Clinical benefit from resection of recurrent glioblastomas: results of a multicenter study including 503 patients with recurrent glioblastomas undergoing surgical resection

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Background. While standards for the treatment of newly diagnosed glioblastomas exist, therapeutic regimens for tumor recurrence remain mostly individualized. The role of a surgical resection of recurrent glioblastomas remains largely unclear at present. This study aimed to assess the effect of repeated resection of recurrent glioblastomas on patient survival.

Methods. In a multicenter retrospective-design study, patients with primary glioblastomas undergoing repeat resections for recurrent tumors were evaluated for factors affecting survival. Age, Karnofsky performance status (KPS), extent of resection (EOR), tumor location, and complications were assessed.

Results. Five hundred and three patients (initially diagnosed between 2006 and 2010) undergoing resections for recurrent glioblastoma at 20 institutions were included in the study. The patients' median overall survival after initial diagnosis was 25.0 months and 11.9 months after first re-resection. The following parameters were found to influence survival significantly after first re-resection: preoperative and postoperative KPS, EOR of first re-resection, and chemotherapy after first re-resection. The rate of permanent new deficits after first re-resection was 8%.

Conclusion. The present study supports the view that surgical resections of recurrent glioblastomas may help to prolong patient survival at an acceptable complication rate.

Keywords: glioblastoma, overall survival, recurrent tumor, surgical resection.

While the treatment of a newly diagnosed glioblastoma is standardized for many cases and includes an ideally complete surgical resection followed by concomitant radiochemotherapy and 6 cycles of temozolomide according to the European Organisation for Research and Treatment of Cancer (EORTC) protocol, the therapeutic regimen upon tumor recurrence or progression has not been standardized thus far. Treatment for recurrent GBM usually consists of second-line chemotheraphy. More recently, repeat radiotherapy has attracted some attention. Repeat surgery is often performed; however, its efficacy is debated. Traditionally, a second surgical resection was believed to be associated with a much higher complication rate than the initial surgery.

While the benefits of a (complete) surgical resection upon initial diagnosis of glioblastoma have been demonstrated by recent publications as achieving the highest level of evidence possible under the given circumstances, studies on the resection of recurrent glioblastomas are scarce and do not allow clear conclusions. Most studies describe only relatively low numbers of patients and provide contradictory results.
with respect to the survival benefit of a surgical resection, even though the more recent literature seems to provide data in favor of prolonged patient survival after repeat surgery. Complication rates vary considerably between studies, and adjuvant treatment does not conform to modern standards (ie, no temozolomide radiochemotherapy following the initial resection).10–23 In the present study, we analyzed patient survival, complication rates, and functional outcomes following surgery for recurrent glioblastoma in a very large cohort of patients treated in the modern era.

Material and Methods

The study was approved by the local ethics committees of the participating centers.

Patient Population

Patients who had a surgical resection for recurrent glioblastoma were identified in the respective departmental databases of the participating neurosurgical institutions. Inclusion criteria were (i) de novo glioblastoma (WHO IV) upon initial tumor diagnosis, (ii) initial diagnosis between January 2006 and June 2010, (iii) surgical tumor resection following initial diagnosis, and (iv) surgical resection of a recurrent tumor or progressive tumor remnant. Patients were excluded (i) in case of (clinically diagnosed) secondary glioblastomas, (ii) if the initially diagnosed tumor was not resected (biopsy only), or (iii) if the patient received a nonsurgical treatment for first tumor recurrence. Consecutive patients fulfilling inclusion and exclusion criteria were collected.

Overall, 509 documentation sets were received and reviewed to assess whether inclusion and exclusion criteria were met and whether documentation was sufficient for database entry. Six patients had to be excluded for violation of inclusion/exclusion criteria or insufficient documentation. Finally, 503 assessable patients from 20 participating neurosurgical departments in Germany, Switzerland, and Austria were entered into the database for further analysis.

Study Parameters

Relevant clinical data were collected by the participating centers through a retrospective chart review and telephone interviews at the discretion of the center, or taken from departmental databases. For each patient, the following parameters were recorded: sex, date of first (second, third, etc.) surgery, age at the respective surgeries, and extent of resection. The extent of the surgical resection (EOR) was categorized as (i) complete, (ii) resection above 90% but incomplete, (iii) resection between 50% and 90%, and (iv) resection of <50%. EOR was assessed at the respective centers, which all used postoperative imaging during the period of patient inclusion as a routine procedure. However, robust data regarding the proportion of patients undergoing early postoperative MRI scanning could not be made available. The clinical status of the patient prior to and after each surgery was assessed using the Karnofsky performance score (KPS). We documented all nonsurgical therapies (ie, radiotherapy and chemotherapy) and recorded all surgical and perioperative complications including transient and permanent new postoperative neurological deficits.

