Microsurgical resection remains a critical therapeutic modality for all gliomas (2, 10, 18, 55). However, there remains no general consensus in the literature regarding the role of extent of resection (EOR) in improving patient outcome (9, 12, 28, 33, 36, 40). With the exception of World Health Organization (WHO) Grade I tumors, gliomas are difficult to cure with surgery alone, and the majority of patients will experience some form of tumor recurrence. Patients with glioblastomas have median survival rates of 12.2 to 18.2 months (11), whereas those with anaplastic astrocytomas can expect to survive 41 months on average (19). Low-grade gliomas carry a better prognosis, although the vast majority of patients eventually die of their disease; 5-year survival percentages range from 42 to 92% in the literature (24, 25, 27, 31, 38, 41, 42, 56).

For all gliomas, the identification of universally applicable prognostic factors and treatment options remains a great challenge. Among the many tumor- and treatment-related parameters, only patient age and tumor histology have been identified as reliable predictors of patient prognosis, although functional status can also be statistically significant. Although the importance of glioma resection in obtaining tissue diagnosis and alleviating symptoms is clear, a lack of Class I evidence prevents similar certainty in assessing the influence of extent of resection.

In fact, despite significant advances in brain tumor imaging and intraoperative technology during the past 15 years, the effect of glioma resection in extending tumor-free progression and patient survival remains unknown.

Although low- and high-grade gliomas are distinct in their biology, clinical behavior, and outcome, understanding the efficacy of surgery remains equally important for each. With this in mind, we have examined every major clinical publication since 1990 that reports on the role of EOR in glioma outcome. Our objective is not only to synthesize a comprehensive assessment of expected EOR in the modern neurosurgical era, but also to critically examine the quality of evidence in the literature for both low- and high-grade gliomas and to identify the magnitude of improvement in patient survival, if any, that can be achieved with the degree of extent of resection.

**CLINICAL MATERIALS AND METHODS**

A literature search of the PubMed database from January 1990 to December 2007 was conducted using the following key words: “high-grade glioma,” “low-grade glioma,” “astrocytoma,” “anaplastic astrocytoma,” “oligodendroglia,” “oligastrocytoma,” "extent of resection, High-grade glioma, Low-grade glioma, Tumor volume"
and "glioblastoma." Series including adult patients with hemispheric gliomas were identified. Reports written in languages other than English and studies in which researchers focused mainly on nonhemispheric gliomas were excluded, as were pediatric series and studies without formal statistical analysis. Before analyzing the studies in detail, we conducted additional screening. Because children with hemispheric gliomas can have a distinct clinical course from that of adults, we excluded series that had both adult and pediatric patients if the adult patients had not been analyzed separately. Similarly, studies including pilocytic and gemistocytic astrocytomas in which data regarding patients with these tumor histologies could not be separated from other low-grade gliomas were also eliminated. Series with small numbers of patients (<75), incomplete methodological data (e.g., specification of how EOR was assessed), or EOR recorded only as a volume of residual tumor (48) were also excluded from analysis, as were studies that only compared resection with biopsy (53). Based on these criteria, we found 28 studies examining EOR for high-grade gliomas and 10 studies examining EOR for low-grade gliomas (Table 1). Since 1990, there have been no Class I studies of glioma EOR that met the criteria mentioned.

For the remaining studies, we considered the statistical issues that affected interpretation of data. This assessment included the identification of potential methodological flaws and information omitted from the study. The methodological parameters we evaluated included choice of statistical tests and adjustment for confounding variables. The specific information we searched for consisted of discussion of how the multivariate analysis, if any, was conducted. Of particular interest was whether a stepwise forward or backward method was used and which variables were considered for inclusion. Because none of these studies were randomized trials, we looked for an indication of how many patients were in each of the subsets because this affects the statistical power required to detect any differences. We also sought information on the extent to which possible predictors were confounded. As an extreme example, it would be possible that all patients in whom a subtotal resection was achieved also underwent radiation therapy, and that none of those in whom a total resection was achieved underwent radiation therapy. Clearly, this would have an impact on the interpretation of the data, although it could be difficult to discern from a review of the paper.

Pre- and postoperative tumor volumes, from which the EOR is calculated, have been considered as possible prognostic factors. Therefore, we identified references, including those with end points other than overall survival, to find studies that included evaluations of the effects of preoperative and residual tumor volumes on outcome. For low-grade gliomas, calculations of tumor volume and, when possible, EOR were based on T2-weighted magnetic resonance imaging (MRI) scans. In all cases, high-grade gliomas were defined by the enhancing region on T1-weighted MRI scans. The time to tumor progression was defined by the radiographic progression of these MRI features. Studies using volumetric analysis were evaluated separately, because this method affects the statistical power required to detect any differences. We also sought information on the extent to which possible predictors were confounded. As an extreme example, it would be possible that all patients in whom a subtotal resection was achieved also underwent radiation therapy, and that none of those in whom a total resection was achieved underwent radiation therapy. Clearly, this would have an impact on the interpretation of the data, although it could be difficult to discern from a review of the paper.

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RESULTS

Nonvolumetric and Volumetric Low-grade Glioma Extent of Resection Studies

Ten studies (5, 16, 25, 27, 31, 38, 41, 46, 51, 56) since 1990 meet the previously mentioned criteria and have applied statistical

