Kinetics of tumor size and peritumoral brain edema before, during, and after systemic therapy in recurrent WHO grade II or III meningioma

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Background. The efficacy of systemic antineoplastic therapy on recurrent World Health Organization (WHO) grades II and III meningiomas is unclear.

Methods. We performed a retrospective multicenter analysis of serial cranial MRI in patients with recurrent WHO II and III meningiomas treated with antineoplastic systemic therapies. Growth rates for tumor volume and diameter, as well as change rates for edema size, were calculated for all lesions.

Results. We identified a total of 34 patients (23 atypical, 11 anaplastic meningiomas) with a total of 57 meningioma lesions who had been treated at 6 European institutions. Systemic therapies included bevacizumab, cytotoxic chemotherapy, somatostatin analogues, and tyrosine kinase inhibitors. Overall, tumor growth rates decreased during systemic therapy by 51% for tumor diameter and 14% for tumor volume growth rates compared with the period before initiation of systemic therapy. The most pronounced decrease in meningioma growth rates during systemic therapy was evident in patients treated with bevacizumab, with a reduction of 80% in diameter and 59% in volume growth. Furthermore, a decrease in size of peritumoral edema after initiation of systemic therapy was exclusively observed in patients treated with bevacizumab (−107%).

Conclusions. Our data indicate that systemic therapy may inhibit growth of recurrent WHO grades II and III meningiomas to some extent. In our small cohort, bevacizumab had the most pronounced inhibitory effect on tumor growth, as well as some anti-edematous activity. Prospective studies are needed to better define the role of medical therapies in this tumor type.

Keywords: anaplastic meningioma, anti-angiogenesis, atypical meningioma, bevacizumab, chemotherapy.

Meningiomas are the most frequent primary intracranial tumors in adults according to local and international brain tumor registries, with an incidence rate of about 30% and a female predominance, followed by glioblastoma and pituitary adenoma.1,2 Based on the World Health Organization (WHO) grade classification, meningiomas are histopathologically

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classified and graded into 3 different subgroups: benign meningiomas (WHO grade I), atypical meningiomas (WHO grade II), and anaplastic or malignant meningiomas (WHO grade III). The majority of these subgroups are benign, followed by atypical (up to 20% of all meningiomas) and anaplastic (about 1%–3% of all meningiomas).

While benign meningiomas are usually curable by surgery, atypical and anaplastic meningiomas are characterized by aggressive behavior and a high recurrence rate. No accepted therapy standard exists for meningiomas after exhaustion of surgical and radiotherapeutic options. A variety of systemic antineoplastic therapeutic agents, including hydroxyurea, temozolomide, irinotecan, interferon-alpha, mifepristone, octreotide analogues, megestrol acetate, bevacizumab, imatinib, erlotinib, and gefitinib, have been investigated in small studies and are being used in the clinical setting. However, the validity of the available studies is limited by small sample sizes, retrospective study designs, heterogeneous patient populations, lack of control arms, and varying response criteria, thus rendering the benefit of these drugs unclear.

In the present study, we aimed to analyze the growth rates of recurrent WHO grades II and III meningiomas before, during, and after treatment with systemic agents in order to provide novel information on the effect of drug treatment on the disease course.

**Materials and Methods**

**Patients**

Institutional review board approval for this retrospective European multicenter study was obtained from each participating institution. All participating institutions were asked to provide radiological as well as predefined epidemiological and clinical data of the patients using a prepared form (see Supplementary Material S1).

The inclusion criteria were as follows: (i) patient has histological diagnosis of WHO grade II or grade III meningioma according to 2007 WHO criteria; (ii) patient has received systemic antineoplastic therapy for tumor recurrence after previous operation and/or radiotherapy; (iii) digital datasets are available of multiple MR examinations taken before, during, and after the administration of systemic antineoplastic therapy.