Data Handling and Statistical Analysis

Paper-based documentation from participating centers was collected, and patients fulfilling the inclusion criteria were entered into a Microsoft Access database. Statistical analyses were performed using R 2.15.1 software (The R Foundation for Statistical Computing). Categorical variables are presented as frequencies and percentages, and continuous variables as medians and ranges. For survival (OAS) assessment, the time period from initial surgery or first surgery of recurrent tumor is given as OAS after initial resection or OAS after first re-resection. Patients not known to have died were censored for survival at the last date of alive contact. We used the Kaplan-Meier method to estimate overall survival and log-rank tests for comparisons of subgroups. Median survival with 95% confidence intervals was reported for the whole study population and relevant subgroups. Hazard ratios and 95% confidence intervals for mortality were estimated with the use of Cox proportional-hazards regression models. In addition, we performed a regression tree analysis, using the package party in R, to find simple rules for discriminating patients with different survival probabilities. All statistical tests were 2-sided with a significance level of 0.05.

Results

Primary Treatment/Initial Surgery

Of 503 patients, 313 were male (62.2%) and 190 female. Median age at initial surgery was 57 years (range: 13–83y). Median Karnofsky performance score (KPS) was 90 (range: 20–100) prior to initial surgery and again 90 (range: 40–100) after the first resective surgery. Initial tumor resection was complete in 238 (53%) of 447 patients for whom information on the extent of resection was available. More than 90% but not 100% of tumor volume, <90% and more than 50%, and <50% were resected in 170 of 447 (38.0%), 38 of 447 (8.5%), and 1 of 447 patients, respectively. Intraoperative and perioperative neurological complications occurred in 26 of 503 patients (5.2%). New neurological deficits were recorded for 53 (10.5%) patients for whom information on the extent of resection was available. More than 90% but not 100% of tumor volume, <90% and more than 50%, and <50% were resected in 170 of 447 (38.0%), 38 of 447 (8.5%), and 1 of 447 patients, respectively. Intraoperative and perioperative neurological complications occurred in 26 of 503 patients (5.2%). New neurological deficits were recorded for 53 (10.6%) of 497 patients for whom information was available underwent radiation and chemotherapy according to the EORTC protocol. Twenty-six (5.2%) patients had radiotherapy alone, and 10 (2.0%) patients had no adjuvant therapy after initial tumor resection.

Surgery for First Recurrence/Progression: Further Treatment

Median time to resection of recurrent tumor was 9.1 months (95% CI: 8.3–9.8). Median KPS prior to first re-resection was 90 (range: 10–100) and again 90 (range: 10–100) after surgery. Tumor re-resection was complete in 237 (54.5%) of 435 patients for whom information on extent of resection...
was available. More than 90% but not 100% of tumor volume, <90% and more than 50%, and <50% were resected in 133 of 435 (30.6%), 62 of 435 (14.3%), and 3 of 435 (0.7%) patients, respectively. Intraoperative and perioperative nonneurological complications occurred in 37 (7.4%) of 503 patients. New neurological deficits were recorded for 75 (16.8%) of 447 patients, which were transient in 41 (9.2%) patients and permanent in the remaining 34 (7.6%) patients. Thirty of 458 patients (6.6%) experienced new deficits of a severity leading to reduction of the KPS of ≥20 (Table 2).

After first re-resection, 124 (25.5%) of 487 patients for whom information on adjuvant therapy was available had no further therapy, 15 (3.1%) patients underwent radiotherapy alone, 278 (57.1%) patients chemotherapy alone, and 70 (14.4%) patients radiotherapy and chemotherapy (Table 2). Chemotherapeutic treatments after resection of recurrent tumors included different protocols of temozolomide (n = 221), other alkylating agents such as ACNU, BCNU, or CCNU (n = 89), bevacizumab (n = 24), and other experimental therapies (n = 14).