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Statistics favor more extensive resections</td>
<td>Vecht et al., 1990 (52)</td>
<td>Barker et al., 1996 (1)</td>
<td>Nakamura et al., 2000 (27)</td>
</tr>
<tr>
<td></td>
<td>Shibamoto et al., 1990 (44)</td>
<td>Leighton et al., 1997 (25)</td>
<td>Lacroix et al., 2001 (22) (volumetric)</td>
</tr>
<tr>
<td></td>
<td>Curran et al., 1992 (6)</td>
<td>van Veelen et al., 1998 (51) (volumetric)</td>
<td>Buckner et al., 2001 (4)</td>
</tr>
<tr>
<td></td>
<td>Simpson et al., 1993 (45)</td>
<td>Keles et al., 1999 (18) (volumetric)</td>
<td>Shaw et al., 2002 (41)</td>
</tr>
<tr>
<td></td>
<td>Dinapoli et al., 1993 (7)</td>
<td></td>
<td>Lamborn et al., 2004 (23)</td>
</tr>
<tr>
<td></td>
<td>Philippon et al., 1993 (31)</td>
<td></td>
<td>Brown et al., 2005 (3)</td>
</tr>
<tr>
<td></td>
<td>Rajan et al., 1994 (38)</td>
<td></td>
<td>Ushio et al., 2005 (50)</td>
</tr>
<tr>
<td></td>
<td>Jeremic et al., 1994 (15)</td>
<td></td>
<td>Stark et al., 2005 (47)</td>
</tr>
<tr>
<td></td>
<td>Nitta and Sato, 1995 (29)</td>
<td></td>
<td>Yeh et al., 2005 (56)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Claus et al., 2005 (5) (volumetric)</td>
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<td></td>
<td></td>
<td></td>
<td>Nomiya et al., 2007 (30)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Smith et al., 2008 (46) (volumetric)</td>
</tr>
<tr>
<td>Statistics do not favor any resection group</td>
<td>Sandberg-Wollheim et al., 1991 (39)</td>
<td>Kowalczuck et al., 1997 (21)</td>
<td>Levin et al., 2002 (26)</td>
</tr>
<tr>
<td></td>
<td>Phillips et al., 1991 (32)</td>
<td></td>
<td>Puduvalli et al., 2003 (37)</td>
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<tr>
<td></td>
<td>Höllerhage et al., 1991 (13)</td>
<td></td>
<td>Tortosa et al., 2003 (49)</td>
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<tr>
<td></td>
<td>Prados et al., 1992 (35)</td>
<td></td>
<td>Johannesen et al., 2003 (16)</td>
</tr>
<tr>
<td></td>
<td>Duncan et al., 1992 (8)</td>
<td></td>
<td>Pope et al., 2005 (34) (volumetric)</td>
</tr>
<tr>
<td></td>
<td>Huber et al., 1993 (14)</td>
<td></td>
<td>Keles et al., 2006 (19) (volumetric)</td>
</tr>
</tbody>
</table>

*All studies reviewed used statistical analysis to examine the efficacy of extent of resection (EOR) in improving survival and delaying tumor progression.*
analysis to examine the role of EOR in improving survival and delaying tumor progression among patients with low-grade gliomas. In none of these studies were patients randomized with respect to the extent of surgery, and in only three studies did they include a volumetric analysis of EOR (5, 46, 51). Of the nonvolumetric studies, six demonstrated evidence supporting EOR as a statistically significant predictor of either 5-year survival or 5-year progression-free survival (Table 2). These studies were published from 1993 to 2007 and most commonly applied a combination of multivariate and univariate analyses to determine statistical significance. In most instances, EOR was defined on the basis of gross total versus subtotal resection. Interestingly, only one nonvolumetric study did not support EOR as a predictor of patient outcome (Table 3). However, this report did not evaluate progression-free survival; instead, it focused solely on 5-year survival. Of the three volumetric low-grade glioma studies reviewed, all demonstrated statistical significance based on 5-year survival (Table 4). For their statistical analyses, two of these volumetric studies divided the EOR percentages into two categories, although the cutoff threshold was different in each publication (75 and 100%, respectively).

**Nonvolumetric and Volumetric High-grade Glioma Extent of Resection Studies**

Twenty-eight studies (1, 3, 4, 6–8, 13–15, 18, 19, 21–23, 26, 29, 30, 32, 34, 35, 37, 39, 44, 45, 47, 49, 50, 52) since 1990 have applied statistical analysis to examine the efficacy of EOR in improving survival and delaying tumor progression among patients with high-grade gliomas. Four of these studies included volumetric analysis of EOR (18, 19, 22, 34) (Table 5). Of the nonvolumetric studies, 14 demonstrated evidence supporting EOR as a statistically significant predictor of either time to tumor progression

### TABLE 2. Positive nonvolumetric low-grade glioma studies

<table>
<thead>
<tr>
<th>Series (ref. no.)</th>
<th>No. of patients</th>
<th>Extent of resection (no. of patients)</th>
<th>5-year progression-free survival</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>GTR (45)</td>
<td>STR (95)</td>
<td>Biopsy (39)</td>
</tr>
<tr>
<td>Philippon et al., 1993 (31)</td>
<td>179</td>
<td>GTR (11)</td>
<td>STR (30)</td>
<td>PR (22)</td>
</tr>
<tr>
<td>Rajan et al., 1994 (38)</td>
<td>82</td>
<td>GTR (85)</td>
<td>STR (23)</td>
<td>NA</td>
</tr>
<tr>
<td>Leighton et al., 1997 (25)</td>
<td>167</td>
<td>Radical (43)</td>
<td>Non-radical (45)</td>
<td>NA</td>
</tr>
<tr>
<td>Nakamura et al., 2000 (27)</td>
<td>88</td>
<td>GTR (29)</td>
<td>STR (71)</td>
<td>Biopsy (103)</td>
</tr>
<tr>
<td>Shaw et al., 2002 (41)</td>
<td>203</td>
<td>GTR (13)</td>
<td>STR (71)</td>
<td>Biopsy (9)</td>
</tr>
<tr>
<td>Yeh et al., 2005 (56)</td>
<td>93</td>
<td>GTR (13)</td>
<td>STR (71)</td>
<td>Biopsy (9)</td>
</tr>
</tbody>
</table>

