

Low-grade glioma surgery

4 objectives in performing surgery for low-grade gliomas ¹⁾:

1. to obtain histological confirmation/molecular genetic analysis. Surgical biopsy or partial resection is recommended in almost all cases to establish the diagnosis since clinical and radiographic data are not definitive ²⁾
2. to improve the neurological condition
3. to reduce the risk of tumor growth
4. to prevent or delay malignant transformation.

Intraoperative mapping and awake craniotomy: Complete resection is often not possible due to the infiltrative nature of low-grade gliomas and their frequent location near or at eloquent areas. Resection can be safely maximized by means of intraoperative mapping and awake-surgeries ³⁾

A meta-analysis of 8091 patients showed that the use of intraoperative stimulation brain mapping achieved more gross total removal with less late severe neurological deficits, and is recommended as a standard for glioma surgery, especially if eloquent areas are involved. ⁴⁾

Multicentric gliomas, previously considered not resectable, can also be resected with aid of awake intraoperative mapping. ⁵⁾

Despite this advance, the role of surgery remains limited for widespread gliomas or very deep-seated lesions.

Technical considerations at surgery: Since the margins of low-grade gliomas may not be readily visible at the time of surgery, adjuncts such as stereotactic and image-guided techniques may also be extremely useful, especially for deep tumors or in areas bordering on eloquent brain. ⁶⁾

The impact of [surgery](#) on outcome of adult patients with low-grade gliomas is controversial ⁷⁾.

Despite the lack of [randomized controlled trials](#) hampering the performance of appropriate [metaanalysis](#), the increasing amount of evidence pointed toward an aggressive surgical strategy.

Although a large amount of data supports resection for symptomatic diffuse low-grade glioma (LGG), the therapeutic strategy regarding incidental LGG (ILGG) is still a matter of debate. Indeed, early “preventive” surgery has recently been proposed in asymptomatic patients with LGG, after showing that the extent of resection was larger than in symptomatic patients with LGG. However, the quality of life should be preserved by avoiding both neurological deficit and epilepsy ⁸⁾.

The largest study in patients with low-grade gliomas, performed by Capelle et al. ⁹⁾, showed a strong impact of the [extent of resection](#) EOR on survival, especially when a radiological complete resection was obtained.

Although non-controlled series have a potential selection bias, similar results were found in a study with an unusual geographic and medical constellation that essentially eliminated the selection bias:

two hospitals in Norway, each taking exclusive care of a large, stable population, followed different strategies for patients with low-grade glioma. One of the hospitals favoured a biopsy followed by a “wait-and-see” strategy, delaying further therapy until malignant progression while the other hospital preferred to perform maximal safe resection whenever possible. Outcome comparison between the two hospitals revealed that patients of the surgery-preferring hospital had a significantly better survival rate, suggesting that a proactive and aggressive treatment plan improves survival of low-grade glioma patients. Moreover, the rate of malignant transformation was twice as high in the “wait-and-see” cohort. Taken together, these findings support a proactive and radical surgical approach for low-grade gliomas rather than a “wait-and-see” strategy ¹⁰⁾.

This surgery has to be performed with the appropriate armamentarium, which is the availability of [intraoperative stimulation mapping](#), especially for those lesions occurring in cortical and subcortical eloquent sites.

According to the recently published [guidelines](#), surgical treatment has been increasingly recognized as the initial therapeutic act of choice for patients diagnosed with a presumed [low-grade glioma](#), given that total resection can improve [seizure control](#), [progression free survival](#) and [overall survival](#), while reducing the risk of malignant transformation and preserving patients' functional status ¹¹⁾.

Treatment options include observation, surgery, radiation, chemotherapy, or a combined approach, and management is individualized based on tumor location, histology, molecular profile, and patient characteristics. Moreover, in this type of brain tumor with a relatively good prognosis and prolonged survival, the potential benefits of treatment must be carefully weighed against potential treatment-related risks ¹²⁾.

Patients with clinically and radiographically suspected LGG have two initial surgical options, biopsy or resection. Biopsy can provide a histological diagnosis with minimal risk but does not offer a direct treatment. Resection may have additional benefits such as increasing survival and delaying recurrence, but is associated with a higher risk for surgical morbidity. There remains controversy about the role of biopsy versus resection and the relative clinical outcomes for the management of LGG.

