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TOPIC REVIEW & CLINICAL GUIDELINES

The role of surgery in the management of patients with diffuse low grade glioma

A systematic review and evidence-based clinical practice guideline

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Abstract

Question Should patients with imaging suggestive of low grade glioma (LGG) undergo observation versus treatment involving a surgical procedure?

Target population These recommendations apply to adults with imaging suggestive of a WHO grade 2 glioma (oligodendroglioma, astrocytoma, or oligo-astrocytoma).

Recommendations Surgical resection is recommended over observation to improve overall survival for patients with diffuse low-grade glioma (Level III) although observation has no negative impact on cognitive performance and quality of life (Level II).

Question What is the impact of extent of resection on progression free survival (PFS) or overall survival (OS) in LGG patients?

Target population These recommendations apply to adults with imaging suggestive of a WHO grade 2 glioma (oligodendroglioma, astrocytoma, or oligo-astrocytoma).

Recommendations *Impact of extent of resection on PFS Level II* It is recommended that GTR or STR be accomplished instead of biopsy alone when safe and feasible so as to decrease the frequency of tumor progression recognizing that the rate of progression after GTR is fairly high.

Impact of extent of resection on OS Level III Greater extent of resection can improve OS in LGG patients.

Question What tools are available to increase extent of resection in LGG patients?

Target population These recommendations apply to adults with imaging suggestive of a WHO grade 2 glioma (oligodendroglioma, astrocytoma, or oligo-astrocytoma).

Recommendations *Intraoperative MRI during surgery Level III* The use of intraoperative MRI should be considered as a method of increasing the extent of resection of LGGs.

Question What is the impact of surgical resection on seizure control and accuracy of pathology in low grade glioma patients?

Target population These recommendations apply to adults with imaging suggestive of a WHO grade 2 glioma (oligodendroglioma, astrocytoma, or oligo-astrocytoma).

Recommendations *Surgical resection and seizure control Level III* After taking into account the patient's clinical status and tumor location, gross total resection is recommended for patients with diffuse LGG as a way to achieve more favorable seizure control.

Accuracy of diagnosis Level III Taking into account the patient's clinical status and tumor location, surgical resection should be carried out to maximize the chance of accurate diagnosis.

Question What tools can improve the safety of surgery for LGGs in eloquent locations?

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Target population These recommendations apply to adults with imaging suggestive of a WHO grade 2 glioma (oligodendroglioma, astrocytoma, or oligo-astrocytoma).

Recommendations *Preoperative imaging Level III* It is recommended that preoperative functional MRI and diffusion tensor imaging be utilized in the appropriate clinical setting to improve functional outcome after surgery for LGG.

Intraoperative Mapping of Tumors in Eloquent Areas Level III Intraoperative mapping is recommended for patients with diffuse LGGs in eloquent locations compared to patients with non-eloquently located diffuse LGGs as a way of preserving function.

Keywords Low grade glioma · Astrocytoma · Oligodendroglioma · Surgery · Observation · Systematic review · Practice guideline

Surgery rationale

The management of suspected diffuse intracranial low-grade glioma (WHO grade II astrocytoma, oligo-astrocytoma, or oligodendroglioma) includes observation through serial imaging, biopsy, or surgical resection. The role for surgical resection remains undefined. Overall survival (OS) is relatively long for this patient population, making its accurate determination difficult without a properly powered trial with significant long-term data collection [1]. This challenge is compounded by the multiple endpoints which must be assessed such as the role for surgical resection, progression free survival (PFS), seizure control in patients presenting with seizures, and functional preservation in patients with tumors in eloquent locations. This guideline systematically reviews the evidence available for surgical resection in the management of newly diagnosed low grade glioma, with an emphasis on these endpoints.

Surgery methodology

Search strategy

The following electronic databases were searched from 1990 to December 2012: PubMed, Embase®, Cochrane database of systematic reviews, and abstracts from the annual meetings of the Society for Neuro-Oncology (SNO), American Association of Neurologic Surgeons (AANS), and Congress of Neurologic Surgeons (CNS).

Eligibility criteria

In order to be included, studies needed to be:

1. Published in English.
2. Involve patients with newly diagnosed WHO grade 2 oligodendroglioma, astrocytoma, or oligo-astroctyoma or imaging suggestive of those diagnoses. In publications with mixed populations, the results of those with newly diagnosed WHO grade 2 tumor must be separable from others.
3. Fully-published peer-reviewed studies or meeting abstracts from national neurosurgical meetings (AANS or CNS) or the SNO annual meeting.
4. Number of study participants with newly diagnosed WHO grade 2 tumor, or imaging suggestive of such a lesion, being five or higher.
5. Enrolled adult patients (18 years of age and older) or provide isolated results for adult patients in a mixed cohort that can be assessed separately.

Study selection and quality assessment

Two independent reviewers evaluated citations using a priori criteria for relevance and documented decisions in standardized forms. Cases of disagreement were resolved by a third reviewer. The same methodology was used for full-text screening of potentially relevant papers. Studies which met the eligibility criteria were data extracted by one reviewer and the extracted information was then checked by a second reviewer.

Evidence classification and recommendation levels

Both the quality of the evidence and the strength of the recommendations were graded according to the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) criteria as noted in the Introduction section of these guidelines (reference to intro/methods chapter needs to be added before publication). These criteria have been reported in methodology papers from previous guideline series [2].

Conflict of interest

Low Grade Glioma Guidelines Task Force members were required to report all possible COIs prior to beginning work on the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines Committee, including potential COIs that are unrelated to the topic of the guideline. The CNS Guidelines Committee and Guideline

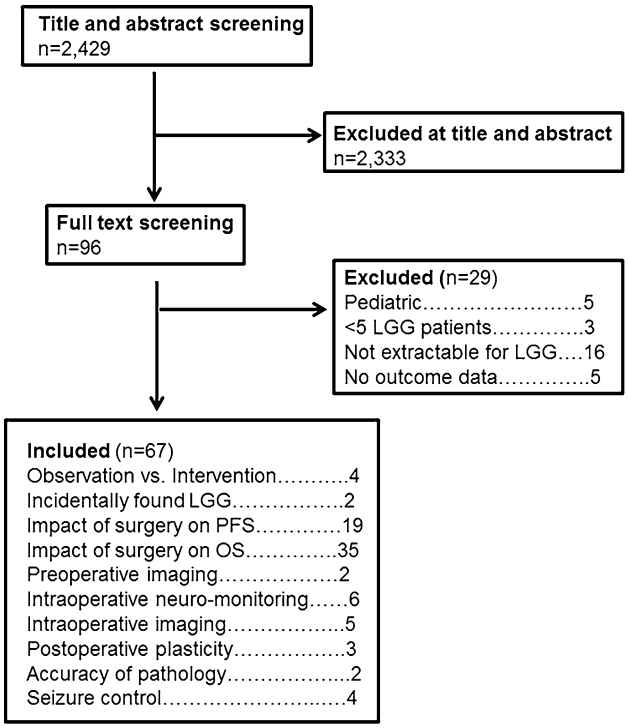

Fig. 1 Flow of studies to final number of eligible studies. Shown here is the process by which 2429 articles identified from title and abstract screening were narrowed to the 67 included articles. Note that when categorizing the number of included articles covering each aspect of surgery the total number of articles in the categories exceeds 67 because some articles produced data covering more than one aspect of surgery

Task Force Chair reviewed the disclosures and either approved or disapproved the nomination. The CNS Guidelines Committee and Guideline Task Force Chair may approve nominations of Task Force Members with possible conflicts and address this by restricting the writing and reviewing privileges of that person to topics unrelated to the possible COIs.

Surgery scientific foundation

Overall, 67 primary studies met the eligibility criteria for this systematic review, including 64 studies that produced class III data and 3 studies producing class II data related to surgery for LGGs. Figure 1 outlines the flow of studies through the review process.

Observation versus intervention

Four retrospective cohort studies [3–6] met the eligibility criteria for comparing a strategy of observation with or without preceding biopsy versus resection. One of these studies provided class II data that non-operated patients with suspected LGG scored better on quality of life tests than patients who underwent surgery for LGG, supporting a wait-and-see policy [5]. Another class III study specifically compared patients with epilepsy and LGG who underwent immediate surgery and adjuvant treatment versus those followed by serial imaging and only treated upon radiographic progression, and reported identical OS in both groups [6]. In contrast to these studies, a pair of studies provided class III data favoring up front surgery and treatment over a wait-and-see approach. The first such study showed that duration of seizure history before surgery adversely impacts OS in LGG patients, making an argument for up-front surgery in patients with seizures and imaging suggestive of LGG [3]. A second more recent study compared outcomes from two Norwegian centers, one of which practices biopsies of LGGs followed by a wait and scan approach, while the other favors early resection of LGGs [4]. The study reported improved OS from patients at the center with early surgical resection [4].

Incidentally found LGGs

While no studies have compared outcomes when observing versus resecting incidentally found LGGs, two retrospective cohort studies reviewed outcomes when operating on incidentally found LGGs and produced class III data [7, 8]. Both studies reported resection of incidentally found LGGs to be safer and associated with better OS than resection of symptomatic LGGs [7, 8].