*GTR, gross total resection; STR, subtotal resection; PR, partial resection; NA, not applicable; NS, not significant. Statistical analysis leading to a nonsignificant trend is indicated as NS. The absence of statistical analysis is indicated as NA.*
or overall survival (Table 6). Although some of these reports showed EOR to affect both tumor progression and overall survival significantly, every study showed a survival benefit through either univariate or multivariate analysis. Ten studies, however, demonstrated no significant benefit based on EOR (Table 7). Notably, the distribution of adjuvant chemotherapy and radiation treatment was comparable among all high-grade glioma EOR studies (Fig. 2). Echoing the nonvolumetric study results, half of all high-grade volumetric studies showed a significant survival advantage with greater extent of resection. Although the high-grade studies reviewed were all modern series conducted by neurosurgeons with access to comparable operative technologies, it remains difficult to define the many inherent disparities among the cases described that may have biased the reported findings. One factor that may distinguish various high-grade glioma studies from one another is the distribution of WHO Grade III and IV histologies among the study patients. After quantifying this parameter in each publication, it remains difficult to draw any firm conclusions based on the data provided. Another dimension of EOR analysis that can greatly affect the reported findings is the method with which the EOR is calculated. Although volumetric MRI analysis is now the accepted standard, many centers still rely on the surgeon’s report or two-dimensional analysis based on postoperative MRI scans. When we examined the distribution of EOR methodologies and compared them with the findings for both low-grade and high-grade gliomas, there did not appear to be any identifiable trend because there was a relatively even distribution of techniques for each study category (Fig. 3).

**Quantification of Improvement in Patient Outcome**

For both low- and high-grade gliomas, we sought to define the mean survival time associated with subtotal versus gross total resection. Although the level of evidence available for each tumor category does not permit a statistical meta-analysis, this measurement provides an overall estimation of the additional survival time these studies suggest may be gained through a greater extent of resection. Not surprisingly, the effect of a greater EOR was more pronounced in the low-grade glioma studies, in which the mean survival changed from 61.1 to 90.5 months (Fig. 4). Among the high-grade gliomas, the improvement was more modest, with an increase from 64.9 to

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**Table 3. Negative nonvolumetric low-grade glioma studies**

<table>
<thead>
<tr>
<th>Series (ref. no.)</th>
<th>No. of patients</th>
<th>Extent of resection (no. of patients)</th>
<th>5-year progression-free survival, %</th>
<th>5-year survival, %</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Univariate P value</td>
<td>Multivariate P value</td>
</tr>
<tr>
<td>Johannesen et al., 2003 (16)</td>
<td>993</td>
<td>GTR (173) STR (689) Biopsy (131)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Table 4. Volumetric low-grade glioma studies**

<table>
<thead>
<tr>
<th>Series (ref. no.)</th>
<th>No. of patients</th>
<th>Extent of resection (no. of patients)</th>
<th>5-year progression-free survival, %</th>
<th>5-year survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Univariate P value</td>
<td>Multivariate P value</td>
</tr>
<tr>
<td>van Veelen et al., 1998 (51)</td>
<td>90</td>
<td>&gt;75 (13) &lt;75 (59)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Claus et al., 2005 (5)</td>
<td>156</td>
<td>100 (56) &lt;100 (100)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Smith et al., 2008 (46)</td>
<td>216</td>
<td>0–40 (21) 41–69 (39) 70–89 (55) 90–99 (26) 100 (75)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

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*GTR, gross total resection; STR, subtotal resection; NA, not applicable; NS, not significant. Statistical analysis leading to a nonsignificant trend is indicated as NS. The absence of statistical analysis is indicated as NA.
75.2 months in WHO Grade III gliomas and from 11.3 to 14.2 months (Fig. 5) in WHO Grade IV tumors.

Detailed Analysis of Low-grade Glioma Studies

Tumor and Treatment Characteristics

Low-grade astrocytomas constituted the vast majority of tumor types in the 10 reports (5, 16, 25, 27, 31, 38, 41, 46, 51, 56) that met our study criteria. However, only three of the studies did not include tumors with an oligodendrocytic component (27, 31, 38). In the seven remaining series, oligodendrogliomas and oligoastrocytomas composed 20% (51), 25% (16), 51% (56), 57% (46), 63% (25), 68% (41), and 78% (5) of the study populations. The histological grading system used for tissue diagnosis was not specified in the series of Rajan et al. (38). In the study conducted by Leighton et al. (25), the Kernohan, modified Ringertz, and WHO classification schemes were used. All other studies used the standard WHO classification system. In general, histopathological reviews of the tumors were not mentioned, and it was consequently unclear which histological criteria were used for inclusion. One study (31), however, cited its own histological criteria, which included hypercellularity and pleomorphism and excluded vascular endothelial proliferation. Interestingly, none of these studies evaluated EOR and its potential effect on the timing of malignant transformation. Overall, however, it remains important to recognize the considerable biological variability that exists within the low-grade glioma category and its potential implications for patient outcome (17, 54).

All studies included a subset of patients treated with both surgical resection and radiation therapy. The proportion of patients with combined therapy varied greatly, however, and comprised 18% (5), 32% (46), 34% (51), 45% (16), 48% (25), 65% (31, 56), 75% (27), and 100% (38, 41) of all patients in each study. In select studies, chemotherapy was also included in the treatment regimen (5, 16, 27, 46). As expected, the timing and specific regimen of radiation and chemotherapy varied greatly among selected studies.

Critique of Statistical Methods

All 10 low-grade glioma studies used a Cox proportional hazards model for statistical analysis and adjusted for possible covariates by using multivariate analyses. The variables of primary interest included patient age, Karnofsky performance status, histological tumor characteristics, and the use of radiation therapy. Every study in our review adjusted for the first three of these variables. Four studies adjusted for radiation therapy at the time of initial surgery (16, 27, 31, 56). In two studies (38, 41), all patients in the series received radiation therapy as part of their treatment regimen, and therefore no adjustment was necessary. One study, by van Veelen et al. (51), did not evaluate radiation therapy as a prognostic factor because of considerable selection bias.