In addition to their initial surgery and resection for recurrent tumor, 82, 11, and 2 patients underwent a third, fourth, and fifth resection for recurrent/progressive tumor. Median duration between second and third resections for 81 patients with a third resection was 7.0 months (range: 1.2–34.3 mo). Median duration between third and fourth resections for 11 patients with a fourth resection was 5.5 months (range: 2.0–18.0 mo).

### Overall Survival and Survival After First Re-resection

Median overall survival of the patients in the present study was 25.0 months (95% CI: 22.5–27.4 mo) after initial surgery for a glioblastoma and 11.9 months (95% CI: 10.8–12.8 mo) after a first resection of a recurrent/progressive tumor (Table 3). After re-resection for a second recurrence/progression, median survival after re-resection and median overall survival after initial surgery was 10.0 months (95% CI: 6.4–12.5 mo) and 29.3 months (95% CI: 24.9–40.6 mo); after a third re-resection 9.0 months (95% CI: 4.0–not available [NA]) and 34.3 months (95% CI: 34.3–NA), and after a fourth re-resection 3.5 months (95% CI: 2.0–NA) and 26.4 months (95% CI: 24.7–NA) (Table 3).

Age at initial surgery and at first re-resection significantly affected survival after initial surgery as well as after first re-resection. While patient performance status (KPS) at the time point of initial resection neither influenced survival significantly after initial resection nor survival after first re-resection, KPS prior to and after first re-resection had a significant influence on survival after first re-resection (Table 4).

The extent of resection at initial surgery did not influence patient survival or time to re-resection in the present cohort; however, a complete resection of the first recurrence/progression

### Table 1. Initial treatment

<table>
<thead>
<tr>
<th>Initial surgery</th>
<th>Age at IS (y)</th>
<th>57 (13–83)</th>
<th>90 (20–100)</th>
<th>90 (40–100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS preop IS</td>
<td></td>
<td>90 (20–100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KPS postop IS</td>
<td></td>
<td>90 (40–100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New deficits IS</td>
<td>n = 54</td>
<td>12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient new deficits IS</td>
<td>n = 30</td>
<td>6.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent new deficits IS</td>
<td>n = 23</td>
<td>5.1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Extent of resection**

| Complete resection | n = 238 | 53.2% |
| ≥90%, <100% resection | n = 170 | 38.0% |
| ≥50%, <90% resection | n = 38 | 8.5% |
| <50% resection | n = 1 | 0.2% |

**Adjuvant therapy**

| RTx only after IS | n = 13 | 2.5% |
| CTx only after IS | n = 13 | 2.5% |
| RTx and CTx after IS | n = 461 | 93% |
| No adjuvant therapy after IS | n = 10 | 2% |

**Duration IS to 1RR (mo)**

| 9.1 (8.3–9.8) |

**Abbreviations:** RTx, radiation therapy; CTx, chemotherapy. KPS, Karnofsky performance status.

### Table 2. First re-resection

<table>
<thead>
<tr>
<th>First re-resection</th>
<th>Age at 1RR (y)</th>
<th>58 (15–84)</th>
<th>90 (10–100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS preop 1RR</td>
<td></td>
<td>90 (10–100)</td>
<td></td>
</tr>
<tr>
<td>KPS postop 1RR</td>
<td></td>
<td>90 (10–100)</td>
<td></td>
</tr>
<tr>
<td>New deficits 1RR</td>
<td>n = 75</td>
<td>16.8%</td>
<td></td>
</tr>
<tr>
<td>Transient new deficits 1RR</td>
<td>n = 41</td>
<td>9.2%</td>
<td></td>
</tr>
<tr>
<td>Permanent new deficits 1RR</td>
<td>n = 34</td>
<td>7.6%</td>
<td></td>
</tr>
</tbody>
</table>

**Extent of resection 1RR**

| Complete resection | n = 237 | 54.5% |
| ≥90%, <100% resection | n = 133 | 30.6% |
| ≥50%, <90% resection | n = 62 | 14.3% |
| <50% resection | n = 3 | 0.7% |

**Adjuvant therapy**

| RTx only after 1RR | n = 15 | 3.1% |
| CTx only after 1RR | n = 278 | 57.1% |
| RTx and CTx after 1RR | n = 70 | 14.4% |
| No adjuvant therapy after 1RR | n = 124 | 25.5% |

**Abbreviations:** 1RR, first re-resection; RTx, radiation therapy; CTx, chemotherapy; KPS, Karnofsky performance status.