Evidence suggests that a greater extent of resection (EOR) extends malignant progression-free survival among patients with low-grade gliomas (LGGs). These studies, however, rely on the combined analysis of oligodendrogliomas, astrocytomas, and mixed oligoastrocytomas-3 histological subtypes with distinct genetic and molecular compositions ¹³⁾.

The following electronic databases were searched in 2012 for the first version of the review: Cochrane Central Register of Controlled Trials (CENTRAL) (2012, Issue 11), MEDLINE (1950 to November week 3 2012), Embase (1980 to Week 46 2012). For this updated version, the following electronic databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL) (2016, Issue 5), MEDLINE (Nov 2012 to June week 3 2016), Embase (Nov 2012 to 2016 week 26). All relevant articles were identified on PubMed and by using the 'related articles' feature.

Jiang et al. also searched unpublished and grey literature including ISRCTN-metaRegister of Controlled Trials, Physicians Data Query and ClinicalTrials.gov for ongoing trials.

Jiang et al. planned to include patients of any age with a suspected intracranial LGG receiving biopsy or resection within a randomized clinical trial (RCT) or controlled clinical trial (CCT). Patients with prior resections, radiation therapy, or chemotherapy for LGG were excluded. Outcome measures included

overall survival (OS), progression-free survival (PFS), functionally independent survival (FIS), adverse events, symptom control, and quality of life (QoL).

A total of 1375 updated citations were searched and critically analyzed for relevance. This was undertaken independently by two review authors. The original electronic database searches yielded a total of 2764 citations. In total, 4139 citations have been critically analyzed for this updated review.

No new RCTs of biopsy or resection for LGG were identified. No additional ineligible non-randomized studies (NRS) were included in this updated review. Twenty other ineligible studies were previously retrieved for further analysis despite not meeting the pre-specified criteria. Ten studies were retrospective or were literature reviews. Three studies were prospective, however they were limited to tumor recurrence and volumetric analysis and extent of resection. One study was a population-based parallel cohort in Norway, but not an RCT. Four studies were RCTs, however patients were randomized with respect to varying radiotherapy regimens to assess timing and dose of radiation. One RCT was on high-grade gliomas (HGGs) and not LGG. Finally, one RCT evaluated diffusion tensor imaging (DTI)-based neuro-navigation for surgical resection.

Since the last version of this review, no new studies have been identified for inclusion and currently there are no RCTs or CCTs available on which to base definitive clinical decisions. Therefore, physicians must approach each case individually and weigh the risks and benefits of each intervention until further evidence is available. Some retrospective studies and non-randomized prospective studies do seem to suggest improved OS and seizure control correlating to higher extent of resection. Future research could focus on RCTs to determine outcomes benefits for biopsy versus resection ¹⁴⁾.

Based on results of three [randomized clinical trials](#) (RCT), [radiotherapy](#) (RT) may be deferred in patients with [low risk low-grade glioma](#) (defined as age <40 years and having undergone a complete resection), although combined chemoradiotherapy has never been prospectively evaluated in the low-risk population. The recent RTOG 9802 RCT established a new standard of care in high-risk patients (defined as age >40 years or incomplete resection) by demonstrating a nearly twofold improvement in overall survival with the addition of PCV (procarbazine, CCNU, vincristine) chemotherapy following RT as compared to RT alone. Chemotherapy alone as a treatment of LGG may result in less toxicity than RT; however, this has only been prospectively studied once (EORTC 22033) in high-risk patients. A challenge remains to define when an aggressive treatment improves survival without impacting quality of life (QoL) or neurocognitive function and when an effective treatment can be delayed in order to preserve QoL without impacting survival. Current WHO histopathological classification is poorly predictive of outcome in patients with LGG. The integration of molecular biomarkers with histology will lead to an improved classification that more accurately reflects underlying tumor biology, prognosis, and hopefully best therapy ¹⁵⁾.

5-aminolevulinic acid fluorescence guided resection of low-grade glioma

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