The criteria used for patient selection in each study varied greatly and, thus, limited the possibility of direct comparison of each series when evaluating the prognostic significance of extent of resection. In studies such as those conducted by Rajan et al. (38) and Shaw et al. (41), all patients received radiation therapy.
### TABLE 6. Positive nonvolumetric high-grade glioma studies

<table>
<thead>
<tr>
<th>Series (ref. no.)</th>
<th>Grade</th>
<th>No. of patients</th>
<th>Extent of resection, % (no. of patients)</th>
<th>Time to tumor progression</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean time to tumor progression, mo</td>
<td>Uni-variante P value</td>
<td>Multi-variante P value</td>
</tr>
<tr>
<td>Vecht et al., 1990 (52)</td>
<td>III, IV</td>
<td>243</td>
<td>Total (15) Large (15) Small (57) Decompression (139) Biopsy (17)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Shibamoto et al., 1990 (44)</td>
<td>IV</td>
<td>135</td>
<td>GTR+STR (50) PR+Biopsy (85)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Simpson et al., 1993 (45)</td>
<td>IV</td>
<td>645</td>
<td>Total (123) Partial (413) Biopsy (109)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Curran et al., 1992 (6)</td>
<td>III</td>
<td>103</td>
<td>GTR (14) PR (58) Biopsy (31)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Dinapoli et al., 1993 (7)</td>
<td>III, IV</td>
<td>346</td>
<td>GTR+STR (246) Biopsy (100)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Jeremic et al., 1994 (15)</td>
<td>IV</td>
<td>86</td>
<td>GTR+STR (61) Biopsy (25)</td>
<td>8.3</td>
<td>5.3</td>
</tr>
<tr>
<td>Nitta and Sato, 1995 (29)</td>
<td>III, IV</td>
<td>101</td>
<td>GTR (26) STR (36) PR (39)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Barker et al., 1996 (1)</td>
<td>IV</td>
<td>222</td>
<td>GTR (28) STR (165) Biopsy (13)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Buckner et al., 2001 (4)</td>
<td>III, IV</td>
<td>275</td>
<td>GTR (99) STR (169) Biopsy (92)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lamborn et al., 2004 (23)</td>
<td>IV</td>
<td>832</td>
<td>GTR (101) STR (469) Biopsy (86)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Brown et al., 2005 (3)</td>
<td>III, IV</td>
<td>124</td>
<td>GTR (49) STR (53) Biopsy (22)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ushio et al., 2005 (50)</td>
<td>IV</td>
<td>105</td>
<td>GTR (35) PR (57) Biopsy (13)</td>
<td>10.3</td>
<td>5.2</td>
</tr>
<tr>
<td>Stark et al., 2005 (47)</td>
<td>IV</td>
<td>267</td>
<td>GTR (167) STR (80) PR (14)</td>
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<td>NA</td>
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<tr>
<td>Nomiya et al., 2007 (30)</td>
<td>III</td>
<td>170</td>
<td>GTR+STR (76) PR+Biopsy (94)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

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*XRT, radiation therapy; Chemo, chemotherapy; GTR, gross total resection; STR, subtotal resection; PR, partial resection; NA, not applicable; NS, not significant. Statistical analysis leading to a nonsignificant trend is indicated as NS. The absence of statistical analysis is indicated as NA.*
postoperatively. In other studies, however, adjuvant radiation and chemotherapy treatment varied significantly and was not applied uniformly to the entire patient population. Although this does not invalidate the analysis of EOR as a predictor, the patient population must be considered to interpret the results.

Treatment with surgical resection at the time of diagnosis also varied from study to study. In the study by van Veelen et al. (51), nearly 20% of patients were initially assigned to a “wait-and-see” treatment category. Similarly, Rajan et al. (38) compared a group of patients in whom surgery was believed to be necessary with a group of patients with presumed low-grade gliomas in whom no surgery was performed. By contrast, eight other studies (5, 16, 25, 27, 31, 41, 46, 56) evaluated only patient populations that had undergone initial surgical resection at the time of diagnosis. Although details regarding timing of surgery were not clearly defined in the majority of studies, all required histological confirmation and, thus, would have excluded any deferred low-grade gliomas that subsequently presented at a higher grade.

The computation of patient follow-up and survival times was not specifically delineated in most studies. With one exception (38), all studies appeared to have calculated these intervals based on the time of surgery. In some patients, surgery was substantially delayed after an initial diagnosis was made based on imaging, and this must be taken into consideration in any interpretation of the data. In addition, as noted earlier, those patients followed up without biopsy who underwent their first surgery at the time of tumor progression would not be included in these studies if the tumor had progressed in grade by the time of surgery.

<table>
<thead>
<tr>
<th>Series (ref. no.)</th>
<th>Grade</th>
<th>No. of patients</th>
<th>Extent of resection, % (no. of patients)</th>
<th>Time to tumor progression</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean time to tumor progression, mo</td>
<td>Uni-variate P value</td>
</tr>
<tr>
<td>Huber et al., 1993 (14)</td>
<td>III, IV</td>
<td>163</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Höllerhage et al., 1991 (13)</td>
<td>IV</td>
<td>118</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Prados et al., 1992 (35)</td>
<td>III</td>
<td>357</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Duncan et al., 1992 (8)</td>
<td>III, IV</td>
<td>235</td>
<td>GTR (39)</td>
<td>STR (121)</td>
<td>Biopsy (75)</td>
</tr>
<tr>
<td>Sandberg-Wollheim et al., 1991 (39)</td>
<td>III, IV</td>
<td>171</td>
<td>GTR (59)</td>
<td>STR (112)</td>
<td>5.5</td>
</tr>
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<td>Phillips et al., 1991 (32)</td>
<td>IV</td>
<td>173</td>
<td>GTR (28)</td>
<td>STR (137)</td>
<td>Biopsy (8)</td>
</tr>
<tr>
<td>Kowalczyk et al., 1997 (21)</td>
<td>III, IV</td>
<td>75</td>
<td>GTR (30)</td>
<td>STR (32)</td>
<td>Biopsy (13)</td>
</tr>
<tr>
<td>Levin et al., 2002 (26)</td>
<td>III</td>
<td>92</td>
<td>GTR (20)</td>
<td>STR (45)</td>
<td>Biopsy (25)</td>
</tr>
<tr>
<td>Puduvalli et al., 2003 (37)</td>
<td>III</td>
<td>106</td>
<td>GTR (30)</td>
<td>STR (61)</td>
<td>Biopsy (14)</td>
</tr>
<tr>
<td>Tortosa et al., 2003 (49)</td>
<td>III</td>
<td>95</td>
<td>GTR (33)</td>
<td>PR (33)</td>
<td>Biopsy (29)</td>
</tr>
</tbody>
</table>