Patient recruitment per institution was as follows: institution 1 (Vienna, n = 14), institution 2 (Leuven, n = 5), institution 3 (Lille, n = 4), institution 4 (Zurich, n = 4), institution 5 (Aarau, n = 4), and institution 6 (Essen, n = 3). First radiological diagnosis of meningioma was made between December 2002 and December 2013, and systemic antineoplastic therapy commenced between October 2005 and October 2013.

**Image Acquisition**

All patients received an MRI examination with a routine clinical imaging protocol of the brain. In total, 224 MRI examinations were included. The mean duration between 2 MRI examinations was 116 days (SD = 88 d). Each MRI examination included at least one T1-weighted sequence without and with contrast enhancement. In addition, a T2-weighted sequence was performed in 90.6% of all MRI examinations (203/224).

**Statistical Analysis**

Resulting measurements from tumor volume, maximum tumor diameter, and the volume of peritumoral edema were submitted for further analysis. All lesions were subdivided into 3 different subgroups related to patients’ therapy status. The subgroup “pretherapeutic” represented all meningiomas before systemic therapy; the subgroup “therapeutic” included a pretherapeutic baseline measurement within 4 weeks before the start of systemic therapy, all measurements during systemic therapy, and the first measurement after systemic therapy if it was performed within 4 weeks after the completion of systemic therapy. All measurements after the systemic therapy are summarized in the “posttherapeutic” subgroup.

Measurements of maximum tumor diameter, maximum tumor volume, and maximum peritumoral edema volume of every lesion were used to derive gradients of decrease and increase, which are specified as average growth rates for tumor volume and diameter and average change rates for edemas throughout the manuscript. Growth and change rates were defined as the decrease or increase in tumor diameter, tumor volume, or peritumoral edema volume over a period of time (t), expressed as cm/t and cm²/t, respectively. The time period was determined by the average MR follow-up interval of the lesions. Pearson correlation coefficient was used to assess the relation between the calculated growth rates of tumor diameter and tumor volume.

A positive growth rate indicated an increase of tumor diameter, tumor volume, or edema volume, while a negative growth rate reflected a decrease of the different measurements. A growth rate of zero indicated no change in volume or diameter.

Statistical Package for the Social Sciences (SPSS) version 20.0 was used for descriptive statistics of the cohorts. Visualizations

**Image Analysis**

The anonymized radiological data for participating patients from all institutions were collected in the form of digital data. The MR images were qualitatively evaluated at institution 1 on a PACS (Picture Archiving and Communication System, Centricity, GE Healthcare) workstation by an experienced neuroradiologist (J.F.) regarding their usability for further postprocessing. Image postprocessing was performed using open-source software (MRICron). Maximum tumor diameter, tumor volume, and volume of peritumoral edema were measured for each of the 224 MRI examinations by the same neuroradiologist (J.F.), blinded to all clinical patient data. T1-weighted postcontrast images were selected to determine the maximum tumor diameter as well as the tumor volume. The T2-weighted images were used to depict tumor edema. Maximum tumor diameter was defined as the biggest diameter of the contrast-enhanced tumor area measured in axial, coronal, or sagittal image dimension. Tumor volume was automatically calculated on the basis of multiple manually defined regions of interests (ROIs) including the whole contrast-enhancing tumor area as well as cystic parts of the tumor in the T1-weighted postcontrast sequences. Analogous to the tumor volume, peritumoral edema was determined using multiple ROIs, including the peritumoral hyperintense signal alterations in T2-weighted images, excluding contrast-enhancing tumor areas.

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Statistical Package for the Social Sciences (SPSS) version 20.0 was used for descriptive statistics of the cohorts. Visualizations
were performed in MatLab (7.14.0, Release 2012a; Mathworks). Testing for group differences between therapies was not utilized because of the small and unbalanced sample size.