Correlating extent of resection (EOR) with progression free survival (PFS)

Nineteen studies attempted to correlate EOR with PFS in LGGs undergoing surgery (Table 1), with two of these studies producing class II data and the other 17 studies producing class III data. A 2002 study producing class II data involved 28 patients prospectively enrolled to correlate EOR with PFS. Resection was stratified into total, subtotal (incomplete when total was the goal), partial (cytoreductive being the goal), and biopsy, and the authors found recurrences to be more common during a 9 year follow-up in patients with reduced EOR [9]. A 2008 study producing class II data prospectively evaluated outcomes of 111 patients after GTR of LGG and found a 52 % risk of tumor progression within 5 years of surgery [10].The lack of comparison to subtotally resected tumors observed during the same interval makes it difficult for a recommendation to emerge, but the higher than expected rate of progression after GTR was a cause for concern. Of the 17 studies producing class III data investigating the correlation between EOR with PFS for LGG, two studies argued a lack of relationship [11, 12], six studies argued that GTR

Table 1 Evidence table

First author (year)	Description of study	Data class	Conclusions
Shaw et al. (2008) [10]	*Study description*	II	Results
RTOG	RTOG phase II multi-center trial of observation after neurosurgeon-determined GTR of LGG in adults <40 years old		*Progression-free survival*
	Patient population		Surgeon asserted GTR for all, but really 3 groups ≤1 cm residual disease, 1–2 cm residual disease, or >2 cm residual disease. PFS at 2 and 5 years were 82 and 48 % for the whole group. Univariate and multivariate analysis revealed that recurrence rate statistically significantly lower if <1 cm residual disease versus other two groups
	111 LGG patients		*Author's conclusions*
	Treatment regimen		Surgeon asserted GTR not always confirmed on postop MRI, and less than 1 cm residual disease improves PFS
	Observation after neurosurgeon-determined GTR for a median follow-up 4.4 years		*Comments and conclusions*
			Conclusions only relevant to young adult LGG patients
Kilic et al. (2002) [9]	*Study description*	II	Results
	LGG patients were prospectively reviewed for the presence of recurrence and histopathological dedifferentiation at their fourth years after the initial treatment		*Progression-free survival*
	Patient population		In the GTR group only 1/7 patients had recurrence, while no upgrade was noted. In the STR group, 6/11 patients had recurrence, with 4/6 becoming higher grade. All of the patients in the partial resection and stereotactic biopsy groups recurred at a higher grade. EOR found to predict PFS
	28 LGG patients		*Author's conclusions*
	Treatment regimen		Results indicate that both tumor progression and histopathological dedifferentiation were less commonly seen when GTR or STR could be achieved. So, surgery, as radical as possible, should be the choice of treatment in LGG
	21 % of patients underwent biopsy and 79 % resection. Of the 22 patients undergoing resection, 7 patients had GTR, 11 had STR (residual tumor when aim was GTR), and 4 patients had a partial resection (cytoreductive surgery). All patients, except for the ones in whom GTR was achieved, received postoperative radiotherapy. There was 4 year minimum follow-up		*Comments and conclusions*
			Defining STR versus partial based on aim of surgery rather than percent resection or volume of residual tumor is subjective
Reijneveld et al. (2001) [5]	*Study description*	II	Results
	Prospective comparison of functional status, QOL, and cognitive status of patients suspected of having a LGG, in whom treatment was deferred, and patients with proven LGG who underwent early surgery		*QOL and cognitive status*
	Patient population		Cognitive status was worse in both groups than in healthy control subjects, but unoperated patients with suspected LGG scored better on most items than patients with proven LGG. Comparing quality of life and cognitive status showed no significant difference
	24 patients with suspected LGG and 24 patients with proven LGG were compared		*Author's conclusions*
	Treatment regimen		These data suggest that a wait-and-see policy in patients with suspected LGG has no negative effect on cognitive performance and QOL and that surgery does not improve "feelings of uncertainty" about the future
	Patients underwent prospective monitoring of functional status, QOL, and cognitive status. Duration of follow-up not specified		*Comments and conclusions*
			Data must be interpreted with caution as patients that can be managed without surgery are likely different than those that need it

Table 1 continued

First author (year)	Description of study	Data class	Conclusions
Jakola et al. (2012) [4]	*Study description* Two centers—one biopsies LGGs followed by a wait and scan approach, while the other favors early resection *Patient population* 66 LGG patients treated at the center following the wait and scan approach, 87 LGG patients treated at the center favoring early resection *Treatment regimen* Patients underwent biopsy followed by serial imaging at one center, or resection followed by serial imaging at another center. Median follow-up, 7.0 (biopsy and watchful wait) and 7.1 (early resection) years	III	Results *Overall survival* OS was better with early resection (P = 0.01). Median survival was 5.9 years (95 % CI 4.5–7.3) with the approach favoring biopsy only while median survival was not reached with the approach favoring early resection. Estimated 5-year survival was 60 % (95 % CI 48–72 %) and 74 % (95 % CI 64–84 %) for biopsy and watchful waiting versus early resection, respectively. In an adjusted multivariable analysis the relative hazard ratio was 1.8 (95 % CI 1.1–2.9, P = 0.03) when treated at the center favoring biopsy and watchful waiting *Author's conclusions* For patients in Norway with LGG, treatment at a center that favored early surgical resection was associated with better overall survival than treatment at a center that favored biopsy and watchful waiting. This survival benefit remained after adjusting for validated prognostic factors *Comments and conclusions* The acquisition of data from two centers following distinct practice patterns may limit applicability of these conclusions
You et al. (2012) [51]	*Study description* Retrospective review of clinical and molecular factors affecting postoperative seizure control after surgical resection of LGG *Patient population* 183 LGG patients *Treatment regimen* EOR retrospectively classified by MRI done within 72 h of surgery by an independent neuroradiologist blinded to outcome. For patients without pre- or postoperative MRI, EOR determined by surgeon's impressions. Seizure control at 12 months evaluated by Engel classification. Duration of follow-up not specified	III	Results *Correlating EOR with seizure control* Of the 183 patients, 35.5 % underwent GTR Of the 183 patients, 134 (73.2 %) patients presented with seizures. In multivariate analysis, patients achieved much better seizure control after gross-total resection (P < 0.001) than after subtotal resection (P = 0.016) *Author's conclusions* Gross total resection of the tumor, was associated with favorable seizure control after surgery for patients with LGGs *Comments and conclusions* Number of cases without MRIs not specified and relying on surgeon's impression for these cases is unreliable
Castellano et al. (2012) [53]	*Study description* Retrospective study assessing the ability of preoperative DTI tractography to predict the extent of the resection achievable in surgical removal of gliomas *Patient population* 46 LGG patients (27 HGG patients analyzed as well) *Treatment regimen* Preoperative MRIs were obtained using a 3T scanner from which DTIs were obtained. Postoperative tumor volumes were placed in 3 categories: <1 cm^3 = total resection, 1–10 cm^3 (subtotal resection), and >10 cm (partial resection). Duration of follow-up not specified	III	Results *Correlating DTI with EOR* The presence of intact fascicles in the corticospinal tract (CST) on preoperative DTI carried a higher probability of total versus subtotal or partial resection (P = 0.02–0.04). The presence of infiltrated or displaced CST or infiltrated IFO (inferior fronto-occipital fibers) was predictive of a lower probability of total resection (P = 0.01–0.04), especially for tumors with preoperative volume <100 cm^3 *Author's conclusions* DTI tractography can thus be considered to be a promising tool for estimating preoperatively the degree of radicality to be reached by surgical resection. This information will aid clinicians in identifying patients who will mostly benefit from surgery *Comments and conclusions* Correlating an imaging feature with resectability could be confounded by other variables such as aggressiveness of individual surgeons

Table 1 continued

First author (year)	Description of study	Data class	Conclusions
Ius et al. (2012) [37]	*Study description* Retrospective study of the role of EOR in OS in LGG patients *Patient population* 190 LGG patients *Treatment regimen* Patients underwent surgery with electrical corticosubcortical stimulation. Median follow-up 4.7 years	III	Results *Correlating EOR with OS* The median preoperative tumor volume was 55 cm^3, and in almost half of the patients the EOR was greater than 90 %. In this study, patients with an EOR of 90 % or greater had an estimated 5-year OS rate of 93 %, those with EOR between 70 and 89 % had a 5-year OS rate of 84 %, and those with EOR less than 70 % had a 5-year OS rate of 41 % ($P < 0.001$). Multivariate analysis showed that OS is influenced by volumetric EOR ($P = 0.001$) *Authors' conclusions* EOR strongly predicts OS in LGG patients undergoing surgery *Comments and conclusions* These patients underwent aggressive resection so the EORs were not evenly distributed despite the large number of cases
Potts et al. (2012) [8]	*Study description* Retrospective study of outcomes after surgery for incidentally found LGGs *Patient population* 35 incidentally found LGGs were compared to 197 symptomatic LGGs *Treatment regimen* All patients underwent surgical resection. Mean follow-up 5.1 years	III	Results *Progression and survival in incidental versus symptomatic LGGs* Patients with incidental lesions were more likely to undergo GTR (60 vs. 31.5 %, $P = 0.001$) and had improved overall survival on Kaplan–Meier analysis ($P = 0.039$, Mantel-Cox test). Progression and malignant progression rates did not differ between the 2 groups *Author's conclusions* In this retrospective cohort of surgically managed LGGs, incidentally discovered LGGs were associated with improved patient survival as compared with symptomatic LGGs, with acceptable surgical risks *Comments and conclusions* Suggests a potential benefit to operating before lesions become symptomatic, but is subject to the limitations of retrospective, single center analysis
Englot et al. (2012) [50]	*Study description* Meta-analysis of effects of surgery on seizures in LGG patients *Patient population* 1181 patients undergoing surgery for newly diagnosed LGG in temporal lobe and epilepsy pooled from multiple studies *Treatment regimen* Surgical resection with documentation of postoperative seizure control for unspecified duration of follow-up	III	Results *Correlating seizure control with EOR* Although only 43 % of patients were seizure-free after STR, 79 % of individuals were seizure-free after GTR (OR 5.00, 95 % CI 3.33–7.14). Furthermore, GTR plus hippocampectomy and corticectomy conferred additional benefit over GTR alone, with 87 % of patients achieving seizure freedom (OR 1.82, 95 % CI 1.23–2.70). Overall, GTR plus hippocampectomy and/or corticectomy over GTR alone significantly predicted seizure freedom (OR 1.18, 95 % CI 1.11–1.26) *Author's conclusions* Gross-total lesionectomy of low-grade temporal lobe tumors results in significantly improved seizure control over subtotal resection. Additional tailored resection including the hippocampus and/or adjacent cortex may further improve seizure control, suggesting dual pathology may sometimes allow continued seizures after lesional excision *Comments and conclusions* Like most meta-analyses, the advantages of a large sample size must be weighed against the heterogeneity of studies being pooled

