Surgery for convexity meningiomas: Simpson grade I resection should still be the goal

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Abstract

Background:
Recently the relevance of Simpson's resection grade as a prognostic factor for recurrence of WHO grade I meningiomas was challenged, contradicting many previous scientific reports and traditional neurosurgical teaching.

Objective:
To study whether the predictive value of Simpson resection grade with respect to meningioma recurrence and overall survival is outdated or still valid.

Material & Methods:
All patients ≥16 years who underwent primary craniotomies for convexity meningiomas at the Oslo University affiliated hospitals (Rikshospitalet and Ullevål University Hospital) in the period 01.01.1990 – 27.01.2011 were included. Overall survival (OS) and retreatment-free survival (RFS) rates were related to patient- and surgery-specific factors.

Results:
Included in the study were 391 consecutive patients. Median age was 60.1 years (range 19 - 92). Female-to-male ratio was 2.1:1. WHO grade was grade I in 352 (90.3%), grade II in 22 (5.6%) and grade III in 16 (4.1%). Follow-up was 100%. Median follow-up time was 7.1 years (range 0.0 – 20.9 years) and total observation time was 3147 patient-years. The 1-, 5- and 10-year OS were 96%, 89% and 78%, respectively. Age, gender, WHO-grade and Simpson grade were significantly associated with OS. The 1-, 5- and 10-year RFS were 99%94% and 90%, respectively. Simpson resection grade and WHO grade were significantly associated with RFS. Odds ratio for recurrence after Simpson resection grade 2/3 and 4/5 were 5.2 and 26.1 times higher than after Simpson grade 1 resection, respectively.

Conclusions:
Simpson grade 1 resection should still be the goal for convexity meningiomas.
Introduction

The crude incidence of all primary intracranial tumors in Norway is 24.2/100,000 person years and meningiomas account for 31% of them, with an incidence of 7.5/100,000 person years. This is in accordance with US data from the CBTRUS. Convexity meningiomas account for 17 – 23% of all intracranial meningiomas. However, the published series are quite small and the largest series from Giombini et al. in 1984 presented 215 patients.

Meningiomas are divided into three grades according to WHO histological classification; WHO I tumors which have a low proliferation rate and usually show a benign course, WHO grade II tumors have intermediate proliferation activity, and grade III tumors with a high proliferation activity and often having a malignant behavior.

Treatment of meningiomas has for decades been radical resection. In 1957, Simpson published his hallmark paper showing a significant correlation between degree of meningioma resection and tumor recurrence. Several later studies have found that both WHO grade and Simpson resection grade are important prognostic factors for tumor recurrence and survival. However, recently Sughrue et al. has challenged the relevance of Simpsons resection grade as a prognostic factor for recurrence of WHO grade I tumors since the authors found that the benefit of more aggressive attempts to resect the tumor with dura and underlying bone was negligible compared with simply removing the entire tumor, or even leaving small amounts of tumor attached to critical structures.

As the finding by Sughrue et al. contradicts many previous scientific reports and traditional neurosurgical teaching, the main objective of the present analysis of 391 consecutive craniotomies for convexity meningioma in adult patients over the last 20-years at Oslo University Hospital, was to study whether the predictive value of Simpson resection grade with respect to tumor recurrence and overall survival is outdated or still valid.
Materials and methods

Patients and population
All patients ≥16 years who underwent primary craniotomy for a convexity meningioma, at the Oslo University Hospital affiliated hospitals (Rikshospitalet and Ullevål University Hospital) in the period 01.01.1990 – 27.01.2011 were included, with the exception of 3 patients that had moved out of the country in the follow-up period. The patients were identified from surgery protocols and the department of pathology’s independent histology registry. Convexity meningiomas were defined as tumors arising from the endocraniar side supratentorially, stretching from lateral to the parasagittal sinus down to the beginning of the skull base. The location was decided based on surgical notes and available images. Patients who had pre-operative radiotherapy (RT), either conventional RT or stereotactic radiosurgery (SRS), were excluded.

Treatment strategy
Patients with a symptomatic meningioma or patients having an asymptomatic meningioma increasing in size over time have been candidates for surgical treatment. Throughout the entire study period, the main treatment strategy has been radical tumor resection. Grade of surgical resection has been scored according to Simpson. Some patients with WHO III grade tumors were referred to postoperative conventional radiotherapy.

