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Comparison of a Strategy Favoring Early Surgical Resection vs a Strategy Favoring Watchful Waiting in Low-Grade Gliomas

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Context There are no controlled studies on surgical treatment of diffuse low-grade gliomas (LGGs), and management is controversial.

Objective To examine survival in population-based parallel cohorts of LGGs from 2 Norwegian university hospitals with different surgical treatment strategies.

Design, Setting, and Patients Both neurosurgical departments are exclusive providers in adjacent geographical regions with regional referral practices. In hospital A diagnostic biopsies followed by a "wait and scan" approach has been favored (biopsy and watchful waiting), while early resections have been advocated in hospital B (early resection). Thus, the treatment strategy in individual patients has been highly dependent on the patient's residential address. Histopathology specimens from all adult patients diagnosed with LGG from 1998 through 2009 underwent a blinded histopathological review to ensure uniform classification and inclusion. Follow-up ended April 11, 2011. There were 153 patients (66 from the center favoring biopsy and watchful waiting and 87 from the center favoring early resection) with diffuse LGGs included.

Main Outcome Measure The prespecified primary end point was overall survival based on regional comparisons without adjusting for administered treatment.

Results Initial biopsy alone was carried out in 47 (71%) patients served by the center favoring biopsy and watchful waiting and in 12 (14%) patients served by the center favoring early resection ($P<.001$). Median follow-up was 7.0 years (interquartile range, 4.5-10.9) at the center favoring biopsy and watchful waiting and 7.1 years (interquartile range, 4.2-9.9) at the center favoring early resection ($P=.95$). The 2 groups were comparable with respect to baseline parameters. Overall survival was significantly better with early surgical resection ($P=.01$). 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 and early resection, respectively. In an adjusted multivariable analysis the relative hazard ratio was 1.8 (95% CI, 1.1-2.9, $P=.03$) when treated at the center favoring biopsy and watchful waiting.

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.

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THE DIFFUSE LOW-GRADE GLIOMAS (LGGs) include World Health Organization (WHO) grade II astrocytomas, oligodendrogliomas, and oligoastrocytomas.[1] Due to diffuse brain infiltration, LGGs are usually not considered surgically curable.[2] In fact, the effect of surgery on survival remains unclear because current evidence relies on uncontrolled surgical series alone.[3,4] Such series can be much affected by selection bias since patients with favorable outcomes may fare better regardless of treatment.[5,6] For example, watchful waiting until progression has been reported safe,[7,8] while others report improved survival and delayed time to malignant transformation if total resection of the tumor is achieved.[9-13] Due to lack of better evidence, management of suspected LGGs has remained one of the major controversies in neuro-oncology[5,14,15] and treatment strategies often differ considerably between neurosurgical centers.[16]

For editorial comment see p 1918.

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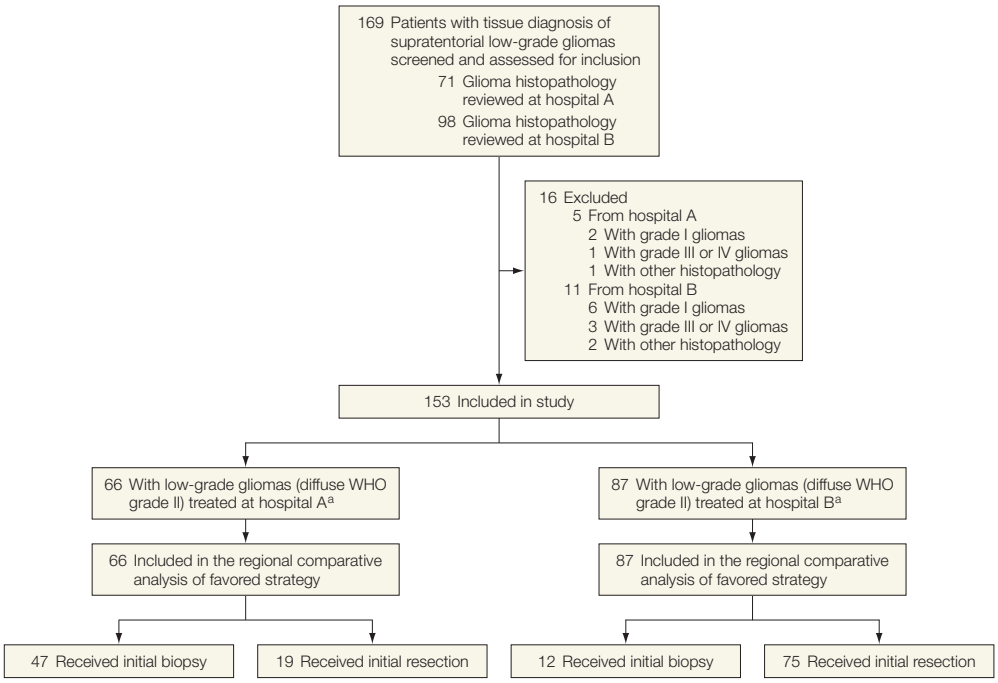
Figure 1. Flow Diagram of Patient Inclusion