### Table 3. Median survival after initial resection and re-resections

<table>
<thead>
<tr>
<th>All patients</th>
<th>Median Survival after IS (95% CI)</th>
<th>25.0 (22.5–27.4)</th>
<th>11.9 (10.8–12.8) after 1RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 503)</td>
<td></td>
<td>19.7 (17.9–23.7)</td>
<td>9.0 (7.1–10.9) after 2RR</td>
</tr>
<tr>
<td>1RR only</td>
<td></td>
<td>22.7 (21.2–26.2)</td>
<td>10.3 (9.0–11.6) after 1RR</td>
</tr>
<tr>
<td>(n = 421)</td>
<td></td>
<td>20.7 (19.2–22.3)</td>
<td>8.0 (6.8–9.8) after 2RR</td>
</tr>
<tr>
<td>2RR (n = 71)</td>
<td></td>
<td>29.3 (24.9–40.6)</td>
<td>10.0 (6.4–12.5) after 2RR</td>
</tr>
<tr>
<td>3RR (n = 9)</td>
<td></td>
<td>34.3 (34.3-n.a.)</td>
<td>9.0 (4.0-n.a.) after 3RR</td>
</tr>
<tr>
<td>4RR (n = 2)</td>
<td></td>
<td>26.4 (24.7-n.a.)</td>
<td>3.5 (2.0-n.a.) after 4RR</td>
</tr>
</tbody>
</table>

**Median survival in months.**

Abbreviations: 1RR, first re-resection; 2RR, second re-resection; 3RR, third re-resection; 4RR, fourth re-resection; CI, confidence intervals; IS, initial surgery.
prolonged survival significantly after first re-resection (Table 4). Four groups were generated when grouping patients according to completeness of resection after initial resection and first re-resection: (i) initially incomplete – re-resection incomplete (ic-ic), (ii) initially incomplete – re-resection complete (ic-c), (iii) initially complete – re-resection incomplete (c-ic), and (iv) initially complete and re-resection complete (c-c). Respective survival times after first re-resection were 10.2 (8.4–13.5) for ic-ic, 12.2 (11.7–25.5) for ic-c, 9.2 (5.3–11.9) for c-ic, and 13.6 (12.0–15.8) for c-c (Fig. 1D, Table 5). These data underline the impact of the EOR at first re-resection. They suggest that a complete resection at first recurrence can largely compensate for an incomplete tumor removal at the initial surgery.

Chemotherapy after first re-resection significantly influenced survival after first re-resection (Fig. 2, Table 4). Tumor location—whether left or right, frontal, parietal, temporal, or occipital—did not significantly influence patient survival. Time from initial surgery to repeat surgery did significantly influence overall survival after initial surgery; however, it did not influence survival after first re-resection.

**Classification and Regression Tree**

A multivariate classification and regression tree algorithm was used to identify factors influencing survival after first re-resection. The parameters “duration between initial surgery and first re-resection,” “age at first re-resection,” “preoperative KPS at first re-resection,” “extent of resection at first re-resection,” and “radiation therapy” or “chemotherapy” following first re-resection were analyzed. A conservative model, which corrected for multiple testing, on the first level split the patients according to postoperative chemotherapy. Patients without chemotherapy after first re-resection had a median survival after first re-resection of 8.9 months (95% CI: 6.7–10.8 mo) (Fig. 3). The group with adjuvant chemotherapy after first re-resection was split on a second level according to the EOR (complete vs incomplete resection). Median survival after complete first re-resection and chemotherapy was 14.2 months (95% CI: 12.7–17.7 mo), and median survival after incomplete first re-resection and chemotherapy was 11.0 months (95% CI: 9.2–13.0 mo) (Fig. 3).

When using an explorative approach without correction for multiple testing, chemotherapy again split on the highest level while a complete resection split both subgroups on the next level. Furthermore, the age and preoperative KPS at first re-resection and duration between initial resection and first re-resection also split groups on further levels (Fig. 3).

**Discussion**

The present study assessed 503 patients undergoing 1–4 re-resections for recurrent glioblastomas. Median overall survival of the assessed patient cohort was 25.0 months after initial surgical treatment and 11.9 months after first re-resection. The extent of resection at first re-resection significantly influenced survival. These data suggest an important influence of aggressive surgical treatment for recurrent glioblastomas on patient survival at an increased, but acceptable, complication rate in comparison with the initial surgery. The present study is the largest study evaluating the effect of repeat surgery in the temozolomide era (ie, in a patient cohort treated predominantly [92.8%] according to the EORTC temozolomide radiochemotherapy protocol following diagnosis and initial resection).