Results

Patient Characteristics

We identified 34 patients with a total of 57 meningioma lesions that had been treated at 6 European institutions. Twenty-three patients (68%) had atypical meningiomas and 11 patients (32%) had anaplastic meningiomas. Systemic therapies included bevacizumab ($n = 5$), cytotoxic chemotherapy ($n = 9$), somatostatin analogues ($n = 9$), and tyrosine kinase inhibitors ($n = 7$). In 4 patients, radiological data during systemic therapy were not available, therefore these patients were included only in the “pretherapeutic” subgroup. Detailed patients’ baseline characteristics and the types of administered systemic therapies are given in Supplementary Material S2 and S3.

Thirty-two meningiomas were analyzable in the pretherapeutic time window, 37 meningiomas in the therapeutic time window, and 26 in the posttherapeutic time window. The mean number of MR examinations was 3.65, range 2–6) for all pretherapeutic MR examinations; 78 days (SD = 23, range = 41–156; mean number of MR examination = 3.13, range = 2–7) for systemic therapy; and 142 days (SD = 79, range = 21–334; mean number of MR examinations = 3.92, range = 2–7) for all posttherapeutic MR examinations.

Analysis of Solid Tumor Lesions

Measurements of maximum tumor diameter and tumor volume were represented as average growth rates and further subdivided into values for pretherapeutic lesions ($n = 32$), therapeutic lesions ($n = 37$), and posttherapeutic lesions ($n = 26$). Overall, diameter and volume growth rate values of the tumor lesions showed a high correlation in total (Pearson correlation coefficient $r = 0.722$; $P = 1.4903 \times 10^{-15}$), in the pretherapeutic ($r = 0.794$; $P = 5.8995 \times 10^{-8}$), therapeutic ($r = 0.52$; $P = 0.001$), and posttherapeutic ($r = 0.892$; $P = 9.144 \times 10^{-19}$) subgroups.

Table 1 and Figs 1A and B and 2A and B detail the tumor growth rates per time window and type of administered therapy. Overall, the mean tumor growth rates decreased by 51% for tumor diameter and 14% for tumor volume in the therapeutic period compared with the pretherapeutic period. Comparing the growth rates between the different therapy types, we observed the highest decrease of growth rate from the pretherapeutic to the therapeutic period in patients treated with bevacizumab (diameter: $-80\%$, volume: $-59\%$), followed by the subgroup of patients treated with chemotherapy (diameter: $-54\%$, volume: $+7\%$) and tyrosine kinase inhibitors (diameter: $-40\%$, volume: $-29\%$). Interestingly, in the posttherapeutic period, patients treated with bevacizumab showed the highest increase, with $200\%$ in growth rates with regard to tumorous lesion diameter and the second highest increase in terms of tumor volume, with $50\%$ in comparison with the therapeutic period. The lowest growth rates in the posttherapeutic period were observed with tyrosine kinase inhibitors, with regard to both tumor diameter and tumor volume.

Furthermore, tumor growth rates were subdivided, regarding tumor histology, into tumor diameter and volume growth rates of WHO grades II and III meningiomas per time window in Table 2. In the pretherapeutic as well as the therapeutic period, tumor growth rates (both diameter and volume) of the different histological meningioma subtypes were approximately balanced, whereas in the posttherapeutic period, tumor growth rates were considerably lower in atypical meningiomas than in anaplastic meningiomas.

A further analysis using Response Evaluation Criteria in Solid Tumors during treatment with systemic therapy (therapeutic period) revealed stable disease (defined as $\leq 30\%$ decrease or $\geq 20\%$ increase in the maximum tumor diameter) in 25 patients and progressive disease (defined as $\geq 20\%$ increase in the maximum tumor diameter) in 12 cases as the best responses during the treatment periods (see Supplementary Material S4).