Grade I tumors were included in the review process to ensure that tumors classified as "unspecified low-grade glioma" were reassessed. After blinded review of histopathology, 153 patients were included in the analysis (91% of screened); 66 (43%) from hospital A and 87 (57%) from hospital B. Zero patients were lost to follow-up at both hospitals. WHO indicates the World Health Organization.
[a]Two cases from hospital A and 3 cases from hospital B were not reviewed due to lack of tissue specimen, and the initial diagnosis was maintained.

In this retrospective population-based parallel cohort study over a 12-year period, we aimed to investigate if early tumor resection, as the preferred strategy, improves survival in patients with LGG compared with a strategy favoring biopsy and watchful waiting.

METHODS

The study is reported based on criteria from the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.[17]

The Norwegian Health Care System and Treating Centers

Norway has a socialized health care system with equal distribution of resources and uniform training and licensing of health care personnel. The population is homogeneous and stable. Four neurosurgical centers offer brain tumor surgery, each serving 1 geographical health region (southeast, west, middle, and north). There is almost perfect correlation between site of residence (address) and receipt of treatment in that site's regional neurosurgical center, which eliminates possible referral bias.[18] Patients in this study were treated at the 2 northernmost neurosurgical centers (middle and north). Both hospitals favor histopathological diagnosis over a wait-and-scan approach.

The neurosurgical department at hospital A invested in its first navigational tool in 1996 and has thereafter published several reports on biopsy procedures.[19-21] The department uses the Medtronic StealthStation as the current neuronavigation system. In hospital A, resection of suspected LGGs has usually only been offered if a safe total resection seemed possible based on preoperative planning or for relieving symptoms of mass effect. In other clinical scenarios, diagnostic biopsies have been performed. Hence, the approach favored by hospital A is biopsy and watchful waiting. Biopsies have in later years been targeted at metabolic "hot spots" based on preoperative perfusion-weighted magnetic resonance imaging (MRI) or MR spectroscopy in selected cases. LGG patients have typically been followed-up with MRI obtained at 3 and 6 months postoperatively and yearly thereafter. Patients have usually been offered surgical resection if the tumors grow or show signs of malignant transformation (ie, new contrast enhancement).

Hospital B introduced the concept of 3-dimensional (3-D) ultrasound in brain surgery and has, since 1998, used the SonoWand neuronavigation system with 3-D ultrasound–based intraoperative imaging in its tumor operations.[22-25] With the use of this technology, an aggressive treatment strategy has been advocated for LGG with maximal safe tumor resection as favored management. Hence, the approach favored by hospital B is early resection. Deviation from this strategy occurred in some elderly patients with comorbidities and in patients with very widespread tumor infil-

tration (eg, gliomatosis cerebri), who have been offered diagnostic biopsies only. The patients have been followed-up with MRI every 6 months in the beginning (postoperatively), and later annually.

Eligible Study Patients and Histopathological Review

Adults 18 years or older with histologically verified supratentorial WHO grade I and II tumors (pilocytic astrocytoma, grade II oligodendroglioma, grade II astrocytoma grade, grade II oligoastrocytoma) diagnosed from 1998 through 2009 were screened for inclusion (FIGURE 1). All screened patients were retrospectively identified from the pathology databases. Only patients with diffuse LGG (WHO grade II) were included and no patients were excluded based on clinical and radiological characteristics (eg, gliomatosis cerebri, contrast enhancement, or poor functional status).

The tumors were classified according to the WHO criteria.[26] To minimize classification bias, a blinded review was performed in which a neuropathologist from the center favoring biopsy and watchful waiting reviewed all LGGs diagnosed at the center favoring early resection and vice versa.[27] The neuropathologists were blinded for previous diagnosis, baseline characteristics, image data, and clinical outcomes. No molecular markers were available in the review process. Discordant results were reassessed by both neuropathologists at a final meeting from which consensus was obtained by evaluation of the slides using a multiheaded microscope. Gemistocytic astrocytomas (grade II tumors associated with more aggressive growth and shorter survival)[2,5] were not registered separately because this information was not available before surgical decision making and since there was no uniform registration during the initial evaluation of histopathology.