Prognosis of patients with glioblastoma is still poor, and median survival within studies is around 14 months, while population-based data show survival times of 4.8–9.7 months only. However, many efforts have been undertaken in recent years to improve treatment of glioblastomas, and presently the treatment is largely standardized following the initial diagnosis. The initial step is, if possible, a maximal surgical resection of the tumor, followed by concomitant radiochemotherapy with temozolomide and subsequently 6 cycles of temozolomide chemotherapy. Despite this standardized initial therapy, all tumors still recur.

Further therapy is no longer standardized upon tumor progression or recurrence. While a vast number of trials evaluating second-line chemotherapies have been published, the role of repeat surgical resection remains unclear. Repeat surgery was believed to be associated with a higher incidence of new neurological deficits, and the oncological benefit of a second resection remained obscure. However, most available studies are of retrospective design and assess only relatively small cohorts of patients. When comparing repeat surgery with nonsurgical therapy from retrospective and prospective data, studies so far have failed to reveal a benefit from repeat resection. Recently, a scale was suggested to select patients with recurrent/progressive glioblastomas for repeat resection. This study showed relative benefits for patients with a KPS >80 who underwent resection of recurrent tumors <50 cm³ of size in noneloquent areas in comparison with patients not fulfilling these criteria. In a retrospective assessment of patients treated between 1997 and 2007, Chaichana et al identified 224 patients who underwent 1, 2, 3, or 4 repeat resections of glioblastomas. Using multivariate analysis and a case control evaluation to correct for selection bias, a survival benefit resulting from repeat resections was shown. Median survival after complete first re-resection and chemotherapy was 14.2 months (95% CI: 12.7–17.7 mo), and median survival after incomplete first re-resection and chemotherapy was 11.0 months (95% CI: 9.2–13.0 mo) (Fig. 3).

**Table 4.** Factors analyzed for prognostic significance for survival after first re-resection

<table>
<thead>
<tr>
<th>Factor</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial surgery</td>
<td></td>
</tr>
<tr>
<td>Age at IS</td>
<td>.009</td>
</tr>
<tr>
<td>KPS preop IS</td>
<td>.801</td>
</tr>
<tr>
<td>KPS postop IS</td>
<td>.296</td>
</tr>
<tr>
<td>Extent of resection</td>
<td>.945</td>
</tr>
<tr>
<td>Duration IS to 1RR</td>
<td>.821</td>
</tr>
<tr>
<td>First re-resection</td>
<td></td>
</tr>
<tr>
<td>Age at 1RR</td>
<td>.017</td>
</tr>
<tr>
<td>KPS preop 1RR</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>KPS postop 1RR</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Tumor location</td>
<td>.075</td>
</tr>
<tr>
<td>Extent of resection</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: 1RR, first re-resection; IS, initial surgery; KPS, Karnofsky performance status.
survival for 1, 2, 3, or 4 resections was 6.8, 15.5, 22.4, and 26.6 months, respectively. Another retrospective series of 107 patients treated between 2005 and 2009 revealed the extent of resection at recurrence as a predictor of overall survival. Tumor volume might be a predictor of chemotherapy outcome in recurrent glioblastoma (ie, cytoreductive surgery could act as a powerful chemotherapy adjunct). The results of the present study support the view that resective surgery for recurrent glioblastoma prolongs patient survival. Median overall survival after re-resection in this series was 11.9 months, which compares surprisingly favorably with major trials on second-line chemotherapy, in which median overall survival was between 4.5 and 10.8 months. Patient survival was superior to the outcome of the best recursive partitioning analysis class patients in comparison with patients enrolled in phase 1 and 2 chemotherapy trials for recurrent glioblastomas (ie, age <50 y, KPS 90–100, median overall survival 10.4 months). Similar to the much smaller study by Bloch et al. the extent of resection at first re-resection correlated with patient survival in our series. Also, as in the study by Chaichana et al. patients with additional re-resections had the relatively best survival.