Table 1 continued

First author (year)	Description of study	Data class	Conclusions
Youland et al. (2012) [14]	*Study description* Follow-up study to Schomas (2009) at same center using same definitions. Schomas studied 1960–1992, Youland 1992–2011 *Patient population* 554 LGG patients *Treatment Regimen* Patients underwent GTR/radical STR (41 %) or STR/biopsy (60 %). There was serial imaging after surgery or biopsy with median follow-up of 5.2 years	III	Results *Correlating EOR with PFS* 10-year PFS for GTR/radical STR versus STR/biopsy was 27 and 14 % ($P < 0.0001$ in both univariate and multivariate analyses) *Correlating EOR with OS* Differences in OS were 66 % for GTR/rSTR versus 48 % for STR/biopsy, a difference only significant in univariate ($P < 0.0001$) not multivariate ($P = 0.06$) analysis *Author's conclusions* This study supports the association between aggressive surgical resection and better OS and PFS *Comments and conclusions* A large number of patients and good distribution amongst the different EORs make this one of the stronger studies producing class III data. The lack of multivariate significance of the impact of EOR on OS but significant impact of EOR on PFS is a finding similar to that of Shaw 2002
Jung et al. (2011) [13]	*Study description* Retrospective analysis of the prognostic factors for progression and malignant transformation in LGGs *Patient population* 86 LGG patients *Treatment regimen* EOR classified as GTR ($n = 40$), STR ($n = 22$), or partial removal PR or biopsy ($n = 24$), with distinction between GTR and PR not specified. Mean duration of follow-up was 4.25 years	III	Results *Correlating EOR with PFS* In multivariate analysis, GTR led to higher PFS ($P = 0.043$) *Author's conclusions* In LGGs, extent of removal associated with tumor progression *Comments and conclusions* Relatively small number of cases, lack of definition of PR, and borderline statistical significance of GTR in multivariate analysis of factors impacting PFS limit impact of result
Sarubbo et al. (2011) [60]	*Study description* Analyzed the neurological and neuro-oncological outcome of patients who underwent surgery fully awake for the resection of LGG in eloquent areas *Patient population* 12 LGG patients *Treatment regimen* During surgery: sensory-motor-evoked potentials, continuous electro-corticography and bipolar/monopolar cortico-subcortical mapping during neuropsychological tests were performed. The resection rate was calculated with neuro-imaging elaboration software	III	Results *Functional outcomes after awake surgery* No permanent post-operative deficits were reported; 2 patients improved after surgery. No impairment of cognitive functions was reported. The KPS improved in 8 patients and was steady in the others. The mean resection rate was 78.3 % *Authors' conclusions* Intraoperative cortical-subcortical stimulation in awake surgery is a safe and reliable technique for direct detection of brain functional areas with no additional morbidity *Comments and conclusions* Small number of patients were studied

Table 1 continued

First author (year)	Description of study	Data class	Conclusions
Ius et al. (2011) [66]	*Study description* To study potentials and limitations of brain plasticity, review of 58 postoperative MRIs of patients operated on for LGG under direct electrical cortico-subcortical stimulation *Patient population* 58 LGG patients *Treatment regimen* Postoperative images were registered on the MNI template to construct an atlas of functional resectability for which each voxel represents the probability to observe residual nonresectable tumor, that is, non-compensable area. The resulting atlas offers a framework to identify areas with high plastic potential (i.e. with probabilities of residual tumor close to 0), with low compensatory capabilities (i.e. probabilities of residual tumor close to 1) and with intermediate level of resectability (probability around 0.5)	III	Results *Areas that could not be safely resected* Left primary motor and somatosensory cortices for upper and lower limbs; left ventral premotor cortex; left posterior superior temporal gyrus (wernike's area), left supramarginal gyrus, left angular gyrus, right primary motor and somatosensory areas for superior and inferior limbs, and right angular gyrus could not be safely resected *Areas that could be safely resected* All other areas, including left and right supplementary motor areas and primary non-dominant sensorimotor area of face and, to a lesser extent, Broca's area and insular lobes, anerior corpus callosum, both cingulate gyri, right and left uncinate fasciculus, anterior part of right and left inferior longitudinal fasciculus, corticospinal tract under primary motor area and deeply at corona radiata, thalamo-cortical tract, stratum sagittale, and anterior part of inferior fronto-occipital fasciuclus could tolerate resection *Authors' conclusions* The proposed atlas of functional resectability of LGG provides a new generic tool to study the potentials and limitations of brain plasticity and the role of interindividual variability for resection of LGGs. In addition, the atlas highlights the existence of a "minimal common brain" among patients *Comments and conclusions* General applicability is unclear
Hosoda et al. (2011) [58]	*Study description* Retrospective analysis of patients undergoing LGG resection with intraop CT (i-CT) compared to an equal number of patients undergoing surgery without i-CT to determine utility of i-CT *Patient population* 46—half undergoing surgery with i-CT and half without (non i-CT) *Treatment regimen* Postoperative CT used to determine EOR. Defined GTR as ≥90 %, STR as 50–90 %, partial resection (PR) as <50 %, and biopsy as <10 %	III	Results *i-CT and EOR* i-CT improves EOR from 13 % STR/61 % PR/26 % biopsy to 39 % GTR/35 % STR/22 % PR/4 % biopsy. 48 % of patients underwent additional resection *i-CT and OS* i-CT improved OS (87 vs. 57 % at 5 years; $P < 0.005$, univariate) *Authors' conclusions* i-CT allows more extensive resection and improves the surgical outcome in patients with LGG *Comments and conclusions* Technique has been replaced by iMRI at most centers
Chang et al. (2011) [59]	*Study description* Retrospective analysis of 281 adults who underwent resection of a supratentorial LGG at a brain tumor referral center *Patient population* 281 LGG patients *Treatment regimen* Preoperative MRIs were retrospectively evaluated blindly for involvement of eloquent brain areas, including the sensorimotor and language cortices, and specific subcortical structures. For high-risk tumors located in presumed eloquent brain areas, long-term survival estimates were evaluated for patients who underwent intraoperative functional mapping with electrocortical stimulation and for those who did not	III	Results *Correlating eloquent LGG location with PFS/OS* Confirmation of tumor overlapping functional areas during intraoperative mapping was strongly associated with shorter survival (OS, HR 9.6, 95 % CI 3.6–25.9). In contrast, when mapping revealed that tumor spared true eloquent areas, patients had significantly longer survival, nearly comparable to patients with tumors that clearly involved only noneloquent areas, as demonstrated by preoperative imaging (OS, HR 2.9, 95 % CI 1.0–8.5) *Author's conclusions* Presumed eloquent location of LGGs is an important but modifiable risk factor predicting disease progression and death. Delineation of true functional and nonfunctional areas by intraoperative mapping in high-risk patients to maximize tumor resection can dramatically improve long-term survival *Comments and conclusions* Large number of patients makes this strong class III evidence

Table 1 continued

First author (year)	Description of study	Data class	Conclusions
Scheie et al. (2011) [29]	*Study description* Analyzed the relationships among clinical variables and outcome in 95 patients (59 LGGs) with oligodendroglial components *Patient population* Of the 95 tumors, 59 were LGGs: 27 oligodendrogliomas, WHO grade II and 32 oligoastrocytomas, WHO grade II *Treatment regimen* GTR defined as >95 % resection. In overall series of 95, 42 GTR, 41 STR and 12 biopsy only. Mean follow-up after procedure was 4.17 years	III	Results *Correlating EOR of LGGs with OS* GTR versus STR/biopsy combined was not predictive of OS in univariate analysis of the LGG tumors in this series *Author's conclusions* While EOR was not the primary variable of interest The results suggest that tumor location, WHO grade, and 1p/19q status, not GTR, are important independent variables associated with survival in oligodendroglial tumors *Comments and conclusions* Study attempts to correlate GTR versus non-GTR with OS in tumors with oligo component but this type of correlation may require stratifying EOR into more categories including PFS, and a larger number of cases
Yordanova et al. (2011) [61]	*Study description* To review outcomes when patients with LGG in nonfunctional areas of left dominant hemisphere underwent electrical mapping to pursue supratotal resection *Patient population* 17 LGG patients undergoing attempted supratotal resection. This series was compared with a control group of 29 patients who had "only" complete resection *Treatment regimen* GTR of all tumors with supratotal resection of 15	III	Results *Achieving supratotal resection* Mapping allowed EOR to increase beyond GTR in all but 2 cases *Supratotal resection and anaplastic transformation* Anaplastic transformation was observed in 7 cases in the control group but not in any case in the series of patients who underwent supracomplete resection ($P = 0.037$) *Supratotal resection and adjuvant treatment* adjuvant treatment was administered in 10 patients in the control group compared with 1 patient who underwent supracomplete resection ($P = 0.043$) *Author's conclusions* These findings support the usefulness of awake surgery with intraoperative functional (language) mapping with the attempt to perform supratotal resection of LGGs involving noneloquent areas in the left hemisphere. The goal of supracomplete resection is to delay the anaplastic transformation, even if it does not yet enable a cure *Comments and conclusions* Will need validation in a larger cohort
Pallud et al. (2010) [7]	*Study description* The clinical and radiological findings, treatments, and outcomes of histologically-proven incidental LGGs were retrospectively compared to symptomatic LGGs *Patient population* 47 histologically-proven incidental LGGs and 1249 symptomatic LGGs *Treatment regimen* Median follow-up was 6.6 years for incidental LGGs, and was not stated for symptomatic LGGs	III	Results *Incidental LGGs and GTR* Compared to symptomatic LGGs, incidental LGGs have female predominance ($P = 0.05$), smaller initial tumor volumes ($P = 0.001$), lower incidence of contrast enhancement ($P = 0.009$), and are more likely to undergo GTR ($P < 0.001$) *Incidental LGGs and survival* Also, incidental LGGs were associated with significant survival benefit compared to symptomatic LGGs in univariate analysis ($P = 0.04$) *Author's conclusions* Incidental LGGs are progressive tumors leading to clinical transformation toward symptomatic LGGs. They may represent an earlier step in the natural history of a glioma than the symptomatic LGGs *Comments and conclusions* Stronger support for incidental LGG resection would be comparing resected incidental LGGs to a wait and see approach for incidental LGGs