Study Variables

Patient and treatment characteristics were retrospectively retrieved from medical records by an author from the center favoring early resection (A.S.J.). In all 169 screened patients, medical records were reviewed before the histopathological review and final inclusion. Preoperative MRIs were available for review in 142 of the 153 patients (89%) with diffuse LGG. The system suggested by Sawaya et al[28] was used for grading eloquence, meaning the proximity of tumors to brain regions perceived critical for basic neurological functions (eg, language area, motor area, visual area). In 16 cases in which preoperative MRI could not be retrieved, the mean diameter from the study group was imputed at the treating department and subsequent images or radiology reports were assessed for grading eloquence. To register and adjust for validated prognostic factors in LGG, the Pignatti score was used (maximum score: age $\geq$40 years, diameter $\geq$6 cm, crossing midline, deficit present, and astrocytoma histology).[29] If biopsy was followed by resection within 3 months, initial management was classified as resection; however, survival was calculated from the date of initial procedure. The Charlson Comorbidity Index was used to assess comorbidity.[30]

Follow-up

All patients were followed up until death or until April 11, 2011. The national population registry (Statistics Norway) provided the patients' current status (dead or alive) as of April 11, 2011, and the date of death. No patients were lost to follow-up.

Statistical Analysis

The prespecified primary end point was overall survival. Surgical morbidity was the prespecified secondary end point. These end points were analyzed with respect to regional treatment policy and not actual treatment, ie, direct regional comparisons including patients at the center favoring biopsy and watchful waiting treated with resection and patients at the center favoring early resection undergoing biopsy only. All analyses were performed using PASW, version 18.0. Statistical significance level was set to P value of .05 or less. All tests were 2-sided.

Central tendencies are presented as mean (SD) or as median (interquartile range [IQR]) when data were skewed. Survival was calculated from date of initial surgical procedure (biopsy or resection). Survival is presented as Kaplan-Meier plots and compared with the log-rank test. Expected survival rates were calculated using life tables. Binomial data were analyzed with Pearson χ^2 test. Comparisons of means between departments were analyzed with independent samples t test, but when data were skewed, the Mann-Whitney U test was used. Cox multivariable analyses were performed to adjust for important prognostic factors.

Ethics and Approvals

The study protocol was approved by the Regional Ethical Committee for Health Region Mid-Norway (reference 2010-3231), and the need for informed consent was waived by the committee.

RESULTS

In the study period, the average populations in the geographical health regions served by the center favoring biopsy and watchful waiting and the center favoring early resection were 462 959 and 641 458, respectively (Statistics Norway). Based on the 169 screened patients, the calculated incidence of LGG was 1.3 per 100 000/year in both health regions. After the central review of histopathology, 153 patients with diffuse LGG (91% of screened cohort) were identified and included in the study; 66 (43%) from the center favoring biopsy and watchful waiting and 87 (57%) from the center favoring early resection.

Baseline characteristics are shown in TABLE 1. There were large regional differences in treatment strategies as biopsy and subsequent watchful waiting was the initial strategy in 47 (71%) of LGG patients served by the center favoring biopsy and watchful waiting compared with only 12 (14%) served by the center favoring early resection

($P<.001$). Among patients who underwent biopsy only, later resection was performed in 14 patients (30%) at the center favoring biopsy and watchful waiting (after a median of 9 months; range, 4-82 months) and in 2 patients (17%) at the center favoring early resection (after 9 and 21 months). At the center favoring biopsy and watchful waiting, more patients presented with seizures (79% vs 59%; $P=.008$). There were otherwise no significant differ-