Follow-up and treatment of recurrent tumors
As the postoperative image surveillance has not followed a rigorous scheme, but left open to the treating physician’s discretion, tumor recurrence was defined as repeat surgery for a tumor recurrence in the same location, SRS started >6 months after primary surgery or conventional RT started >6 months after primary surgery. Retreatment-free survival (RFS) was defined as time from primary surgery to any such retreatments of a recurrent tumor. Our follow-up data are 100% with respect to treatment for recurrent tumor given within our health region (South-Eastern Norway), and for treatment performed outside our health region if referred from a cancer center in our health region.

Data
Data was obtained from medical records including clinic records of pre- and postoperative visits, operative notes, discharge summaries, pathology reports, and radiological data. The
following variables were registered: gender, age, presenting symptoms (seizures, headache, neurological deficits), preoperative Karnofsky score, tumor location, Simpson resection grade, WHO histopathological grade, re-operation for tumor recurrence, conventional RT (as part of primary treatment or for tumor recurrence), SRS (as part of primary treatment or for tumor recurrence). Vital status (dead or alive) and time of death was obtained from the Norwegian Population Register January 27th, 2011. Surgical mortality was defined as death of any cause within 30 days of surgery.

The histopathological criteria for meningioma grading have changed over the last 20 years. From 1990 to 2001, the tumors were classified as benign, atypical or anaplastic. The present WHO-grading system for meningioma was implemented in 2001, which divide the tumors into grade I, II and III. For this study, we reclassified the tumors operated before 2001 to the WHO classification; benign = WHO grade I, atypical = WHO grade II and anaplastic = WHO grade III.

Statistics
Univariate statistics were calculated without assuming a gaussian distribution using Wilcoxon test when the variable was continous. With categorical variables univariate statistics were calculated using Pearsons chi-squared test. In ordinal variables the proportional odds likelihood test was used.

Survival curves were generated using the Kaplan Meier estimator. The logrank test was used to compare different survival curves. Survival curves for the general population was created using life tables from Statistics Norway matched on age, cohort and sex.

The Simpson scale was investigated for simplification first non-parametrically by utilizing a recursive partioning analysis (RPA) and subsequently parametrically utilizing multiple cox-model comparisons. The RPA searches all possible splits between the variable values seeking to maximise an information measure difference between the two nodes yielding a tree. To overcome the problems of overfitting and selection bias in the traditional recursive partioning models, we used statistical stopping criteria for growing the tree based on permutation tests. In our analysis, alpha for stopping the growth of the tree was set at 0.05 and log-rank scores were used for the right censored data.
The parametric analysis was done estimating the cox proportional hazard model incorporating all five levels of the Simpson scale (full model). Subsequently, we dichotomized the Simpson grade in different categories and performed cox regression on these models. Finally, we created a model comparing grade 1, grade 2 and grade 3-5. The Akaike information criterion (AIC) is presented as a measure of model fit and represents the trade-off between accuracy and model complexity. As a discrimination measure, we present the concordance index. This gives a measure of whether a high predicted probability of recurrence is actually corresponding with high recurrence and vice versa. A concordance of 0.5 is non-informative. These models were then compared to the full model using ANOVA techniques since they can be seen as nested within the full model. R 2.13.0 was used for all statistics. A p-value less than 0.05 was considered significant.

**Ethics**

The hospitals’ Data Protection Officials approved the study.
Results

Patient characteristics

This series includes 391 consecutive patients undergoing craniotomy for a convexity meningioma. Patient characteristics are given in table 1. The median age at time of surgery was 60.1 years (range 19 - 92 years) and the female to male ratio was 2.1:1. The meningiomas were symptomatic in 354 patients (90.5%). Of the 37 patients with asymptomatic tumors, 22 had documented tumor growth over time before surgery. Histological examination revealed WHO grade I meningioma in 352 (90.3%), WHO grade II in 22 (5.6%) and WHO grade III in 16 (4.1%).

A primary craniotomy was performed in all patients. Six patients died within 30 days of surgery, giving a surgical mortality of 1.5%. Macroscopically complete removal with excision of the dural attachment and abnormal bone (Simpson grade 1) was achieved in 315 patients (80.8%), macroscopically complete removal with coagulation of the dural attachment (Simpson grade 2) in 46 patients (11.8%), macroscopically complete removal without excision or coagulation of the dural attachment (Simpson grade 3) in 16 patients (4.1%), partial removal leaving tumor in situ (Simpson grade 4) in 12 patients (3.1%) and biopsy only (Simpson grade 5) in 1 patient (0.3%). Four patients (1.0%) received conventional RT postoperatively as part of primary treatment (Table 1).