* XRT, radiation therapy; Chemo, chemotherapy; GTR, gross total resection; STR, subtotal resection; PR, partial resection; NA, not applicable; NS, not significant. Statistical analysis leading to a nonsignificant trend is indicated as NS. The absence of statistical analysis is indicated as NA.
The duration of clinical follow-up also varied significantly in these 10 studies. In two studies, Claus et al. (5) and Rajan et al. (38), a relatively short mean clinical follow-up (≤36 mo) combined with a high proportion of patients still alive at the time of review placed in doubt the precision of their reported 5- and 10-year survival estimates. A low number of patient deaths at the time of analysis also raises the question of the statistical power available for testing a multivariate hypothesis in these studies. In contrast, the remaining studies were comparably more robust and consisted of few or no patients lost to follow-up, mean clinical follow-up periods of at least 3 years, and proportionally higher mortality at the end of the study period. Based on the limited information provided, the remaining studies appear to contain sufficient information for stable 5-year survival estimates.

In all the studies, there were adequate numbers of patients in the most extensively resected group relative to the total number of patients studied. In every nonvolumetric study except two (27, 38), the EOR was classified as gross total, subtotal, or biopsy. For Rajan et al. (38), however, the categorization of the EOR may have reduced the chance of observing a survival benefit with increased resection. Specifically, the authors divided EOR into four groups, separating subtotal resection into “subtotal” and “partial.” Because of the statistical test procedure used, this separation of the subtotal resection group into two cohorts likely reduced the statistical power available to detect a survival advantage for the gross total resection group. In fact, the observed 5-year survival rates for the subtotal and partial resection groups were 52 and 50%, respectively, whereas the 5-year survival rate for the gross total resection group was 90%. Conversely, the study by Nakamura et al. (27) relies on only two categories of extent of resection: radical and nonradical. Although the distribution of patients in each category is nearly even (43 versus 45), such an approach may overestimate...
the importance of EOR because the nonradical cohort likely contains a wide spectrum of surgical results.

**Study Findings Related to Prognostic Effect of Extent of Resection**

Using univariate analysis, the prognostic effect of EOR was found to be statistically significant in seven of 10 studies. Similarly, multivariate analysis also revealed the EOR to be prognostic in seven of 10 studies. In addition to knowing whether EOR was a statistically significant prognostic factor, it is also helpful to know the estimated impact of more extensive resections. Figure 4 illustrates the mean survival in the reviewed studies based on gross total and subtotal resection. The survival difference after gross total resection was calculated to be nearly 30 months, although this figure can only be interpreted as an approximation because it is derived from the outcome of different patient cohorts from different study protocols.

**Detailed Analysis of High-grade Glioma Studies**

**Tumor and Treatment Characteristics**

Of the 28 high-grade glioma articles reviewed (1, 3, 4, 6–8, 13–15, 18, 19, 21–23, 26, 29, 30, 32, 34, 35, 37, 39, 44, 45, 47, 49, 50, 52), only seven studies consisted solely of WHO Grade III tumors (6, 19, 26, 30, 35, 37, 49), whereas 12 studies analyzed only WHO Grade IV tumors. The remaining studies included patients with both Grade III and IV gliomas. No study included anaplastic oligodendrogliomas in their inclusion criteria. The majority of high-grade glioma studies (n = 16 [57%]) specified that they used the WHO standardized histological grading system for tissue diagnosis and inclusion in the study, whereas most of the remaining studies did not identify their grading system specifically. Select studies used nonstandard classification schemes. For example, in the study conducted by Levin et al. (26), a modified Ringertz classification scheme was cited. Other grading systems included the St. Anne-Mayo (7) and Scherer (47) systems. In most cases, the histopathological criteria for diagnosis were not mentioned explicitly, and it was consequently unclear which criteria were used for inclusion.

Although heterogeneity in study designs led to variability in patient selection, the use of adjuvant treatment regimens such as radiation therapy and chemotherapy was generally consistent among the 28 high-grade glioma studies. Among the studies showing a positive correlation between EOR and patient outcome, every study used radiation therapy after surgical resection, although two studies did so in only 83% (47) and 32% (52) of their patients, respectively. Similarly, many of these positive studies also reported a high incidence of adjuvant chemotherapy use, with seven of the studies (3, 4, 6, 15, 23, 29, 50) noting that 100% of their patients receive some form of chemotherapy after resection. Among negative studies, every group reported adjuvant radiation therapy to some extent, whereas only one study (8) did not use adjuvant chemotherapy and another (34) did not specify whether patients had received chemotherapy. As with the low-grade glioma studies, the timing and specific regimen of radiation and chemotherapy varied greatly.

**Critique of Statistical Methods**

Eleven studies accrued patients from current or previously completed Phase II or III clinical trials (1, 3, 4, 6, 7, 15, 23, 26, 32, 35, 45). Although this lends credibility to their data collection by confirming standardization of many study parameters, it also introduces inherent limitations in posing a question that the study was not designed to address from the outset. Nevertheless, these 11 studies allowed for some of the largest sample sizes to be analyzed. Every other study was a retrospective, single-institution series of patients with high-grade gliomas analyzed by the neurosurgeons involved.

Of the 26 studies that defined the specific statistical tests used for data analysis, 25 used a Cox proportional hazards model for statistical analysis and adjusted for possible covariates by using multivariate analyses. Two studies (23, 34) also added a recursive partitioning analysis and one (4) added Classification and Regression Tree analysis. Three studies (18, 44, 47) did not explain their statistical methods sufficiently. As with the low-grade glioma studies, the variables of primary interest included patient age, Karnofsky performance status, histological tumor characteristics, and the use of radiation therapy.