Table 1. Baseline and Treatment Characteristics

Baseline	No. (%)[a] Biopsy and Watchful Waiting Preferred, Hospital A (n = 66)	No. (%)[a] Resection Preferred, Hospital B (n = 87)	*P* Value
Initial procedure			
Biopsy	47 (71)	12 (14)	<.001
Resection	19 (29)	75 (86)	
Age, mean (SD), y	45 (15)	44 (16)	.67
Age ≥40 y	37 (55)	48 (56)	.91
Year of surgery, mean (SD)	2003 (3)	2003 (3)	.96
Men	25 (38)	40 (46)	.32
Preoperative Karnofsky performance status ≥80, normal activity[b]	51 (77)	71 (82)	.51
Charlson comorbidity index, median (IQR)[c]	0 (0-0)	0 (0-0)	.70
Maximal tumor diameter, mean (SD), mm	52 (17)	48 (22)	.33
Tumor diameter ≥60 mm	19 (29)	24 (28)	.87
Midline or bilateral involvement	10 (15)	11 (13)	.66
Preoperative contrast enhancement	13 (20)	15 (17)	.70
Eloquent location[d]	17 (26)	29 (35)	.23
Histopathology			
Grade II astrocytoma	55 (83)	62 (71)	.19
Grade II oligodendroglioma	6 (9)	16 (19)	
Grade II oligoastrocytoma	5 (8)	9 (10)	
Pignatti score[e]			
0	2 (3)	6 (7)	.68
1	22 (33)	29 (33)	
2	21 (32)	27 (31)	
3	12 (18)	18 (21)	
4	7 (11)	4 (5)	
5	2 (3)	3 (3)	
Time from image finding to diagnostic procedure, median (IQR), d	15 (9-35)	35 (22-67)	<.001
Initial symptoms			
Seizure	52 (79)	51 (59)	.008
Seizures without additional symptoms	43 (65)	47 (54)	.17
Headache	15 (23)	24 (28)	.50
Neurological deficits	17 (26)	25 (29)	.68
Asymptomatic	1 (2)	3 (3)	.46
Later or repeated resection			
1 time	18 (27)	22 (26)	.77
2 times	1 (2)	6 (7)	
Several times	1 (2)	1 (1)	
Any resection during follow-up	33 (50)	77 (89)	<.001
Early, first 6 mo, postoperative radiotherapy	19 (29)	37 (43)	.09
Ever radiotherapy	46 (71)	55 (63)	.33
Early, first 6 mo, postoperative chemotherapy	13 (20)	18 (21)	.92
Ever chemotherapy	39 (60)	39 (45)	.06
Years of follow-up, median (IQR)	7.0 (4.5-10.9)	7.1 (4.2-9.9)	.95

Abbreviation: IQR, interquartile range.
[a] Data are shown as No. (%) unless otherwise indicated.
[b] Karnofsky performance status is an 11-point scale ranging from 0 (death) to 100 (normal activity without any symptoms).[31]
[c] Charlson comorbidity index[30] is a weighted score of 20 conditions in which a higher score means more comorbidity.
[d] Eloquent indicates grade 3 as defined by Sawaya et al.[28]
[e] The Pignatti score[29] is a summation of validated prognostic factors in low-grade gliomas. The range is from 0 to 5 and with higher scores being associated with worse prognosis.

ences in clinical presentation or known prognostic factors. Median follow-up was 7.0 years (IQR, 4.5-10.9) at the center favoring biopsy and watchful waiting and 7.1 years (IQR, 4.2-9.9) at the center favoring early resection ($P=.95$).

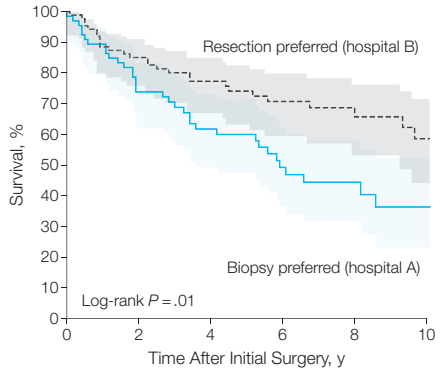
At end of follow-up, 34 patients (52%) from the center favoring biopsy and watchful waiting had died compared with 28 patients (32%) from the center favoring early resection. Overall survival was significantly longer if treated at the center favoring early resection over biopsy and watchful waiting ($P=.01$; FIGURE 2). The survival advantage increased with time. While 1-year survival was 89% (95% CI, 81%-87%) vs 89% (95% CI, 83%-95%), the expected 3-year survival was 70% (95% CI, 58%-82%) vs 80% (95% CI, 72%-88%), expected 5-year survival was 60% (95% CI, 48%-72%) vs 74% (95% CI, 64%-84%), and expected 7-year survival was 44% (95% CI, 30%-58%) vs 68% (95% CI, 58%-78%). Median survival at the center favoring biopsy was 5.9 years (95% CI, 4.5-7.3) while median survival is not yet reached where initial resection was preferred.

As presented in TABLE 2, there were no significant differences in surgical complications (9% vs 8%; $P=.82$) or acquired deficits (18% vs 21%; $P=.70$) between centers. Later malignant transformation was more common when biopsy only was the favored initial management (56% vs 37%; $P=.02$).