<table>
<thead>
<tr>
<th>N</th>
<th>Yes N = 25</th>
<th>No N = 366</th>
<th>Combined N = 391</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex : Male</td>
<td>391</td>
<td>341 (11)</td>
<td>31% (115)</td>
</tr>
<tr>
<td>Female</td>
<td>391</td>
<td>56% (14)</td>
<td>69% (251)</td>
</tr>
<tr>
<td>Age</td>
<td>391</td>
<td>50.7 61.6 66.8</td>
<td>49.9 60.0 71.8</td>
</tr>
<tr>
<td>Karnofsky</td>
<td>391</td>
<td>70 80 90</td>
<td>80 80 90</td>
</tr>
<tr>
<td>Raised ICP : Yes</td>
<td>391</td>
<td>16% (4)</td>
<td>28% (104)</td>
</tr>
<tr>
<td>No</td>
<td>391</td>
<td>84% (21)</td>
<td>72% (262)</td>
</tr>
<tr>
<td>Neurological deficit : Yes</td>
<td>391</td>
<td>56% (14)</td>
<td>49% (180)</td>
</tr>
<tr>
<td>No</td>
<td>391</td>
<td>44% (11)</td>
<td>51% (186)</td>
</tr>
<tr>
<td>Seizure : Yes</td>
<td>391</td>
<td>32% (8)</td>
<td>43% (158)</td>
</tr>
<tr>
<td>No</td>
<td>391</td>
<td>68% (17)</td>
<td>57% (208)</td>
</tr>
<tr>
<td>Simpson grade : 1</td>
<td>390</td>
<td>46% (10)</td>
<td>84% (305)</td>
</tr>
<tr>
<td>2</td>
<td>28% (7)</td>
<td>11% (39)</td>
<td>12% (46)</td>
</tr>
<tr>
<td>3</td>
<td>8% (2)</td>
<td>4% (14)</td>
<td>4% (16)</td>
</tr>
<tr>
<td>4</td>
<td>24% (6)</td>
<td>2% (6)</td>
<td>3% (12)</td>
</tr>
<tr>
<td>5</td>
<td>0% (0)</td>
<td>0% (1)</td>
<td>0% (1)</td>
</tr>
<tr>
<td>Histology : WHO I</td>
<td>390</td>
<td>60% (15)</td>
<td>92% (337)</td>
</tr>
<tr>
<td>WHO II (atypical)</td>
<td>8% (2)</td>
<td>5% (20)</td>
<td>6% (22)</td>
</tr>
<tr>
<td>WHO III (anaplastic)</td>
<td>32% (8)</td>
<td>2% (8)</td>
<td>4% (16)</td>
</tr>
</tbody>
</table>

Tests used:
1 Pearson test; 2 Wilcoxon test; 3 Proportional odds likelihood ratio test

Table 1: Patient characteristics and risk factors for recurrence.
Overall survival

Overall survival stratified by WHO grade is presented in figure 1. Overall 1-, 5- and 10-year survival rates in our series were 96%, 89% and 78%, respectively. In univariate and multivariate analysis, age, gender, WHO-grade and Simpson grade were significantly associated with OS (Table 2). Simpson resection grade 4/5, WHO grade III (anaplastic) tumors, advanced age and male gender were associated with less favorable OS. Overall survival was also compared to sex-, age, and birth-cohort matched controls (Fig. 1).

![Overall survival](image)

**Figure 1**: Overall survival of convexity meningiomas compared to age-, sex- and birth-cohort matched general population.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Hazard ratio</th>
<th>Multivariate Hazard ratio</th>
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</thead>
<tbody>
<tr>
<td>Simpson</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2+3</td>
<td>1.437 (0.455,2.414)</td>
<td>1.479 (0.468,2.523)</td>
</tr>
<tr>
<td>4+5</td>
<td>3.110** (1.308,7.255)</td>
<td>2.47** (1.053,5.795)</td>
</tr>
<tr>
<td>Age</td>
<td>1.051*** (1.008,1.129)</td>
<td>1.105*** (1.098,1.138)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.00   (0.493,0.526)</td>
<td>0.53** (0.338,0.83)</td>
</tr>
<tr>
<td>Female</td>
<td>1.00   (0.493,0.526)</td>
<td>0.53** (0.338,0.83)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO I</td>
<td>1.377 (0.597,3.179)</td>
<td>1.149 (0.489,2.701)</td>
</tr>
<tr>
<td>WHO II (atypic)</td>
<td>1.377 (0.597,3.179)</td>
<td>1.149 (0.489,2.701)</td>
</tr>
<tr>
<td>WHO III (anaplastic)</td>
<td>3.42** (1.755,6.695)</td>
<td>2.52** (1.285,4.985)</td>
</tr>
</tbody>
</table>