Table 1 continued

First author (year)	Description of study	Data class	Conclusions
Sanai et al. (2010) [20]	*Study description* Retrospective review of insular LGGs undergoing resection to determine impact of EOR on PFS and OS *Patient population* 70 craniotomies were performed on patients with insular LGGs of 115 total insular glioma surgeries *Treatment regimen* Median follow-up was 4.2 years	III	Results *Correlating EOR with PFS and OS* In multivariate analysis, EOR defined volumetrically as a continuous variable led to higher PFS ($P = 0.0414$) and higher OS ($P = 0.04$) *Author's conclusions* Aggressive resection of insular gliomas of all grades can be accomplished with an acceptable morbidity profile and is predictive of improved OS and PFS. Among insular LGGs, a greater EOR is also associated with longer malignant PFS. Data in this study also suggest that insular gliomas generally follow a more indolent course than similar lesions in other brain regions *Comments and conclusions* Class III data showing a benefit of increased EOR on survival of insular glioma patients
De Benedictis et al. (2010) [62]	*Study description* To retrospectively compare EOR between traditional and awake craniotomy for LGG *Patient population* 9 LGG patients *Treatment regimen* Patients underwent surgery with awake speech mapping after initial surgery done with patient asleep	III	Results *Comparison of EOR between first asleep surgery and second awake surgery* GTR in 5 cases and STR in 4 cases, with EOR improved in all cases compared to the first surgery ($P = 0.04$) *Author's conclusions* Awake surgery with speech mapping significantly improves EOR for LGGs in functional regions *Comments and conclusions* Supports awake speech mapping for LLGs in functional regions
Chaichana et al. (2010) [19]	*Study description* To determine factors that were independently associated with recurrence and malignant degeneration in patients who underwent resection of LGG *Patient population* 191 consecutive LGG patients *Treatment regimen* Surgical resection (64 % STR, 36 % GTR), with unspecified duration of follow-up	III	Results *Correlating EOR with risk of malignant degeneration* Independent factors that reduced the risk of malignant degeneration included GTR (RR 0.526, 95 % CI 0.221–1.007, $P = 0.05$) *Author's conclusions* The identification of factors like GTR associated with recurrence and malignant progression may help guide treatment strategies aimed at delaying recurrence and preventing malignant degeneration for patients with hemispheric LGGs *Comments and conclusions* Large number of patients makes this strong class III evidence in support of GTR of LGG to reduce risk of high grade transformation
El-Hateer et al. (2009) [28]	*Study description* Retrospective review of factors predicting outcome in oligodendrogliomas *Patient population* 69 patients (all with oligodendrogliomas) *Treatment regimen* 13 % biopsy, STR 59 %, GTR 27 %. Median follow-up 6.1 years	III	Results *Correlating EOR with OS* In multivariate analysis, increasing EOR did not affect OS *Author's conclusions* This retrospective review confirms the indolent but progressively fatal nature of LGOs. Contrast enhancement was the most evident single prognostic factor. Stratifying EOR into GTR/STR/biopsy did not predict OS *Comments and conclusions* Correlation of EOR with OS might not be as strong as correlation of EOR with PFS and might require more categories of EOR and more patients to detect or might be stronger with non-oligo LGGs

Table 1 continued

First author (year)	Description of study	Data class	Conclusions
Bauman et al. (2009) [11]	*Study description* To report the long-term follow-up of a cohort of adult patients with supratentorial LGG treated at a single institution *Patient population* 145 LGG patients *Treatment regimen* EOR divided into biopsy (21 %), STR (30 %), and near-total (90 % or higher)/GTR (49 % of patients) *Median follow-up 8.75 years*	III	Results *Correlating EOR with PFS* Biopsy/STR did not affect PFS (P = 0.055 univariate) *Correlating EOR with OS* Biopsy/STR worsened OS (P = 0.026 univariate, P = 0.024 multivariate) *Author's conclusions* LGG is a chronic disease, with most patients dying of their disease. However, long-term survival with good function is possible. Survival is determined primarily by the disease factors with selection and timing of adjuvant treatments having less influence on outcome *Comments and conclusions* While this study and one other [25] found that surgery impacts OS but not PFS in large cohorts, 2 other studies [14, 16] have produced class III data showing an impact on PFS but not OS, and many studies have shown an impact on both
Ahmadi et al. (2009) [21]	*Study description* Analysis of data from 130 adult LGG patients. EOR was evaluated in correlation to OS and PFS using Cox regression multivariate analysis *Patient population* 130 LGG patients *Treatment Regimen* 70 % GTR, 30 % STR/biopsy. Median follow-up 7.8 years	III	Results *Correlating EOR with PFS* In univariate analysis, GTR versus STR/biopsy did not correlate with PFS (P = 0.472) *Correlating EOR with OS* In univariate analysis, GTR versus STR/biopsy correlated with OS (P = 0.024). In multivariate analysis, EOR > 90 % resection led to higher OS (P = 0.005) *Author's conclusions* Retrospective evaluation of LGG patients with a long follow-up period showed that extended surgery would be the most effective therapy for LGG patients *Comments and conclusions* While this study found that surgery impacts OS but not PFS in a large cohort, other studies have produced class III data showing an impact on PFS but not OS or an impact on both
Simon et al. (2009) [38]	*Study description* Retrospective summary of experience with microsurgical resection of insular tumors *Patient population* 30 LGGs (all insular) taken from a larger group of 94 patients *Treatment regimen* Three groups: >90 % resection (n = 40), 70–90 % resection (n = 45) and <70 % resection (n = 9). Median follow-up 3.1 years	III	Results *Correlation between EOR and PFS* In univariate analysis, increasing EOR led to higher PFS (P = 0.023). In multivariate analysis, EOR (>70 % vs. other) increased PFS (P = 0.006) *Correlation between EOR and OS* In univariate analysis, increasing EOR between these groups led to higher OS (P = 0.006). In multivariate analysis, EOR (>70 % vs. other) increased OS (P < 0.001) *Author's conclusions* Insular tumor surgery carries substantial complication rates. However, surprisingly similar figures have been reported in large unselected craniotomy series and also after alternative treatment regimens. In view of the oncological benefits of resective surgery, our data would therefore argue for microsurgery as the primary treatment for most patients with a presumed insular WHO Grade I–III tumor *Comments and conclusions* Class III data supporting resection of insular LGG

Table 1 continued

First author (year)	Description of study	Data class	Conclusions
Schomas et al. (2009) [22]	*Study description* To retrospectively evaluate survival and predictive factors in LGG patients *Patient population* 314 LGG patients *Treatment regimen* In addition to STR and GTR, an intermediate category called radical subtotal resection (rSTR) was defined as: (i) when the operative report described "radical subtotal resection"; (ii) when GTR was clearly the goal of the operation but minimal known tumor was left in situ; or (iii) when imaging reports indicated small, questionable amounts of residual tumor after GTR. 13 % of patients received GTR, 11 % received rSTR, 41 % received STR, and 35 % biopsy. Median follow-up 17.3 years	III	Results *Correlating EOR with PFS* Undergoing less than rSTR adversely impacted PFS on univariate ($P < 0.001$) and multivariate ($P < 0.001$) analyses. GTR versus rSTR, and STR versus biopsy did not influence PFS on univariate analysis *Correlating EOR with OS* Because GTR versus rSTR, and STR versus biopsy did not influence PFS on univariate analysis, they were not used for comparison in OS analysis. Undergoing less than radical STR adversely impacted OS in univariate ($P < 0.001$) and multivariate ($P = 0.03$) analyses *Author's conclusions* A substantial proportion of LGG patients have a good long-term prognosis after GTR and rSTR, with nearly half of patients free of recurrence 10 years after diagnosis *Comments and conclusions* Excellent long-term follow-up and multiple EOR categories make this solid class III data
McGirt et al. (2008) [23]	*Study description* Retrospective review to determine if EOR affects survival or disease progression in patients with supratentorial LGGs *Patient population* 170 LGG patients *Treatment regimen* EOR defined as GTR (complete resection of the preoperative FLAIR signal abnormality), near total resection (NTR) (<3-mm thin residual FLAIR signal abnormality around the rim of the resection cavity only), or STR (residual nodular FLAIR signal abnormality). GTR, NTR, and STR were achieved in 65 (38 %), 39 (23 %), and 66 (39 %) cases, respectively. Median follow-up 4 years	III	Results *Correlating EOR with PFS* GTR versus STR were independently associated with increased PFS (HR 0.56; 95 % CI 0.32–0.98; $P = 0.043$) in multivariate analysis *Correlating EOR with OS* GTR versus STR were independently associated with increased OS (HR 0.36; 95 % CI 0.16–0.84; $P = 0.017$) in multivariate analysis *Author's conclusions* GTR was associated with a delay in tumor progression and malignant degeneration as well as improved OS independent of age, degree of disability, or histological subtype. GTR should be safely attempted when not limited by eloquent cortex *Comments and conclusions* Solid class III data in a large cohort
Smith et al. (2008) [39]	*Study description* Retrospective study to assess the influence of EOR on long-term outcomes of LGGs *Patient population* 216 LGG patients *Treatment regimen* Extent of resection range 0–100 % (median, 88 %) assessed volumetrically and analyzed as a continuous variable as opposed to cut point cohorts. Median follow-up 4.4 years	III	Results *Correlating EOR with PFS* In multivariate analysis, PFS was predicted by volumetric EOR (HR 0.983; 95 % CI 0.972–0.995; $P = 0.005$) *Correlating EOR with OS* In multivariate analysis, OS was predicted by volumetric EOR (HR 0.972; 95 % CI 0.960–0.983; $P < 0.001$) *Author's conclusions* Improved outcome among adult patients with hemispheric LGG is predicted by greater EOR *Comments and conclusions* Measuring EOR as a continuous variable in a large number of patients produces strong class III data

Table 1 continued

First author (year)	Description of study	Data class	Conclusions
Durmaz et al. (2008) [30]	*Study description* Retrospective study of factors predicting OS in LGG patients undergoing surgical resection *Patient population* 53 LGG patients *Treatment regimen* GTR = no enhancing tumor (n = 24), STR = 50–99 % resection (n = 29). Median duration of follow-up not specified	III	Results *Correlating GTR/STR with OS* Although the difference between GTR versus STR was not statistically significant according to univariate log rank tests and univariate multiple Cox regression analyses ($P > 0.05$), GTR versus STR was a significant independent prognostic factor when the Cox Regression Backward Stepwise multivariate (Wald) method was performed ($P < 0.05$) *Author's conclusions* The correlation between EOR and OS in LGG patients argues for surgical resection of LGG patients *Comments and conclusions* Study includes a small number of patients and 2 EOR categories
Chang et al. (2008) [49]	*Study description* Retrospective cohort study to identify factors that influenced perioperative seizure characteristics and postoperative seizure control. *Patient population* 332 LGG patients *Treatment regimen* 44 % underwent GTR while 56 % underwent STR or biopsy. Follow-up years not specified	III	Results *LGGs and seizures* Most LGG patients present with seizures (81 %). 67 % were seizure free 12 months postop and 17 % had meaningful improvement. Seizure control was more likely to be achieved after GTR than after STR/biopsy alone (OR 16, 95 % CI 2.2–124, $P = 0.0064$) *Author's conclusions* The majority of patients with LGG present with seizures; in approximately half of these patients, the seizures are pharmacoresistant before surgery. Postoperatively, >90 % of these patients are seizure free or have meaningful improvement. A shorter history of seizures and gross-total resection appear to be associated with a favorable prognosis for seizure control *Comments and conclusions* Class III evidence for GTR controlling seizures in LGG patients
Benzagmout et al. (2007) [67]	*Study description* Retrospective cohort study of outcomes after awake resection of LGGs in Broca's area in patients without aphasia to assess plasticity *Patient population* 7 patients with LGGs in Broca's area (revealed by partial seizures) and no preoperative aphasia *Treatment regimen* Patients had a language fMRI scan and then underwent operation while awake using intrasurgical electrical mapping Mean follow-up of 3.4 years	III	Results In patients with no aphasia despite LGG in Broca's area, brain plasticity allows tumor removal without language impairment. *Author's conclusions* Our results indicate that, in patients with no aphasia despite LGGs within Broca's area, thanks to brain plasticity, the tumor can be removed while involving this "unresectable" structure without inducing sequelae and even improving the quality of life when intractable epilepsy is relieved on the condition that subcortical language connectivity is preserved *Comments and conclusions* The cohort in this study was small