Despite balanced study groups, we explored whether the statistically nonsignificant differences in established prognostic factors still in sum could explain the demonstrated survival difference. In a post hoc Cox multivariable model in which treatment center was included together with the Pignatti scores, the significant survival difference remained with a relative hazard ratio (HR) of 1.8 (95% CI, 1.1-2.9; $P=.03$). To explore whether there could be an unmeasured difference in care quality between centers or an unknown confounder independent from the diverging surgical strategies, we created another Cox regression model including the actual treatment ("as treated") in addition to the Pignatti scores and treating center. With this approach, there was no survival difference between centers ($P=.93$) with an HR of 1.0 (95% CI, 0.5-2.0).

A post hoc subgroup analysis of the largest histopathological entity, namely the grade II astrocytomas, demonstrated median survival of 5.6 years (95% CI, 3.5-7.6) at the center favoring biopsy and watchful waiting vs 9.7 years (95% CI, 7.5-11.9) at the center favoring early resection ($P=.05$). Another post hoc survival analysis excluding patients initially treated different from the favored local strategy (ie, excluding resections from the center favoring biopsy and watchful waiting and biopsies from the center favoring early resection) was performed. Median survival at the center favoring biopsy only was 5.8 years (95% CI, 3.0-8.7) while median survival was not reached at the center favoring early resection ($P<.001$, FIGURE 3). Estimated 5-year survival was 57% (95% CI, 41%-73%) vs 81% (95% CI, 71%-91%), respectively.

Figure 2. Survival Analysis Comparing Favored Surgical Strategies for Low-Grade Gliomas



No. of patients at risk

Biopsy preferred	66	46	36	21	11	6
Resection preferred	87	71	50	40	23	13

This is a regional comparison of results of the 2 favored surgical strategies (but including patients at hospital A treated with resection and patients at hospital B undergoing biopsy only). Biopsy preferred (hospital A): 29% initial resections. Resection preferred (hospital B): 86% initial resections. There was a significant difference in survival between patients treated at the 2 hospitals ($P=.01$). The shaded areas indicate 95% CIs. Median survival was 5.9 years (95% CI, 4.5-7.3) in the center in which biopsy and watchful waiting was preferred. Median survival was not reached in the center in which early resection was the preferred strategy.

Table 2. Complications and Malignant Transformations

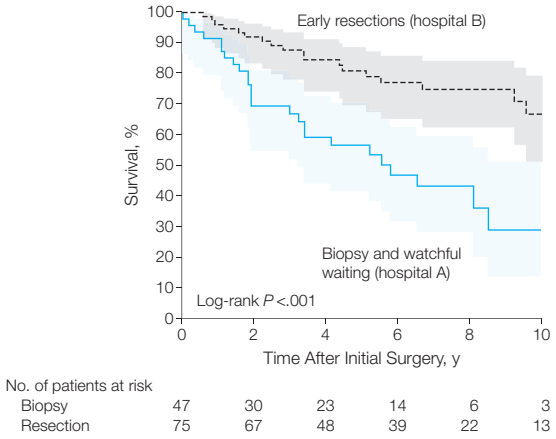
Outcome	No. (%) Biopsy and Watchful Waiting Preferred, Hospital A (n = 66)	No. (%) Resection Preferred, Hospital B (n = 87)	*P* Value
Surgical complications	6 (9)	7 (8)	.82
New or worsened neurological deficits[a]	12 (18)	18 (21)	.70
Perioperative death, 30-d mortality	1 (2)	0	.25
Malignant transformation[b]	37 (56)	31 (37)	.02

[a] Report of any new deficits or worsened neurological function of any magnitude in the postoperative (30-d) period.
[b] Malignant transformation defined as new contrast enhancement or malignant histopathology from later operation.

COMMENT

In this comparative population-based study in patients with newly diagnosed LGG, a survival benefit was observed for patients treated at a hospital advocating early resection as opposed to diagnostic biopsy and subsequent watchful waiting.

Figure 3. Survival When Treated in Accordance With Favored Strategy



This analysis excludes patients who initially received treatment different from the local favored strategy (excluding the 19 patients with initial resections at hospital A and the 12 patients who were only initially biopsied at hospital B). A survival benefit of resection was seen with median survival of 5.8 years (95% CI, 3.0-8.7) at hospital A while median survival was not reached at hospital B ($P < .001$). Shaded areas indicate 95% CIs.