*** P<0.001
** P<0.01
* P<0.05

**Table 2**: Univariate and multivariate regression analyses of factors associated with overall survival.
Retreatment-free survival

Follow-up data were collected for 100% of the patients and the median follow-up time was 7.1 years (mean 8.0 and range 0.0 – 20.9 years). The total observation time for this cohort was 3147 patient years. During this observation period, 25 patients (6.4%) were treated for recurrence with either surgical resection, SRS or conventional RT and the median time to treatment of a recurrence was 3.8 years (range 0.5-9.0 years). The overall RFS after 1-, 5- and 10-years, irrespective of WHO grade, were 99%, 94% and 90%, respectively. Overall RFS stratified by WHO grade is presented in figure 2.

Figure 2: Retreatment-free survival of convexity meningiomas.

In univariate and multivariate analysis, Simpson resection grade and WHO grade were significantly associated with need for retreatment (Table 3). Overall recurrence rates were 3.2% for Simpson resection grade 1, 15.2% for grade 2, 12.5% for grade 3, 50.0% for grade 4, and 0.0% for grade 5. Odds ratio for recurrence after Simpson resection grade 2/3 and 4/5 were 5.2 and 26.1 higher than after resection grade 1, respectively (Table 3).

Overall recurrence rates were 4.3% for WHO grade I meningioma, 9.1% for grade II and 50% for grade III. Odds ratio for recurrence of WHO II (atypic) and WHO III (anaplastic) tumors were 2.2 and 22.5 higher than for WHO grade I tumors, respectively (Table 3).

Table 3: Univariate and multivariate regression analyses of factors associated with retreatment-free survival.
WHO grade I convexity meningiomas

A separate univariate and multivariate analysis of the 352 patients with WHO grade I convexity meningiomas was performed (Figure 3). Simpson resection grade was significantly associated with RFS (Table 4). The 1-, 5- and 10-year RFS rates, irrespective of Simpson resection grade, were 100%, 97% and 93%, respectively. Odds ratio for recurrence after Simpson resection grade 2/3 and 4/5 were 6.4 and 15.2 times higher than after Simpson grade 1 resection, respectively (Table 4).

Figure 3: Retreatment-free survival of WHO grade I convexity meningiomas stratified for Simpson grade.

During the total observation time, overall recurrence rate for patients with Simpson grade I resection of a WHO I meningioma was 1.7% (5/287). The conditional RPA analysis generated two terminal nodes; one comprising the Simpson grade I group, the other group comprising all other Simpson grades (p<0.001), i.e. the only significant difference with respect to RFS was between a Simpson grade 1 resection and a Simpson 2-5 resection. The two Kaplan-Meier curves for the terminal nodes are presented in figure 4. There was insignificant evidence for any difference in retreatment-free survival between Simpson grades 2, 3, 4 and 5. The Simpson scale was treated as an ordinal variable.
Figure 4: Results of the conditional Recursive Partioning Analysis (RPA) with the two resulting Kaplan-Meier survival plots. The only significant split with respect to recurrence-free survival is between a Simpson grade 1 resection and a Simpson 2-5 resection (p<0.001). There was insignificant evidence for any difference in retreatment-free survival between Simpson grades 2, 3, 4 and 5.
Discussion

Ever since Simpson demonstrated the association between resection grade and tumor recurrence, Simpson grade 1 resection has been the goal of meningioma surgery. Recently, Sughrue et al. challenged the relevance of Simpson’s resection grade as a prognostic factor for recurrence of WHO grade I meningiomas as the authors only found a negligible benefit of more aggressive attempts to resect the tumor with dura and underlying bone as compared to simply removing the entire tumor, or even leaving small amounts of tumor attached to critical structures. However, in their series of 373 patients, Sughrue et al. grouped together a variety of meningioma locations with quite few patients in each, except for skull base meningiomas. For instance, only 77 of their patients were convexity meningiomas, the most commonly encountered meningioma location in most surgical series. The question of whether important differences with respect to location are “washed out” by grouping them for statistical analysis can therefore be raised. As the findings by Sughrue et al. contradict the general consensus of Simpson grade 1 resection of WHO grade I meningiomas as treatment goal, we wanted to study more specifically the predictive value of Simpson resection grade with respect to overall survival and tumor recurrence in convexity meningiomas.