Clinical follow-up among the high-grade glioma studies was only specified in seven of 28 studies (1, 3, 30, 35, 43, 45, 49). In these studies, however, follow-up was greater than 1 year and averaged 2 to 3 years for most patients, a sufficient quantity of time for patients with Grade IV gliomas, who typically survive 12.2 to 18.2 months (11), but possibly an insufficient interval for patients with Grade III gliomas. Nevertheless, with most studies not reporting this parameter, it is unclear whether the duration of clinical follow-up was sufficient to analyze survival. Similarly, only 10 studies (1, 3, 6, 7, 13, 19, 22, 39, 45, 49) reported the total number of deaths among their patient population.

With respect to EOR classification, significant differences existed among the 24 nonvolumetric high-grade glioma studies. Although the majority of studies (n = 17 [61%]) divided resections qualitatively into gross total, subtotal, and partial or biopsy categories, others used as few as two categories (7, 15, 30, 39, 44) or as many as five (52). These assessments were typically made based on the surgeon’s assessment or nonvolumetric postresection imaging. Nevertheless, the inclusion of more subdivisions can dilute the study’s ability to generate the statistical power necessary to uncover statistical significance, whereas overgeneralizing the results may also lead to inaccurate analysis. It is interesting to note, however, that the study with the most EOR categories (5), by Vecht et al. (52), demonstrated that a greater EOR is a significant predictor of survival among patients with Grade III and IV gliomas.

**Study Findings Related to Prognostic Effect of Extent of Resection**

Among the 16 high-grade glioma studies demonstrating a statistically significant survival benefit with greater EOR, this
prognostic factor was determined through univariate analysis in 11 studies. Additionally, multivariate analysis confirmed that EOR was a significant patient survival prognostic factor in 12 studies. Of note, three studies demonstrated conflicting statistical results between uni- and multivariate analyses of patient survival, although it was the authors’ interpretation in all three series that their findings supported EOR as a predictor of survival. Time to tumor progression was another commonly used end point in EOR studies. However, only five studies demonstrated statistical significance through either univariate or multivariate analysis. Overall, though, our analysis of these 28 high-grade glioma studies strongly suggested an implicit benefit in terms of patient survival with greater extent of resection. Accordingly, the mean survival after gross total versus subtotal resection in the high-grade glioma studies differed by nearly 3 months.

Guidelines for Glioma Extent of Resection

It is clear that a lack of Class I evidence prevents the establishment of convincing criteria guiding either low- or high-grade glioma EOR. Although our analysis reveals a growing correlation between greater EOR and patient survival, it remains each practitioner’s responsibility to determine whether the magnitude and quality of evidence is sufficient to influence their practice standards. In our practice, EOR is based on the functional nature of the tissue, not on its perceived biological aggressiveness. Although one study in this series controls for tumor location and eloquence when assessing EOR (23), this remains a confounding factor in most other reports.

Many critical questions remain unanswered in the literature. It is unclear whether the emerging correlation between aggressive glioma resection and survival holds true for both first-time and recurrent operations. The effect of EOR for different ages and histological subtypes must also be studied, although at least one study has addressed the former (20). Additionally, the question of the impact of surgical resection on patient survival must be asked in the context of current prognostic factors (e.g., 1p/19q and 06-methylguanine-deoxyribonucleic acid methyltransferase-methylation status) as well as in the context of specific adjuvant therapy regimens. Future studies linking EOR and outcome should use these markers as stratification factors in the analysis. Similarly, the efficacy of adjuvant therapies must also be studied in the context of EOR.

In the future, the universal application of volumetric analysis may lead to additional studies demonstrating clinical benefit of greater EOR. This may be particularly true for patients with low-grade gliomas because all three low-grade volumetric studies reported here did show a significant increase in 5-year survival. The same cannot be said for high-grade glioma studies, however, because only two of four volumetric analyses demonstrated a survival advantage with greater resection.

CONCLUSIONS

Our review of the available studies for both low-grade and high-grade hemispheric gliomas in adults indicates that there continue to be limitations in the quality of data examining the effect of EOR on patient survival. There is growing evidence, however, that more extensive surgical resection may be associated with more favorable life expectancy for both patients with low-grade gliomas and those with high-grade gliomas. In addition to providing longer overall survival, more aggressive resections for low-grade gliomas may also affect the risk of malignant transformation among low-grade gliomas. Because no Class I evidence exists to support a particular management paradigm, the optimal combination of surgery and various therapeutic options remains unknown. It is unlikely that a prospective, randomized study will be designed to address these issues; thus, we believe retrospective, matched studies or prospective observational trials may be a more practical solution.

REFERENCES


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COMMENTS

In this article, Sanai and Berger undertake an extensive review of the available literature published since 1990 examining the effect of extent of surgical resection on patient survival for low-grade gliomas (LGGs) and high-grade gliomas (HGGs). In total, 10 studies on LGGs and 28 studies on HGGs were reviewed. To date, no Class I evidence exists that supports better patient outcomes with more extensive resection for either LGGs or HGGs.

The conclusions the authors make are that the mounting evidence seems to be in support of improved patient survival for both LGGs and HGGs with more extensive surgical resection. As noted by the authors, this evidence more strongly supports this conclusion for LGG than HGG. The majority of studies available used nonvolumetric analyses to determine the extent of resection, with many relying on surgeon estimate, a measure known to be fraught with inaccuracy. However, three studies available for patients with LGGs that used volumetric analysis for determining the extent of resection did show a significant increase in 5-year survival. The evidence is less convincing for HGG, however, with only two of four studies using volumetric measures showing a survival advantage with greater extent of resection.

One limitation of the LGG study analysis, as noted by the authors, is the variability with which study populations included patients with tumors harboring oligodendrogial components. The percentage of patients with an oligo component to their tumors ranged from 20 to 78% in 7 of 10 of the LGG studies. Another limitation noted by the authors is the heterogeneity with which adjuvant radiation and chemotherapy were used in the treatment of patients with LGGs across the studies examined.

