the past, RT was discussed controversially for atypical meningiomas, and often institutions withheld early RT in patients with incompletely resected tumors with small residual lesions, or in completely resected meningioma patients (19, 22). One main argument commonly used against early RT was the development of neurocognitive deficits during follow-up, arguing that these might outweigh the benefit from early RT with respect to local control. However, using modern radiation techniques, sparing of normal tissue is possible, and therefore the risk for treatment-related neurocognitive impairment is very low. It could be shown that patients treated with surgery and postoperative RT

### Table 2 Prognostic factors for overall and progression-free survival analyzed in univariate analysis

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Overall survival (p)</th>
<th>Progression-free Survival (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology (atypical vs. anaplastic)</td>
<td>0.022*</td>
<td>0.017*</td>
</tr>
<tr>
<td>Gender (male vs. female)</td>
<td>0.16</td>
<td>0.36</td>
</tr>
<tr>
<td>KPS (≥80 vs. &lt;80)</td>
<td>0.57</td>
<td>0.53</td>
</tr>
<tr>
<td>Age (&lt;60 vs. ≥60)</td>
<td>0.19</td>
<td>0.38</td>
</tr>
<tr>
<td>Resection status (complete vs. subtotal)</td>
<td>0.82</td>
<td>0.23</td>
</tr>
<tr>
<td>Radiation quality (Ph vs. Ph + C12)</td>
<td>0.9</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Abbreviations: C12 = carbon ion radiotherapy; KPS = Karnofsky performance score; PH = photon radiotherapy; * significant.
did not show an increase neurocognitive impairment as compared with patients treated with surgery alone supporting the idea that adjuvant RT does not lead to the highly feared neurocognitive sequelae (23). A second long-term analysis in a large group of meningioma patients supported these results, concluding that late neurocognitive deficits are observed in meningiomas patients and are likely to be associated with various factors such as antiepileptic drugs or tumor location, but not with RT (24). Therefore, this argument should not be used against early postoperative RT, and the main focus should be put on local control and outcome.

Therefore, in view of all recent data on atypical and anaplastic meningiomas, our policy is to favor early RT using modern RT techniques. Additionally, study concepts aiming at an increase in local control by local dose-escalation should be evaluated and brought forward to continuously improve outcome. Therefore, our treatment recommendations from a radiation oncologist’s point of view are summarized in Fig. 3.

**Conclusion**

Atypical and anaplastic meningiomas are associated with aggressive growth and high local recurrence rates. Management should include neurosurgical resection, as complete as possible, followed by adjuvant RT. Modern RT techniques offer the possibility of dose escalation given the apparent dose–response relationship in high-grade meningiomas while sparing normal tissue avoiding RT-associated neurocognitive sequelae.

**References**