Table 1 continued

First author (year)	Description of study	Data class	Conclusions
Carrabba et al. (2007) [63]	*Study description* Retrospective cohort study to evaluate the effect which subcortical motor mapping had on postoperative morbidity and EOR in patients with gliomas involving motor areas or pathways *Patient population* 26 with LGG patients in motor area (of 146 total tumors) *Treatment regimen* Surgical resection with intraoperative cortical and subcortical motor mapping. Follow-up years not specified	III	Results *Finding tracts while resecting LGGs* Of 26 LGGs, subcortical tracts were found in 23 (89 %), while subcortical was not found in 3 (12 %). Rate of permanent deficits not stated distinctly for the LGG subset of the patients in this series, but overall rate of permanent deficits was 6.5 % when tracts found and 3.5 % when tracts not found *GTR in LGGs undergoing subcortical motor mapping* GTR was achieved in 46.1 % of all LGG patients. GTR was achieved in 10 of the 23 (44 %) patients in whom subcortical tracts were found and in 2 of the 3 in whom subcortical tracts were not found (67 %) *Author's conclusions* Subcortical mapping is a reliable method for keeping the rate of permanent deficits low, although the rate is somewhat higher if tracts are actually identified *Comments and conclusions* Few LGG patients in the series
Duffau et al. (2006) [65]	*Study description* Retrospective cohort study with co-temporaneous cohorts *Patient population* 42 LGG patients (all insular dominant hemisphere) with no preoperative deficits *Treatment regimen* Surgery with intraoperative stimulation to determine functional role of insula in all patients. Follow-up years not specified	III	Results *Immediate outcomes after dominant insular surgery* Post-operatively, the patients experienced a transient hemiparesis in 21 cases, language disorders in 10 cases, an athymhormic syndrome in 7 cases, a Foix–Chavany–Marie syndrome in 3 cases, and micturition disturbances in one case *Outcomes 3 months after dominant insular surgery* Despite this immediate post-surgical worsening, all the patients recovered their preoperative neurological status within 3 months, except in three cases due to a deep stroke *Author's conclusions* These results show that the insula, a complex associative multimodal structure poorly studied until now, can be functionally compensated. Such a plastic potential may have important fundamental and clinical implications, in particular in oncological neurosurgery *Comments and conclusions* Class III data supporting safety of dominant insula surgery for LGG with intraoperative stumulation
Nimsky et al. (2006) [56]	*Study description* Retrospective cohort study to investigate how functional neuronavigation and intraoperative high-field MRI influence glioma resection. *Patient population* 19 LGG patients (of 137 total tumors) *Treatment regimen* All patients underwent resection using iMRI. Follow-up years not specified	III	Results *iMRI and EOR* iMRI showed GTR after first scan in 53 % of LGGs. In 26 % of LGGs, resection was extended due to iMRI, increasing GTR rate to 58 % ($P > 0.05$) *Author's conclusions* The combination of iMRI and functional navigation allows safe extended resections in glioma surgery. iMRI data can be used to localize the tumor remnants reliably and compensate for the effects of brain shift. However, despite extended resections, the increase in GTR rate after achieved by iMRI was not statistically significant *Comments and conclusions* LGG patients are a small portion of the overall cohort

Table 1 continued

First author (year)	Description of study	Data class	Conclusions
Claus et al. (2006) [48]	*Study description* Population-based estimate of long-term survival as well as patterns of care for patients with LGG examined by age at diagnosis, gender, and race from a national database *Patient population* 2009 LGG patients (from SEER national database) *Treatment regimen* 27 % biopsy, 73 % resection. Follow-up of 4–32 years	III	Results *Correlating biopsy versus resection with OS* Surgery improves OS relative to biopsy ($P < 0.05$) with the hazard ratio generated by the Cox model not specified *Author's conclusions* Data for patients diagnosed with LGGs revealed increasing survival times over the past 25 years with a subset of patients surviving for decades. Differences in survival by race, gender, histology, and first course of treatment were appreciated. These data suggested that the clinical course of LGG for some patients may be more encouraging than previously perceived and that the identification of this group of patients may allow refinement of current treatment protocols *Comments and conclusions* Advantage of large number of patients is somewhat offset by heterogeneity in data, lack of central pathologic review, and lack of central imaging review when using large nationwide databases
Hall et al. (2005) [54]	*Study description* Retrospective cohort study to determine the safety and efficacy of using functional magnetic resonance imaging (fMRI) to guide the resection of LGGs *Patient population* 14 LGG patients *Treatment regimen* Guided by fMRI, 8 GTRs and 6 STRs were performed. Median follow-up of 2.1 years	III	Results In every case, the preoperative brain activation study accurately determined the location of neurologic function. After surgery, one patient had a transient hemiparesis and another had a temporary apraxia. Eight patients had radiographically complete resections and 5 with oligodendrogliomas had incomplete resections because of the proximity of their tumors to functional areas. Only one patient with an astrocytoma in the motor strip received postoperative radiation therapy. To date, radiographic tumor progression has not been seen in any patient with either a partial or a complete resection *Author's conclusions* fMRI was accurate for identifying areas of neurologic function before surgical resection of LGG. Patients with complete radiographic resections or with incompletely resected oligodendrogliomas can be safely followed radiographically after surgery. Radiation therapy was reserved for infiltrating astrocytomas that were not completely resectable *Comments and conclusions* Small cohort of patients supporting use of fMRI to guide LGG resection
Yeh et al. (2005) [25]	*Study description* Retrospective cohort study to evaluate the treatment outcomes, prognostic factors and radiation-related late complications, as well as to assess whether or not post-operative radiotherapy has benefit on local control and overall survival in LGG *Patient population* 93 LGG patients *Treatment regimen* Two groups: 80 % resection (n = 13), 20–80 % resection and biopsy only (n = 80 combined). Median follow-up of 9.2 years	III	Results *Correlating >80 % resection with PFS* >80 % resection predictive of PFS, (5-year PFS: 84 vs. 41 %; $P = 0.0073$) in multivariate analysis *Correlating >80 % resection with OS* >80 % resection predictive of OS, (5-year OS 92 vs. 52 %; $P = 0.0349$) in multivariate analysis *Author's conclusions* EOR is associated with improved PFS and OS in LGG *Comments and conclusions* Class III data stating that over 80 % resection for LGG improves PFS and OS

Table 1 continued

First author (year)	Description of study	Data class	Conclusions
Claus et al. (2005) [15]	*Study description* Retrospective age-adjusted and histologic-adjusted assessments of the association between EOR and risk of either recurrence or death for neurosurgical patients who undergo resection of LGG using iMRI guidance. *Patient population* 156 LGG patients *Treatment regimen* Patients underwent iMRI-guided resection (64 % STR, 36 % GTR). Mean followup of 3 years	III	Results *Correlating STR versus GTR with recurrence and death* After adjustment for age, STR patients had 1.4-times the risk of recurrence (P = 0.5) and 4.9-times the risk of death (P = 0.05) as patients who underwent GTR *Comparing OS to national data bases* The 1-, 2-, and 5-year age-adjusted and histologic-adjusted death rates for patients who underwent surgical resection using intraoperative MRI guidance were 1.9 % (95 % CI 0.3–4.2 %), 3.6 % (95 % CI 0.4–6.7 %), and 17.6 % (95 % CI 5.9–29.3 %), respectively, which lower than the expected rates reported using the national SEER data base (P = 0.05) *Author's conclusions* Number of deaths after iMRI-guided resection was less than expected by SEER data base analysis *Comments and conclusions* None of the findings achieve statistical significance
Nimsky et al. (2004) [55]	*Study description* Retrospective study to investigate the contribution of high-field intraoperative magnetic resonance imaging (iMRI) for further reduction of tumor volume in glioma surgery *Patient population* 9 LGG patients (of 182 total cases) *Treatment regimen* Follow-up years not specified	III	Results *Benefit of iMRI in LGG resection* Two patients had residual on iMRI that could not be re-resected due to eloquent location. The remaining seven underwent additional resection after iMRI with one ending up with GTR. Percentage of final tumor volume was significantly reduced after iMRI in LGG (10.3 ± 11.5 % vs. 25.8 ± 16.3 %; P < 0.05) *Author's conclusions* Despite extended resections, introduction of high-field iMRI in conjunction with functional navigation did not translate into an increased risk of postoperative deficits. The use of high-field iMRI increased radicality of resection in LGG surgery without additional morbidity *Comments and conclusions* Class III evidence supporting the use of iMRI in LGG resection
Duffau et al. (2003) [64, 68]	*Study description* Retrospectively investigate the importance of mapping cortical and subcortical functional regions by using intraoperative real-time direct electrical stimulations during resection of LGGs *Patient population* 103 LGG patients *Treatment regimen* Cortical and subcortical functional regions mapped using intraoperative real-time direct electrical stimulation during resection. Follow-up years not specified	III	Results *Short- and long-term neurologic outcomes* Despite an 80 % rate of immediate postoperative neurological worsening, 94 % of patients recovered their preoperative status within 3 months—10 % even improved—and then returned to a normal socioprofessional life *Extent of resection* 80 % of resections were classified as total or subtotal based on MRI *Author's conclusions* The use of functional mapping of the white matter together with cortical mapping allowed the authors to optimize the benefit/risk ratio of surgery of low-grade glioma invading eloquent regions. Intraoperative real-time cortical and subcortical stimulations is a valuable adjunct to the other mapping methods *Comments and conclusions* Class III data supporting intraoperative cortical and subcortical mapping of functional regions during LGG resection