This critical review of the literature serves to highlight the lack of Class I evidence available regarding the question of whether aggressive resection translates into improved outcomes for patients with LGGs or HGGs. The mounting evidence may lean in favor of greater surgical resection improving outcomes for patients with LGGs but does not seem as strong for those with HGGs. Despite the fact that the studies included in this review constitute series from a “modern neurosurgical era,” advances in our understanding of the molecular biology of brain tumors continue to reshape the way in which modern neuro-oncology is practiced. The question regarding whether the extent of surgical resection affects patient survival must be asked in the context of modern molecular and cellular biology of these tumors.

The authors offer a literature review of mostly retrospective clinical reports to assess the impact of extent of resection on survival. It is not surprising that they found in favor of more aggressive surgery. Although the authors address the limitations of this type of report, readers should interpret these conclusions in the context of an evidence-based treatment plan. Most authors agree that “biological” factors (e.g., age, Karnofsky performance score, and histology) have a profound impact on survival and that these parameters are not under the control of the physician. I happen to agree with the authors’ conclusions, but optimal management of a glioma only begins with surgery. Also, improvements in adjuvant therapy and patient selection for radiation, chemotherapy, or clinical trials will have a growing impact on survival. These nonsurgical treatments are ultimately going to be the source of significantly longer survival. Regardless, many patients with large unresectable HGGs can barely get through radiation therapy without progressive symptoms, steroid toxicity, and rapid deterioration. Adjuvant therapy takes time (weeks), and without removal of the mass, current treatment cannot address this problem. Because most gliomas are not curable, we should continue to balance surgical decisions with the potential impact of morbidity on quality of life. Aggressive surgery that leads to longer survival but with major disability is a Faustian bargain.

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The authors have evaluated the literature during a 17-year period that investigates the relationship of the extent of resection of HGG and LGG with survival. They acknowledge the lack of Class 1 evidence and that their analysis depends largely on their inclusion and exclusion criteria for the articles. With this limitation, they conclude that there does seem to be a correlation between the extent of resection with patient survival in both HGGs and LGGs. However, in any nonrandomized study, it is always possible that the extent of resection is just a surrogate marker for the biological behavior of the tumor. I agree with the authors that there probably never will be a prospective randomized controlled study that will give the necessary Class I evidence. Nevertheless, it does seem reasonable to advise a resection that is as maximal as possible, provided that this does not result in neurological deficit. With the exception of some World Health Organization (WHO) Grade I gliomas, surgery does not cure either HGG or LGG, and it is unreasonable to undertake a resection that has a high risk of significant morbidity. Inevitably, the “cure” for glioma will come from the development of biological therapies based on a better understanding of the molecular and cellular biology of these tumors.

Andrew H. Kaye
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In this comprehensive review of the English language literature on gliomas, Sanai and Berger find that greater resection seems to have a survival advantage for gliomas of all grades. For WHO Grade II gliomas, major resection increased the mean survival from 61 to 90.5 months for WHO Grade II gliomas and from 11.3 to 14.2 months for WHO Grade IV gliomas. There are no other interventions that have as significant an effect on survival. Although few of the articles studied had Class 1 data, the conclusions add to the growing belief that attempted volumetric resection of gliomas is a worthwhile endeavor.

There are some potential methodological weaknesses to the article. It includes only reports in English, leaving some potential of missing contributions in other languages. It does not include articles that just compare biopsy and resection. Its decision to exclude pediatric tumors, pilocytic astrocytomas, and gemistocytic astrocytomas on the one hand, and to exclude small reports with unclear end points on the other hand

Paul Kongkham
James T. Rutka
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I happen to agree with the authors’ conclusion that there does seem to be a correlation between the extent of resection with patient survival in both HGGs and LGGs. However, in any nonrandomized study, it is always possible that the extent of resection is just a surrogate marker for the biological behavior of the tumor. I agree with the authors that there probably never will be a prospective randomized controlled study that will give the necessary Class I evidence. Nevertheless, it does seem reasonable to advise a resection that is as maximal as possible, provided that this does not result in neurological deficit. With the exception of some World Health Organization (WHO) Grade I gliomas, surgery does not cure either HGG or LGG, and it is unreasonable to undertake a resection that has a high risk of significant morbidity. Inevitably, the “cure” for glioma will come from the development of biological therapies based on a better understanding of the molecular and cellular biology of these tumors.
are not weaknesses but strengths given the need for uniform measurement characteristics and biological behavior.

Their findings are an important commentary on the status of the glioma surgical literature. Virtually no articles had a prospective or randomized design. Only a few had volumetric assessment of residual tumor. The studies varied in their use of radiation therapy for LGGs, making it an important confounding variable.

With the increasing need for evidence-based medicine, neurosurgical oncologists as a community should be thinking hard about how randomized prospective studies could be mounted to answer more definitively the question posed by this article: Does the extent of resection affect outcome in glioma management? Thus far, such studies have been thwarted by poor accrual in North America and Europe. It may be that Brazil, China, India, and other countries, with large numbers of patients, a rapidly emerging academic infrastructure, and a lack of the patient selection bias that confounds much American or European management, may be able to support such studies.

Currently, it seems that major resection is appropriate for gliomas of all grades. The National Comprehensive Cancer Network has acknowledged this in its guidelines (1), and it seems increasingly to be the approach that neurosurgeons are adopting. This approach raises the further issue of what techniques are needed to achieve such resections, for example, image-guided surgery, intraoperative imaging, brain mapping preoperatively with functional magnetic resonance imaging and diffusion tensor imaging, and surgery with intravenous anesthesia (2). Sanai et al. (3) have recently demonstrated the power of brain mapping in resecting gliomas. In the present review they have challenged us with a demonstrated need for better studies, as well as showing that present data support major resection for gliomas of all grades.