The data presented here might be representative for a fairly large proportion of patients with recurrent glioblastoma, even though selection of patients for repeat resections was at the
discretion of the respective centers, and not all patients undergoing surgery in the study period might have been reported. The median time to secondary surgery of 9.1 months in this series closely resembles the typical time course for glioblastoma recurrence.\textsuperscript{1,32} Therefore, the inclusion of a relevant number of biologically favorable tumors or even WHO grade 3 tumors in this series is very unlikely. Regrettably, data on MGMT promotor methylation status could not be made available. Patient age and KPS prior to resection of the recurrent/progressive tumor were comparable to nonsurgical studies.\textsuperscript{1,32}

Regarding prognostic factors, as expected age and KPS influenced survival after re-resection. Surprisingly, the duration between initial surgery and re-resection did not influence survival after re-resection. However, this might be due to a selection bias since patients with early progression/recurrence were probably not chosen for a re-resection by the contributing centers. Median time to re-resection for first recurrence was 9.1 months in this study, and we included only 96 patients with first re-resection for a recurrence after <5 months. Although previous studies could prove the importance of a complete tumor resection at initial surgery, the present study failed to show such an influence. This may be explained by the large number of complete resections at initial surgery and small variance of the extent of resection data. The extent of re-resection significantly influenced survival after re-resection, thus underlining the relevance of cytoreduction but also of a complete surgical resection of recurrent tumors. The strongest factor for survival after a repeat resection was the option of further adjuvant therapy (primarily chemotherapy) (ie, a re-resection should be part of a multidisciplinary treatment plan).

The oncological benefits of a re-resection need to be balanced against the complication rates of repeat surgery. A recent publication on surgical outcomes in recurrent glioma reported overall complication rates of 12.8%, 27.0%, 22.0%, and 22.2% and neurological complication rates of 4.8%, 12.1%, 8.2%, and 11.1% after first, second, third or fourth and more surgeries, respectively.\textsuperscript{15} The complication rates of the present series increased slightly from initial surgery to first re-resection with 5% versus 7% nonneurological complications and 7% versus 9% and 5% versus 8% transient and permanent neurological deficits, respectively. The figures for

\begin{table}[h]
\centering
\caption{Survival after first re-resection according to extent of resection at initial surgery and first re-resection} \label{tab:surgery}
\begin{tabular}{|c|c|c|c|}
\hline
Extent of Resection IS and & Number of & Median Survival after 1RR & \\
1RR & Patients & (95\% CI) & \\
\hline
Incomplete-incomplete & 115 & 10.2 (8.4–13.5) & \\
Incomplete-complete & 80 & 12.2 (11.7–25.5) & \\
Complete-incomplete & 78 & 9.2 (5.3–11.9) & \\
Complete-complete & 144 & 13.6 (12.0–15.8) & \\
\hline
\end{tabular}
\end{table}

Abbreviations: 1RR, first re-resection; CI, confidence interval; IS, initial surgery.

Fig. 2. Kaplan Meier survival analysis after first re-resection depending on adjuvant therapy after first re-resection.

Fig. 3. Conservative (left) and explorative (right) classification and regression tree model of factors influencing survival after first re-resection. Median overall survivals are given in the respective Kaplan Maier plots.
repeat surgeries are well within the range reported for initial tumor resections. We would like to conclude that repeat surgery certainly does carry higher complication rates than primary operations. However, this increase is fairly small and clearly acceptable, at least in the patient population that we studied.

Certainly, the design of the study is inherent to several limitations that include the retrospective character without predefined criteria regarding the indication for repeated surgical resection. Since a central imaging review is missing, standardized information on tumor size, location, and extent of resection are not available. This could hamper the results if only small-sized recurrent tumors would have been included. Furthermore, a centralized pathological review is not available; however, the clinical course of the study population resembles the typical time course of glioblastoma patients, thereby ruling out the inclusion of a larger number of biologically less aggressive tumors.

**Conclusion**

Our data suggest that aggressive surgical resection of recurrent/progressive glioblastomas, followed by adjuvant therapy, could contribute to increased overall survival. Survival in the present series compared favorably with the figures reported in most chemotherapy trials for recurrent glioblastomas. A beneficial influence of repeat surgery on survival is also suggested by the correlation between the extent of resection and survival. The associated complication rate is acceptable. We will readily acknowledge the limitations of this analysis as outlined above. Nevertheless, we feel that repeat resection of a recurrent/progressive glioblastoma should be considered whenever safely possible. The surgery should aim at a maximum safe resection and should be followed by adjuvant chemotherapy.

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None declared.

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