Table 1 continued

First author (year)	Description of study	Data class	Conclusions
Duffau et al. (2003) [64, 68]	*Study description* To describe functional recovery after surgical resection of LGG in eloquent brain areas, and discuss the mechanisms of compensation *Patient population* 77 patients starting with no neurologic deficit and LGG in eloquent area *Treatment regimen* Follow-up years not specified	III	Results *Recovery from postoperative deficits* All patients had immediate postoperative deficits with recovery occurring within 3 months in all but 4 cases (definitive morbidity 5 %) *Author's conclusions* Spatio-temporal functional re-organization is possible in peritumoral brain, and that the process is dynamic. The recruitment of compensatory areas with long term perilesional functional reshaping would explain why: before surgery, there is no clinical deficit despite the tumour growth in eloquent regions; immediately after surgery, the occurrence of a deficit, which could be due to the resection of invaded areas participating (but not essential) to the function; and why 3 months after surgery, almost complete recovery had occurred. This brain plasticity, which decreases the long term risk of surgical morbidity, may be used to extend the limits of surgery in eloquent areas *Comments and conclusions* Plasticity can be difficult to verify due to the challenge in knowing whether the function always resided in peritumoral brain and merely needed to recover from postoperative edema before resumption of function
Shaw et al. (2002) [16] RTOG	*Study description* Retrospective subset analysis of data from a prospective RCT of 2 different radiotherapy regimens *Patient population* 203 LGG patients *Treatment regimen* 51 % biopsy, 35 % STR, and 14 % GTR. Follow-up of 6.43 years for those surviving	III	Results *Correlating GTR versus STR/biopsy with PFS* GTR good for PFS in uni- (0.0138) and multivariate ($P = 0.0349$) models *Correlating GTR versus STR/biopsy with OS* GTR good for OS only in univariate ($P = 0.0116$) not multivariate ($P = 0.36$) model *Author's conclusions* While not the primary goal of this study, the retrospective subset analysis provides class III data supporting an impact of GTR on PFS but not OS In multivariate models *Comments and conclusions* Impact of GTR on PFS but not OS in multivariate models is similar to finding of Youland 2012
Gunnarsson et al. (2002) [52]	*Study description* Retrospective report of operating on LGG patients with seizures *Patient population* 5 LGG patients (all presenting with seizures and low grade astroctyomas) *Treatment regimen* Median follow-up of 12 months	III	Results No postoperative neurologic deficits and 3 of 5 patients seizure-free postoperatively, with other 2 experiencing improved seizure frequency or severity. While not quantified, all patients reported improved quality of life in all domains: physical, psychological, and work-performance *Author's conclusions* Resections of low-grade astrocytomas in patients with medically intractable seizures are safe procedures that effectively control seizures in the majority of patients, resulting in significant improvement in the patients' quality of life *Comments and conclusions* This study has a small number of patients

Table 1 continued

First author (year)	Description of study	Data class	Conclusions
Pignatti et al. (2002) [33]	*Study description*	III	Results
EORTC 22844 and 22845	Cohort study of simultaneously- and prospectively-acquired cohorts within an EORTC phase III RCT analyzed retrospectively		*Correlating 90–100 % resection with OS*
	Patient population		90–100 % excision versus other categories predicted OS in univariate analysis (P = 0.034), but results from multivariate analysis (P = 0.046) failed to meet the authors' 1 % threshold
	610 LGG patients		*Author's conclusions*
	Treatment regimen		In adult patients with LGG, older age, astrocytoma histology, presence of neurologic deficits before surgery, largest tumor diameter, and tumor crossing the midline were important prognostic factors for survival. These factors can be used to identify low-risk and high-risk patients
	EOR was divided into biopsy, less than 50 % resection, 50–89 % resection, and 90–100 % resection. Followup years not specified		*Comments and conclusions*
			While not the primary purpose of the study, Class III evidence supporting a lack of significant correlation between over 90 % resection and OS
Jackson et al. (2001) [69]	*Study description*	III	Results
	Retrospective cohort study reviewing a consecutive series of patients whose imaging studies suggested glioma and who underwent stereotactic biopsy at outside hospitals followed by craniotomy/resection at the authors' tertiary center (within 60 days). The majority of tumors were located either in eloquent brain or near-eloquent brain, and this frequently was the rationale cited for performing stereotactic biopsy		*Diagnostic discrepancy between biopsy and resection*
			Diagnoses based on biopsy or resection in the same patient differed in 40 of 82 cases (49 %). Discrepancy reduced to 30 of 80 cases (38 %) when biopsy pathology reviewed by the resecting center's pathologist. The discrepancy would have affected treatment in 27 of 82 cases (33 %) and prognosis in 40 of 82 cases (49 %). Major neurologic complications occurred in 10 (12.3 %) of 81 surgical patients and 3 (3.7 %) of 81 patients undergoing biopsy
	Patient population		*Author's conclusions*
	81 LGG patients		Stereotactic biopsy is frequently inaccurate in providing a correct diagnosis and is associated with additional risk and cost. If stereotactic biopsy is performed, expert neuropathology consultation should be sought
	Treatment regimen		*Comments and conclusions*
	All patients underwent resection 60 or fewer days after biopsy. Follow-up years not specified		Class III evidence supporting resection over biopsy for accuracy of pathologic diagnosis
Schneider et al. (2001) [57]	*Study description*	III	Results
	Retrospective cohort study with co-temporaneous cohorts to evaluate the effectiveness of intraoperative MR guidance in achieving GTR of LGGs		8 patients had residual tumor on intraoperative MR images taken when surgeon designated resignation to be complete, with 7 undergoing additional resection. Overall, 6 patients with GTR, 5 with over 90 % resection, and 1 with 85 %
	Patient population		*Author's conclusions*
	12 LGG patients		Surgical treatment of low-grade gliomas under intraoperative MR guidance provides improved resection results with maximal patient safety
	Treatment regimen		*Comments and conclusions*
	Patients underwent surgery within a vertically open 0.5-T MR system. Follow-up years not presented		Small cohort supporting use of intraoperative MR to increase GTR rate in LGGs

Table 1 continued

First author (year)	Description of study	Data class	Conclusions
Sakata et al. (2001) [40]	*Study description* Retrospective multi-institutional study of patients with supratentorial LGG treated with surgery and postoperative radiotherapy at five university hospitals *Patient population* 82 (56 astrocytoma, 13 oligodendroglioma, 13 olgioastroctyomas) LGG patients *Treatment regimen* Astrocytoma: minimal biopsy or <50 % removal (n = 30), 50–89 % bulk (n = 26) or total (≥90 %) removal (n = 40). Median followup of 4.08 years	III	Results *Correlating GTR/STR with OS* Over 50 % removal improved OS for astyrocytoma (univariate). Analysis not performed for oligodendroglioma due to too few cases with <50 % removal *Author's conclusions* Oligodendroglioma has a more protracted course of disease progression than astrocytoma. This particular feature and the sensitivity of LGGs to chemotherapy as well as their relevant prognostic factors, such as age, histopathology and amount of tumor removal, should be taken into account before any decision on treatment methods for LGGs is made *Comments and conclusions* Univariate analysis limited to astrocytoma
Lo et al. (2001) [35]	*Study description* Retrospective cohort study with co-temporaneous cohorts to evaluate the impact of EOR on survival of patients with supratentorial LGG treated with postoperative radiation therapy (PORT) *Patient population* 65 (36 astrocytomas and 29 oligodendrogliomas) LGG patients *Treatment regimen* 12 GTR, 27 minimal or subtotal resections (MR/SR), and 26 biopsies. Median followup of 5.08 years	III	Results *Correlating GTR/STR with OS* EOR predicted OS in multivariate analysis, P = 0.0008 *Author's conclusions* Our data suggest that EOS correlates with OS and DSS in patients who have PORT. GTR should be the goal if technically achievable without causing significant morbidity, and its combination with PORT is compatible with long-term survival *Comments and conclusions* Class III data correlating EOR with OS
Arienti et al. (2001) [36]	*Study description* Retrospective cohort study with co-temporaneous cohorts to identify prognostic factors of survival. Twelve elements of disease and treatment were evaluated for patients with diffuse low-grade astrocytoma treated with surgical resection and radiotherapy *Patient population* 49 (all astroctyomas) LGG patients *Treatment regimen* Follow-up years not specified	III	Results *Correlating GTR/STR/biopsy with OS* GTR (10 patients) improves OS relative to STR (34 patients) or biopsy (5 patients) in univariate analysis (P < 0.05) *Author's conclusions* The most appropriate therapy for treating low-grade astrocytomas is still an open subject. However, recent studies have shown that the prognostic value of a group of factors is useful to plan controlled studies that compare differentiated treatment protocols *Comments and Conclusions* Implications limited by small cohort and univariate analysis
Nakamura et al. (2000) [41]	*Study description* Retrospective cohort study with co-temporaneous cohorts to identify prognostic factors for low-grade astrocytomas. Consecutive adult patients with supratentorial low-grade astrocytomas were retrospectively reviewed to determine specific factors influencing outcome *Patient population* 88 (all astrocytomas) LGG patients *Treatment regimen* Surgical resection for all (43 radical resections with radical defined as >90 %, 45 nonradical resections). Minimum followup of 3.0 years	III	*Results* *Correlating radical/nonradical resection with OS* EOR divided into these 2 categories improved OS in univariate (P < 0.001) and multivariate (P < 0.001) analyses *Author's conclusions* Radical surgical removal is the most important factor in the management of low-grade astrocytomas. Radiation therapy appears to be effective in improving the prognosis regardless of the extent of surgical resection or the p53 status *Comments and conclusions* Class III data supporting radical resection of low-grade astrocytomas