Peter M. Black
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Sanai and Berger address the central question of modern tumor neurosurgery: whether more extensive resections of low-grade and malignant gliomas are consistently beneficial to patients in a measurable way. Their systematic review aimed at a comprehensive collection of studies in English assessing progression-free survival and overall survival of patients with malignant HGGs or LGGs. Ten studies on LGGs and 28 studies on HGGs were located and analyzed; none were randomized studies on surgery. The authors concluded that there was “growing evidence” in favor of longer survival after more extensive resections, for both HGGs and LGGs.

No two groups would approach this question quite the same way. First, the question being asked needs to be a clear one. We know from daily practice that “extent of resection questions” arise in at least two different ways. There may be no issue of what techniques are needed to achieve such resections, for example, image-guided surgery, intraoperative imaging, brain mapping preoperatively with functional magnetic resonance imaging and diffusion tensor imaging, and surgery with intravenous anesthesia (2). Sanai et al. (3) have recently demonstrated the power of brain mapping in resecting gliomas. In the present review they have challenged us with a demonstrated need for better studies, as well as showing that present data support major resection for gliomas of all grades.


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No two groups would approach this question quite the same way. First, the question being asked needs to be a clear one. We know from daily practice that “extent of resection questions” arise in at least two distinct flavors: the decision to try for the most complete resection possible, once craniotomy has been elected; and the more basic decision of whether to perform a craniotomy for resection at all, rather than a needle biopsy. The authors’ exclusion of biopsy/resection studies limits the conclusions of the review to the question of pushing extent of resection to the maximum in open operations. It also means that, formally, any results within included studies that use a biopsied group as part of the calculation (e.g., a hazard ratio compared by including biopsy, subtotal, and total resection groups in the same calculation) should be omitted. Yet most analyses included here did, in fact, include biopsied patients in their calculations: 21 of 28 articles on HGGs and 6 of 10 articles on LGGs.

In 5 articles on HGGs (3, 5, 8, 17, 21) and 1 article on LGGs (16a), the reported survival comparisons are explicitly for biopsied patients compared with some or all of the resected patients. This makes it difficult to define precisely the question that this review is trying to answer.

As with almost any synthetic review, it is possible to question the details of the search strategy’s design and execution. Duplicate publication causes difficulty in synthetic reviews, and three of the authors’ 28 HGG studies contain largely overlapping patient cohorts (1, 11, 15); two of these studies were counted as favoring resection, and one study was counted as not favoring resection. There seem to have been some errors in data extraction, such as a study in which postoperative computed tomography was “not available on a routine basis” that the review classified as a “volumetric” study (22), and one study described by its authors as volumetric that the review classified as nonvolumetric (10). At least one article included pyclocytic astrocytomas (9). Some additional malignant glioma studies in the literature seem similar to others the authors included, particularly reports of randomized trials on radiation or chemotherapy that addressed extent of resection only secondarily.

Systematic reviews’ results are basically the results of the component articles reviewed, magnified and sharpened. All articles reviewed here are nonrandomized studies. Ideally, we would prefer evidence from randomized clinical trials (RCTs) in which the randomization was to different degrees of extent of resection, but this is generally held to be unethical or impractical, although one such study has been successfully completed and reported (23). Studies have shown that nonrandomized comparisons often give similar answers to RCTs on treatment questions, but only when the nonrandomized studies closely mimic the RCTs with which they are compared (2, 4). Specifically, the control group in the nonrandomized studies should be treated concurrently with the treatment group (not a problem here), and all patients in both treatment and control groups should be equally eligible for both treatments being studied. This is a major problem with the 38 studies reviewed by Sanai and Berger, only one of which actually stated that all patients enrolled had been eligible for gross total resection (13), and only two of which reported more than 49% gross total resections actually achieved (12, 19). Patients received gross total resections, less extensive resections, or biopsies largely on the basis of the resectability of their tumors, rather than by randomization. When eligibility for treatment (i.e., resectability) is a prognostic factor for outcome, this “confounding by indication” prevents a valid nonrandomized comparison between treatments.

The studies cited by Sanai and Berger differ from hypothetical RCTs testing surgery in another important respect. An RCT testing extensive resections would take careful account of patients injured by surgery. Nearly all articles reviewed here represent examples of two types of analysis: those originating in cooperative group cancer trials (12 HGGs and 1 LGG) and those representing the experience of specialist centers (17 HGGs and 9 LGGs). Nearly all prospective glioma trials enroll patients after recovery from surgery (because of the requirement for pathological diagnosis) and have explicit lower bounds on functional status at the time of enrollment, that is, postoperatively. Patients who die or are disabled after surgery will not be included in these studies as a matter of design. In other words, there is a selective loss to follow-up of the patients explicitly injured by the therapy we want to test (surgery). Further, patients entering clinical trials (at least in the United States) are a highly selected group who differ significantly from
patients who do not enter trials. Only approximately 2 to 3% of patients with malignant glioma diagnosed in the United States enter clinical trials (FG Barker, WT Curry, unpublished data). Trial patients tend to be younger, male, and better educated; to have higher socioeconomic status; and to make more aggressive treatment choices after protocol treatment is completed. As with the trial-based studies, most of the single-institution patient series included here also explicitly excluded patients who died early (presumably as a complication of surgery) and those with very low functional status. In contrast, of the four explicitly or quasi-population-based studies included by Sanai and Berger (6, 9, 12, 16), only one declared an advantage for surgery, a lower proportion than for studies originating in specialist centers or cooperative trials.

In conclusion, multiple studies based on cooperative group trials and treatment at specialist centers showed longer survival for patients with more extensive glioma resections, even after adjustment for age and functional status, but a true adjustment for resectability is almost never present in such reports (with 18 being a welcome exception). In the future, authors should consider what study designs can best add to the body of literature summarized here. Possible trial designs include true randomized trials of surgery (23), randomized trials of surgical techniques designed to improve extent of resection (20, 24), or nonrandomized trials in which resectability is an entry criterion and is adjusted for using propensity scores or multivariate analysis. As this review emphasizes, more retrospective studies that do not adjust for tumor resectability will have little to contribute to this important question.

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