Overall survival

Our series of 391 convexity meningiomas patients is, to the best of our knowledge, the largest published series as the three largest previous studies are by Giombini et al. in 1984 (n = 215), Morokoff et al. in 2008 (n = 163) and Sanai et al. in 2010 (n = 141). Overall 1-, 5- and 10-year survival rates in our series were 96%, 89% and 78%, respectively. Simpson resection grade 4/5, WHO III (anaplastic) tumors, high age and male gender were all significantly associated with less favorable survival (Table 2). Morokoff et al. had in their series of convexity meningiomas a 5-year overall survival rate of 90 %, almost identical to our series. None of the other recent large convexity meningioma series have reported overall long-term survival rates.

WHO grade, Simpson resection grade and high age are all well known risk factors for survival of meningioma patients. Less known is male gender as a significant risk factor for shorter survival. This can partly be explained by the fact that men are overrepresented among patients with WHO grade II and III tumors.
In order to relate OS to that of the general population, we stratified OS by WHO grade and compared it to sex-, age, and birth-cohort matched controls (Fig. 1). The analysis demonstrates that perhaps contrary to common perception amongst neurosurgeons, even WHO grade I convexity meningiomas pose a survival hazard.

**Risk of recurrence**

During a total observation time for our cohort of 3147 patient years, 25 patients (6.4%) were treated for recurrence and the overall recurrence rate after 1-, 5- and 10-years, irrespective of WHO grade, were 1.0%, 4.6% and 6.3%, respectively. In univariate and multivariate analysis, WHO grade and Simpson grade were significantly associated with need for retreatment (Table 3), confirming previous reports by Jääskeläinen et al.\(^7\) and Morokoff et al.\(^3\)

With respect to WHO grade, we found odds ratios for recurrence of WHO II and WHO III convexity meningiomas of 2.3 and 22.5 times higher than that of WHO grade I tumors, respectively (Fig. 2, Table 3). In 1986, Jääskeläinen et al.\(^7\) published their much-cited paper on recurrence rates after meningioma surgery where they found recurrence rates after 5- and 10-years of 3% and 9%, respectively, for WHO grade I, 38% and 49%, respectively, for WHO grade II and a 5-year recurrence rate of 78% for Grade III tumors. In our convexity meningiomas, overall recurrence rates were 4.3% for WHO grade I meningioma, 9.1% for grade II and 50% for grade III. In our series, the 5- and 10-year recurrence rates were 2.3% and 4.3%, respectively, for WHO I 9.1% and 9.1%, respectively, for WHO grade II meningeomas, and a 5-year recurrence rate of 50% for Grade III tumors.

With respect to Simpson grade, the odds ratios for recurrence after Simpson grade 2/3 and 4/5 were 5.2 and 26.1 higher than after resection grade 1, respectively (Table 3). Thus, the recurrence rate after Simpson grade 1 resection was significantly lower than after Simpson resection grades 2 and 3, in stark contrast to Sughrue et al.\(^8\) We further analyzed the Simpson grading scale using a conditional RPA approach. Our results indicate that a Simpson grade I resection has a superior retreatment-free survival compared to the other Simpsons grades. Furthermore, the analysis did not reveal any significance in retreatment free survival between the other Simpson grades. This is also in accordance with general principles of tumor biology; i.e. that tumor recurrence is reduced by removing all tumor cells.
Limitations of the study
The first limitation is the retrospective analysis with its limitations of data collection inherent in such studies. Secondly, the specific causes of death amongst our patients have not been established. Lastly, the conditional RPA analysis is limited by the small number of recurrences necessitating retreatment in the different Simpson grade classes.

Strengths of the study
Firstly, this is the largest published series of convexity meningiomas. Secondly, only convexity meningiomas were included in this study, as meningiomas in locations that frequently prevent Simpson grade 1 and 2 resections, e.g. skull base meningiomas and parasagittal meningiomas involving the superior sagittal sinus, might potential confound the analysis. Thirdly, follow-up was 100%, the median follow-up time was 7.1 years (mean 8.0 and range 0.0 – 20.9 years) and the total observation time for this cohort was 3147 patient years. Lastly, OS is seen in the context of the general population, as OS was compared to sex-, age-, and birth-cohort matched controls.

Conclusions
In the largest series of convexity meningiomas published to date, two main factors for recurrence were identified, namely Simpson resection grade and WHO grade. In our series, the recurrence rate after Simpson grade 1 resection was significantly lower than after Simpson resection grad 2 and 3. Thus, we still believe that Simpson grade 1 resection should be the goal for convexity meningiomas.
References