Table 1 continued

First author (year)	Description of study	Data class	Conclusions
Grabenbauer et al. (2000) [12]	*Study description* Retrospective cohort study with co-temporaneous cohorts to assess treatment outcome and prognostic factors following postoperative external radiotherapy in 77 patients with LGG *Patient population* 77 (45 astrocytomas; 14 oligo; 18 mixed) LGG patients *Treatment regimen* Biopsy or partial resection (<50 %) in 25 patients, Subtotal (over 50 % but not complete) or total resection in 52 patients. Followup years not specified	III	Results *Correlation of EOR and PFS/OS* EOR stratified in these 2 categories did not predict PFS or OS in univariate analysis *Author's conclusions* A minimum total dose of 52 Gy is recommended for the postoperative radiotherapy in LGG. Tumors with CT enhancement seem to need further intensification of treatment *Comments and conclusions* EOR correlation to PFS/OS was not the primary goal of the study and was only attempted in univariate fashion
Bauman et al. (1999) [32]	*Study description* Retrospective study in which databases from 3 centers were pooled and analyzed to determine which groupings of prognostic factors best predicted OS for patients with LGGs treated with surgery and immediate or delayed radiotherapy *Patient population* 401 LGG patients *Treatment regimen* Two groups: 90 % or greater resection (n = 124) and less than 90 % resection (n = 277). Follow-up years not specified	III	Results Correlating EOR with OS These 2 categories of EOR did not predict OS in univariate analysis (P = 0.6). *Author's conclusions* Clusters of pretreatment prognostic factors described subgroups of low-grade glioma patients with divergent overall survivals. Consideration of these prognostic subgroups may be important when considering timing of interventions for these patients and in the stratification of patients for clinical trials *Comments and conclusions* EOR was just one of many variables analyzed and interactions between EOR and other variables were not addressed
Afra et al. (1999) [3]	*Study description* Retrospective cohort study with co-temporaneous cohorts to correlate preoperative history with postoperative survival in LGG patients *Patient population* 348 LGG patients *Treatment regimen* Follow-up years not specified	III	Results *Correlating GTR/STR with OS* OS for patients with a history of seizures longer than 3 years was 57.5 months, compared to 67.6 months in patients with a history of seizures shorter than 3 years (P = 0.03) *Author's conclusions* Considering the frequent malignant transformation among patients with a long history of seizures, followed by a relatively shorter survival, it may be supposed that an early radical removal in suitable cases might prevent the late dedifferentiation and recurrence *Comments and conclusions* Indirectly argues for early removal in patients with seizure
Iwabuchi et al. (1999) [34]	*Study description* Retrospective cohort study with co-temporaneous cohorts to evaluate the principal prognostic factors and effect on survival in 56 adults with supratentorial low grade astrocytomas. Fifteen factors were evaluated with uni- and multivariate analysis to investigate their importance in predicting OS *Patient population* 56 (all astrocytomas) LGG patients *Treatment regimen* Three groups: Total or subtotal (n = 15), partial (n = 8) or biopsy (n = 33). EOR defined by surgeon's impression and definition of partial resection is not specified. Follow-up years not specified	III	Results *Correlating GTR/STR with OS* EOR (3 groups) predicted OS in univariate (P < 0.01) but not multivariate analysis *Author's conclusions* The usefulness of cytoreductive surgery in the management of LGG remains unclear, but the extent of surgery is determined by the characteristics of the tumor and the potential of the patient *Comments and conclusions* Subjective definition of EOR limits impact

Table 1 continued

First author (year)	Description of study	Data class	Conclusions
van Veelen et al. (1998) [6]	*Study description* Retrospective cohort study of patients with low grade astrocytoma was carried out because the best management of such patients remains controversial. Prognostic factors were identified by multivariate analysis. Special attention was paid to the effect of extent and timing of surgery *Patient population* 90 (all astrocytomas) LGG patients *Treatment regimen* 66 % of patients underwent <75 % removal, 14 % underwent >75 % removal, and 20 % underwent biopsy. Follow-up of 4–18 years	III	Results *Correlating EOR with OS* EOR (3 categories) predicted OS in univariate (P = 0.002) and multivariate (P = 0.04) analysis. Thirty patients presented with epilepsy, with 13 operated on immediately and 17 followed up and treated after clinical and radiographic progression and OS was identical in both groups (63 %). *Author's conclusions* Due to the retrospective nature of the study only restricted conclusions can be drawn. Low grade glioma with epilepsy as the single symptom has a much better prognosis than if accompanied by other symptoms. This prognosis is not influenced by the timing of surgery. It seems, therefore, safe to defer surgery until clinical or radiological progression in LGG with epilepsy only *Comments and conclusions* Class III data correlating EOR with OS. Broader implications of deferred surgery are unclear because that analysis was applied to the small subset with epilepsy
Jeremic et al. (1998) [42]	*Study description* Retrospective subset analysis of data from a prospective Phase 2 trial investigating the feasibility, toxicity and antitumor efficacy of hyperfractionated radiation therapy in adult patients with incompletely resected supratentorial LGG *Patient population* 37 LGG patients *Treatment regimen* All patients underwent incomplete resection, defined as partial (50–90 %, n = 18) or "biopsy" (<50 %, n = 19). Median follow-up of 6.2 years	III	*Results* *Correlating EOR with OS* Partial resection improved OS relative to "biopsy" in univariate analysis (P = 0.009) (multivariate not done) *Author's conclusions* While designed to look at feasibility and toxicity of hyperfractionated radiation therapy for incompletely resected LGG, univariate analysis found that resection over 50 % improved OS relative to resection less than 50 % *Comments and conclusions* This is an unconventional use of the term biopsy. Lack of multivariate analysis and the fact that it was done as part of a study to analyze hyperfractionated radiation therapy in which EOR was not a primary variable limits impact somewhat
Peraud et al. (1998) [17]	*Study description* Retrospective cohort study with co-temporaneous cohorts to resolve divergent opinions about the prognostic value of the extent of surgery and of different histological subtypes in supratentorial astrocytomas WHO grade II *Patient population* 75 LGG patients *Treatment regimen* 4-year PFS 74 % for GTR (40 patients) versus 20 % for STR (35 patients) (P = 0.04). Followup year not specified	III	Results *Correlating GTR/STR with OS* GTR better than STR for 4 year OS (96 vs. 64 %) in univariate analysis (P = 0.01) *Author's conclusions* Gross total resection should be the leading therapeutic option for patients with astrocytomas WHO grade II *Comments and conclusions* Class III data favoring GTR over STR across mixed histologic subtypes of LGGs

Table 1 continued

First author (year)	Description of study	Data class	Conclusions
Lote et al. (1997) [47]	*Study description* Retrospective cohort study with co-temporaneous cohorts to determine survival, prognostic factors, and treatment efficacy in LGG *Patient population* 379 LGG patients *Treatment regimen* 97 patients with symptoms of mass effect (nausea/emesis or steroid dependency), 282 patients with no symptoms of mass effect. Followup years not stated	III	Results *Correlating GTR/STR with OS* Resection only improves OS relative to biopsy in patients have symptoms of mass effect ($P = 0.03$) like altered visual fields, cranial nerve palsies, paresis *Author's conclusions* Prognosis in LGG following postoperative radiotherapy seems largely determined by the inherent biology of the glioma and patient age at diagnosis *Comments and conclusions* While the notion of resection benefiting only those with mass effect is intriguing, the subjectivity in defining mass effect makes it difficult to broadly apply these findings
Leighton et al. (1997) [25]	*Study description* Retrospective cohort study with co-temporaneous cohorts to review the outcomes of patients with LGG diagnosed by modern imaging and treated at a center where postponing radiotherapy was common practice *Patient population* 167 LGG patients *Treatment regimen* All patients underwent surgical resection. Median follow-up of 4.2 years	III	Results *Correlating GTR/STR with PFS* Minimal residual tumor after surgery did not predict PFS ($P > 0.05$) in multivariate analysis *Correlating GTR/STR with OS* Minimal residual tumor after surgery (as opposed to bulk disease, neither was defined quantitatively) improved OS ($P = 0.006$) *Author's conclusions* Patients with LGG diagnosed by modern imaging can be expected to live a long time; timing of radiotherapy may be a less important determinant of survival than nontreatment variables and residual tumor bulk *Comments and conclusions* One of two studies, along with Bauman 2009 to find an impact of EOR on OS, but not PFS
Bahary et al. (1996) [43]	*Study description* Retrospective cohort study with co-temporaneous cohorts of LGG patients treated in the CT scan era *Patient population* 63 LGG patients *Treatment regimen* Three groups: biopsy ($n = 5$), partial resection ($n = 34$), and GTR ($n = 14$). Median follow-up of 4.5 years	III	Results *Correlating GTR/STR with OS* EOR improves OS ($P = 0.002$) in multivariate analysis. *Author's conclusions* Prognostic factors having independent significant impact on survival were: extent of surgery, age gender and tumor volume. As well, survival for patients with low-grade astrocytoma in the CT scan era appears to be improved compared to historical controls in the literature *Comments and conclusions* Older study that may still be relevant if EOR noted on CT scan correlates with EORs seen on modern MR imaging

Table 1 continued

First author (year)	Description of study	Data class	Conclusions
Piepmeier et al. (1996) [18]	*Study description* Retrospective cohort study with co-temporaneous cohortst to determine specific outcome factors, including time to recurrence, incidence of anaplastic transformation, and survival *Patient population* 55 (all astrocytomas) LGG patients *Treatment regimen* GTR in 31 patients and STR in 24 patients. Medial follow-up of 8 years	III	Results *Correlating GTR/STR with PFS and OS* GTR improves PFS (P = 0.0003) and OS (P = 0.0013) *Author's conclusions* The benefit in patients who underwent aggressive surgery seems to result from a significant decrease in the risk of recurrence when compared with patients who underwent anything less than GTR. Our data also suggest that variability in the natural history of LGGs has a strong influence in determining survival and that tumors associated with chronic epilepsy are much less likely to become more malignant over time *Comments and conclusions* Class III data supporting GTR of astrocytomas
Scerrati et al. (1996) [44]	*Study description* Retrospective cohort study with co-temporaneous cohorts correlating EOR with OS *Patient population* 131 LGG patients *Treatment regimen* S1 = radical/total resection (58 %); S2 = subtotal < 10 % residual tumour (23 %); S3 = partial-10–50 % residual tumour (18 %). Median follow-up of 7.75 years	III	Results *Correlating EOR with OS* EOR affected OS in univariate analysis for total and subtotal surgical resections (S1 and S2; P < 0.001). In multivariate analysis, EOR was the only variable retaining a significant effect on OS (P = 0.001, HR 2.20). *Author's conclusions* The data strongly support the role of a surgical removal as extensive as possible in the treatment of LGGs *Comments and conclusions* Large cohort and multiple EOR categories make this strong class III data
Karim et al. (1996) [26] EORTC 22844	*Study description* Cohort study of simultaneously- and prospectively-acquired cohorts within an EORTC RCT—equivalent to a prospective cohort study *Patient population* 379 LGG patients *Treatment regimen* Three groups: >90 % remove d bulk, 50–89 % removed, <50 % removed. Median followup of 6.17 years	III	Results *Correlating GTR/STR with OS* EOR predicted OS (P < 0.01 univariate, P < 0.05 multivariate) and PFS (P < 0.001 univariate, P < 0.05 multivariate) *Author's conclusions* While this study did not reveal the radiotherapeutic dose–response for patients with LGG, the importance of other parameters like EOR was verified *Comments and conclusions* Strong class III data due to large number of patients even though the EOR-OS correlation was not the primary purpose of the study
Singer et al. (1995) [31]	*Study description* Retrospective cohort study with co-temporaneous cohorts *Patient population* 43 LGG patients *Treatment regimen* 23 patients underwent biopsy, 17 patients underwent STR, and 3 patients underwent GTR	III	Results *Correlating GTR/STR versus biopsy with OS* Surgery (STR/GTR) versus biopsy did not affect OS (P = 0.5) in univariate analysis *Author's conclusions* In this series, there was no survival difference between LGG patients who had open biopsy and those who underwent subtotal/total resection *Comments and conclusions* Small sample size could contribute to these results