Table 1. Growth rates of all solid tumor lesions

<table>
<thead>
<tr>
<th>Time Window</th>
<th>Systemic Therapy</th>
<th>Analyzable Meningiomas, n</th>
<th>Length of Time Window, days</th>
<th>Change in Diameter per Time [cm/time]</th>
<th>Change in Volume per Time [cm$^3$/time]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Pretherapeutic</td>
<td>All</td>
<td>32</td>
<td></td>
<td>139.98</td>
<td>123.61</td>
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<td></td>
<td>All</td>
<td>37</td>
<td></td>
<td>78.00</td>
<td>22.58</td>
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<td></td>
<td>75.56</td>
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<td></td>
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<td>4</td>
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<td>73.25</td>
<td>14.84</td>
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<td></td>
<td>Tyrosine kinase inhibitor</td>
<td>11</td>
<td></td>
<td>76.64</td>
<td>27.84</td>
</tr>
<tr>
<td>Therapeutic</td>
<td>All</td>
<td>26</td>
<td></td>
<td>141.92</td>
<td>78.52</td>
</tr>
<tr>
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<td></td>
<td>78.40</td>
<td>4.66</td>
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<td>Chemotherapy</td>
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<tr>
<td></td>
<td>Tyrosine kinase inhibitor</td>
<td>3</td>
<td></td>
<td>154.50</td>
<td>0.00</td>
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</table>
Analysis of Peritumoral Edema

Changes of peritumoral edema were defined as the change rates of maximum peritumoral edema volume over a period of time and were evaluated during the pretherapeutic period in 12 meningiomas, during the therapeutic period in 36 meningiomas, and during the posttherapeutic period in 25 meningiomas. In the overall cohort, mean change rates of peritumoral edema volume were positive in all time periods and were highest in the pretherapeutic and lowest in the posttherapeutic period (Table 3, Fig. 1C). Comparing edema volume change rates between the patient populations treated with different therapies, a decrease in edema volume was evident exclusively in the therapeutic period in patients treated with bevacizumab, with a change rate of $-0.007 \text{ cm}^3/\text{t}$ ($SD = 0.0210$) (resulting in a reduction of peritumoral edema change rate of 7% compared with the pretherapeutic period). The remarkable effect of bevacizumab on peritumoral edema change rates during the therapy period in comparison with all other included systemic therapies is visualized in Fig. 2C.

A reduction in peritumoral edema volume change rate by 29% compared with the pretherapeutic period was detected during the application of chemotherapy, while in the case of somatostatin analogues and tyrosine kinase inhibitors, peritumoral edema showed an increase in change rates of 95% and 15%, respectively. After the termination of systemic therapy, no change of peritumoral edema volume was determined in the chemotherapy subgroup. The second lowest peritumoral edema change rate after termination of systemic therapy was determined in the bevacizumab cohort, whereas patients who were treated with somatostatin analogues or tyrosine kinase inhibitor showed the highest posttherapeutic peritumoral edema change rates.

Fig. 1. Visualization of change gradients of (A) tumor diameter, (B) tumor volume, and (C) peritumoral edema before (continuous lines), during (dashed lines), and after (dotted lines) systemic therapy. The slopes describe the direction (decrease or increase) and steepness (intensity) for the 3 groups, respectively. A very steep line therefore indicates a rapid increase. As clearly visible, growth velocity for all 3 measures (diameter growth rate, volume growth rate, edema change rate) degrades from before to after therapy.
Moreover, peritumoral edema change rates were evaluated with regard to the different histological meningioma subgroups in Table 2. Remarkably, peritumoral edema volume change rates were lower in atypical meningiomas in the pretherapeutic as well as in the therapeutic period than in anaplastic meningiomas, while there was almost no difference in the posttherapeutic period. Moreover, during systemic therapy, atypical meningiomas showed increased peritumoral edema change rates, while the peritumoral edema in anaplastic meningiomas decreased in comparison with the pretherapeutic period. After systemic therapy, peritumoral edema volumes showed the lowest change rates in atypical as well as...
Discussion