Table 1 continued

First author (year)	Description of study	Data class	Conclusions
Touboul et al. (1995) [46]	*Study description* Retrospective cohort study with co-temporaneous cohorts *Patient population* 110 LGG patients *Treatment regimen* 37 % surgery, 63 % biopsy. Mean follow-up not specified	III	Results *Correlating surgery versus biopsy with OS* Surgery improves OS relative to biopsy (P = 0.012) in multivariate analysis *Author's conclusions* Surgical resection improves the survival of LGG patients relative to biopsy *Comments and conclusions* As the authors themselves point out, patients who underwent surgical resection were those in the best condition, having tumors that were easily accessible and less invasive
Nicolato et al. (1995) [45]	*Study description* Retrospective cohort study with co-temporaneous cohorts to investigate the importance of 32 prognostic factors in predicting survival in 76 adult patients with LGGs *Patient population* 76 LGG patients *Treatment regimen* All patients underwent surgical resection. Median followup of 6.8 years	III	Results *Correlating GTR/STR with OS* GTR predicts OS in univariate (P = 0.0001) and multivariate (P < 0.05) analysis *Author's conclusions* Radical resection of the neoformation, a higher preoperative KPS, and an age younger than 50 years are strongly correlated with survival *Comments and conclusions* Class III data supporting GTR of LGGs
Berger et al. (1994) [27]	*Study description* Retrospective cohort study with co-temporaneous cohorts correlating EOR with PFS in LGG patients *Patient population* 53 LGG patients *Treatment regimen* All patients underwent surgical resection. Mean followup of 3.475 years	III	Results *Correlating GTR/STR with PFS* Patients with 100 % resection (n = 13) had recurrence-free follow up (mean 54 months). In the remaining patients (n = 40), as the percent of resection decreased, incidence of recurrence increased and time to progression decreased (P = 0.03) *Author's conclusions* For tumors greater than 10 cm^3, the authors' data suggest that a greater percent of resection and a smaller volume of residual disease conveys a significant advantage in terms of incidence of recurrence and the recurrent tumor phenotype, for patients with LGGs, compared with those who have a less aggressive resection or biopsy. While this may also be the case with tumors less than 10 cm3, further follow-up is necessary to determine the effect of surgery on recurrence patterns for this subset of patients *Comments and conclusions* Class III data supporting GTR of larger LGGs

specifically increased PFS [13–18], and nine studies argued that EOR increased PFS [19–27], with most using multivariate analysis to address the influence of confounding variables.

Correlating extent of resection with overall survival (OS)

Thirty-five retrospective studies attempted to correlate EOR with OS in LGGs undergoing surgery, all producing class III data (Table 1). Six of these studies showed no correlation between EOR and OS [12, 28–32]. Three studies showed a correlation between EOR and OS in univariate analyses, but the correlation was not significant in associated multivariate analyses [16, 33, 34]. Of the remaining 26 studies, six showed that achieving radiographic GTR of an LGG increases OS [15, 17, 18, 23, 35, 36], 17 showed that increasing EOR leads to increased OS [6, 11, 20–22, 24–26, 37–45], and three showed that surgical resection prolonged OS relative to biopsy [46–48].

Ability of intraoperative imaging to improve extent of resection

Four retrospective studies [15, 55–57] have investigated intraoperative MRI and one investigated intraoperative CT [58] as tools to maximize extent of resection. All five studies produced class III data suggesting that intraoperative imaging improved extent of resection. A 2001 study showed OS to correlate with EOR, with 8 of 12 patients undergoing resection of additional tissue noted on iMRI, leading to 6 more GTRs [57]. A 2004 study showed that 7 of 9 patients underwent additional resection of tumor noted on iMRI, with the other 2 having residual tumor in eloquent areas that could not be resected [55]. A 2005 study reported improved OS in patients whose LGGs were resected with iMRI compared to rates reported in national databases [15]. And a 2006 study reported an increase in GTR rate from 53 to 58 % after resection of residual tumor seen on iMRI [56].

Correlating resection with seizure control

Four retrospective cohort studies [49–52] met the eligibility criteria for attempting to determine if surgical resection of a LGG in a patient with a seizure history improves seizure control. Three studies presented class III data arguing that gross total resection of a LGG improves seizure control [49–51]. The fourth study was a smaller 5 patient study involving patients with medically refractory epilepsy with LGG resection leading to 3 patients becoming seizure free [52].

Accuracy of pathology from resection versus biopsy and impact on treatment

One retrospective study investigated how frequently pathology results differ between biopsy and subsequent resection of the same tumor and produced class III data supporting the hypothesis that the pathologic diagnosis obtained through a surgical resection can differ from that of a biopsy of the same tumor. The surgical resection typically yields more aggressive histologic grade than the biopsy [69], presumably due to spatial heterogeneity, which is an added benefit to resection.

Role of advanced preoperative imaging modalities in safe maximal surgical resection

Two retrospective cohort studies have investigated the role of advanced preoperative imaging modalities in safe maximal surgical resection. One study presented class III data suggesting that preoperative DTI tractography correlated with extent of surgical resection [53]. Another non-controlled study presented class III data in which functional MRI (fMRI) could be used to localize eloquent areas before surgery [54].

Ability of intraoperative neuromonitoring to improve neurologic outcomes after surgical resection

Seven retrospective studies with class III data investigated the impact of intraoperative neurophysiological monitoring of language [59–62], motor function [63], or both [64, 65] on neurologic outcomes after surgical resection of LGGs in eloquent locations. Sarubbo et al. reported no permanent deficits with 78 % volumetric resection achieved and KPS improved in 8 of 12 patients [60]. Chang et al. reported patients with tumor in locations proven to be eloquent by mapping exhibited a worse OS in comparison to those with tumors in non-eloquent locations by mapping [59]. Yordanova et al. reported a technique in which resection proceeded until mapping indicated a need to stop, even if that meant resecting beyond the MRI boundary of tumor. This lead to supra-total resections in 15 of 17 cases, with improved PFS compared to a control group of patients undergoing total resections of LGGs [61]. De Benedictis et al. reported 9 cases in which patients underwent repeat awake craniotomies, after asleep surgery, with EOR improved in all 9 cases at the time of the second surgery [62]. A study of motor mapping used both cortical and subcortical mapping and identified subcortical tracts in 89 % of 26 LGGs, with the GTR rate improving from 44 to 67 % when tracts were not identified by subcortical mapping [63]. While finding these tracts subcortically was

associated with higher immediate postoperative deficits, these deficits usually resolved within 1 month [63]. In 2003, Duffau et al. investigated cortical and subcortical language and motor mapping during 103 resections of LGGs, with 94 % of cases leading to favorable functional results [64]. A follow up study by the same group 3 years later reported results with motor and/or language mapping during resection of insular LGGs with no permanent deficits, but EOR an OS were not commented on [65].

Ability of postoperative plasticity to improve neurologic outcomes after surgical resection

Three retrospective studies produced class III data investigating postoperative plasticity, the ability of other brain locations to compensate for resected areas, after resection of LGGs in eloquent locations. Ius et al. retrospectively analyzed 58 postoperative MRIs and reported areas that could not safely tolerate resection, which included left primary motor and somatosensory cortices for upper and lower limbs, left ventral premotor cortex, left posterior superior temporal gyrus (Wernicke's area), left supramarginal gyrus, left angular gyrus, right primary motor and somatosensory areas for superior and inferior limbs, and right angular gyrus [66]. In one study, awake intraoperative mapping of 7 patients with LGGs in Broca's area and intact preoperative language revealed a shift in language towards other locations, with recruitment of the ventral and dorsal premotor cortices, orbitofrontal cortex, and insula, whereas no or few language sites were detected within Broca's area. The retrospective nature of this study made it difficult to determine if this represented plasticity stimulated by the LGG or if these patients had variable localization of language prior to developing LGG [67]. In 2003, Duffau et al. reported 77 patients with LLGs undergoing surgical resection with intraoperative speech and/or motor mapping. While all patients experienced postoperative neurologic deficits, all but 4 cases improved at 3 months, which the authors argue reflects plasticity. [68]. It should be noted that they did not identify the locations to where function had been transferred.

Surgery conclusion

While the lack of class I evidence and limited examples of class II evidence restricts our ability to definitively recommend surgery for LGGs, the literature is supportive of several potential benefits of surgery for patients with diffuse LGGs. The three examples of class II evidence support the lack of a negative impact from a wait and see approach on cognitive performance and quality of life, less frequent tumor progression with GTR or STR compared to biopsy alone, and a surprisingly high rate of progression even after GTR. Most of the class III evidence supports a benefit of surgery on survival, with the impact of surgery being greater on PFS [with 17 of 19 (89 %) studies supporting some benefit of surgery on PFS] than on OS [for with 26 of 34 (76 %) studies supporting a benefit of surgery]. Class III studies also promote benefits of surgery on seizure control and accuracy of pathology, and suggest that plasticity and neuro-monitoring can improve functional outcomes after surgery for LGGs in eloquent locations.

Key issues for future investigation

While difficulty creating prospective randomized trials comparing surgery versus no surgery for LGGs will likely limit the availability of class I evidence, future investigation should include class II studies prospectively correlating volumetric extent of resection with PFS and OS in large cohorts of patients. Such studies should be conducted with more uniform measurement of EOR than the variable criteria currently used, and should also incorporate the surgical adjuncts for which class III evidence exists, including preoperative functional MRI along with intraoperative MRI and brain mapping (Table 1).

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