The role of systemic therapies in recurrent WHO grades II and III meningiomas is ill-defined. So far, medical therapy of these tumors has been evaluated only in case reports, retrospective patient series, and small and uncontrolled prospective studies. The 6-month progression-free survival (PFS-6) rates reported among these studies show a high variability, ranging from 3% to 64.3%. A recent systematic analysis proposed a PFS-6 rate of 26% as the benchmark for historical comparisons.14 Considering this benchmark, hydroxyurea, octreotide analogues, gefitinib, and erlotinib were deemed ineffective,4,13,16 while anti-angiogenic drugs, including bevacizumab, vatalanib, and sunitinib showed potential activity, with PFS-6 rates of 37.5% to 64.3%.11,14,17 –19 Interestingly, our data support a potential role of anti-angiogenic treatment in recurrent WHO grades II and III meningioma, as the most pronounced decrease of tumor growth rates was observed in patients put on bevacizumab therapy. Of note, however, we observed evidence for drug-induced tumor growth inhibition also for the other types of systemic therapies analyzed in our series, although to a considerably smaller extent than for bevacizumab. The activity of bevacizumab or other anti-angiogenic agents targeting the vascular endothelial growth factor (VEGF) pathway in WHO grades II and III meningioma seems rational from a pathobiological point of view, as prominent expression of VEGF and its receptors as well as neo-angiogenesis have repeatedly been shown in this tumor type.20,21 Ongoing prospective studies (NCT00972335, NCT01125046) will provide more data on the role of bevacizumab for aggressive meningiomas. A point of caution, however, may be deduced from our observation of increased growth rates after cessation of bevacizumab therapy that were not noted in patients treated with other drugs. “Rebound effects” characterized by more malignant behavior after termination of bevacizumab therapy have been described for vestibular schwannoma, and further studies should address this issue also in meningioma.22

Bevacizumab has shown considerable and clinically relevant anti-edematous properties in gliomas and brain metastases. Our data indicate that this effect is also relevant in meningioma patients, as we saw shrinking of peritumoral edema volumes exclusively in patients under bevacizumab treatment. This finding is well in line with reports showing an important role for VEGF in edema formation in meningioma.23 – 25 Thus, bevacizumab treatment may be of particular clinical benefit in meningioma patients with symptomatic peritumoral edema and may help to decrease symptomatic burden and corticosteroid need.

Our study has several limitations; despite the multicenter approach, we were able to assemble only a relatively small patient cohort in this rare tumor type. In a number of cases we were unfortunately not able to retrospectively retrieve the neuroimages (or only neuroimages of insufficient quality), because they were done at external institutions. To overcome the individual bias of heterogenic time periods between the MR follow-up examinations at each center, growth rates were calculated in patients put on bevacizumab therapy. Of note, however, we observed evidence for drug-induced tumor growth inhibition also for the other types of systemic therapies analyzed in our series, although to a considerably smaller extent than for bevacizumab. The activity of bevacizumab or other anti-angiogenic agents targeting the vascular endothelial growth factor (VEGF) pathway in WHO grades II and III meningioma seems rational from a pathobiological point of view, as prominent expression of VEGF and its receptors as well as neo-angiogenesis have repeatedly been shown in this tumor type.20,21 Ongoing prospective studies (NCT00972335, NCT01125046) will provide more data on the role of bevacizumab for aggressive meningiomas. A point of caution, however, may be deduced from our observation of increased growth rates after cessation of bevacizumab therapy that were not noted in patients treated with other drugs. “Rebound effects” characterized by more malignant behavior after termination of bevacizumab therapy have been described for vestibular schwannoma, and further studies should address this issue also in meningioma.22

### Supplementary Material

Supplementary material is available at Neuro-Oncology Journal online (http://neuro-oncology.oxfordjournals.org/).

### Table 3. Changes of peritumoral edema volume

<table>
<thead>
<tr>
<th>Time Window</th>
<th>Systemic Therapy</th>
<th>Analyzable Meningiomas, n</th>
<th>Length of Time Window, days Mean</th>
<th>SD</th>
<th>Change in Volume per Time [cm³/time] Mean</th>
<th>SD</th>
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Conflict of interest statement. None declared.

References