Until now, the evidence concerning surgical strategies in LGG has been conflicting and based on case series alone. While some clinicians support a wait-and-scan policy in selected patients,[7,32] others have reported an association between survival and extent of resection.[9-13] The infrequent nature of the disease and the need for long follow-up combined with strong and diverse local treatment traditions[1,12-15] make it highly unlikely that a conventional randomized study of surgical management will be conducted in the near future.

Our study is a result of a naturally occurring and practically random experiment of different management strategies in 2 adjacent regions. The homogeneous Norwegian population and health care system and the blinded histopathological review ensured comparable study populations. The observed incidence was within limits expected from the literature and equal in both regions, demonstrating that inclusion was population based.[33,34] The external validity is presumably high due to the pragmatic design with treatment, inclusion, and follow-up of unselected patients in a real-life clinical setting.

Because as-treated analyses are associated with selection bias and inflated effects, we analyzed survival, a hard clinical end point, by making regional comparisons regardless of actual therapy. This is the least biased but also the least-sensitive method for detecting differences. Still, overall survival was significantly longer at the center favoring a strategy with early resection, a finding that remained after adjusting for validated prognostic factors. Since some patients were managed contrary to the local treatment strategy, this direct regional comparison presumably underestimates the survival benefit of early resection over biopsy and watchful waiting. Conversely, the posthoc analysis in which early resections from the center favoring biopsy only and biopsies from the center favoring early resection were excluded overestimates the survival gain since patients with good prognostic scores from the center favoring biopsy only and patients with poor prognostic scores from the center favoring early resection were censored.

The true survival benefit of early resections is probably somewhere between the results given by these 2 analytic approaches. Despite the clear survival advantage seen, clinical judgment is still necessary in individual patients with suspected LGG since results will depend on patient and disease characteristics together with surgical results in terms of resection grades and complication rates. Nevertheless, based on the observed regional survival difference in the present study, both involved centers now advocate early resections as the initial recommendation in most patients.

Most patients with suspected LGG have normal activity at the time of diagnosis with a reasonably long life expectancy regardless of treatment. The perceived risks of early and aggressive surgery can therefore seem unwarranted for both patients and physicians. In the present study, the survival difference between hospitals increased over time with an estimated absolute survival difference of 14% at 5 years that increased to 24% at 7 years from diagnosis. Since most deaths from brain tumors are preceded by progressive symptoms, the possible early advantage of biopsy and watchful waiting for quality of life may be lost over time. However, due to crude measurements and the retrospective review in the present study, a firm conclusion concerning surgical morbidity is not warranted. Also, the direct regional comparison is not the most sensitive for detecting differences between treatment groups. However, serious morbidity after brain tumor surgery is today relatively infrequent[23,28] and surgery-related deaths are uncommon, especially in low-grade conditions.[18] When taking the necessary means to avoid neurological deterioration by using modern technology such as 3-D ultrasound, intraoperative MRI,[35] or mapping techniques,[36] safe resections are most often achievable.

Considering the slow but often constant growth rate (median, 4.4 mm/y) in LGGs,[37] it seems biologically plausible that the survival benefit of early resection may be due to reduction of viable tumor cells capable of undergoing malignant transformation. In fact, malignant transformations were more common at the hospital favoring biopsy and watchful waiting. However, this finding should be interpreted with some caution since both detection bias

and difficulties with image interpretation after adjuvant therapy (ie, radiation necrosis, pseudopregression)[38] remain possibilities.

Since this is a progressive disease, many patients will ultimately cross over to the resection group, but the objective of this study was not to assess any resection during the course of the disease, but to test the effect of initial surgical management strategies on survival. With such a long course of disease, some may argue that the results also may be affected by subsequent therapy, but there is no consensus with respect to the potential benefits of adjuvant therapy in LGG.[15,39] Regarding surgical rescue therapy (ie, repeated resections), there was no difference between institutions. Although a difference in administration of early radiotherapy was seen, this is not expected to interfere with the primary end point since randomized controlled trials assessing the efficacy of radiotherapy in LGG patients have detected no effect on overall survival.[40-42] However, the observed difference in malignant transformation may potentially be influenced by the difference in early radiotherapy treatment.[15,41]

The main limitation of this study is the retrospective assessment of baseline and treatment variables. However, survival is a robust end point that is unaffected by the retrospective collection of data. Some patients may die of unrelated causes, but disease-specific mortality was not assessed in this study. The study groups were balanced with respect to comorbidity and age, and according to a study from the Norwegian Cancer Registry, the difference between overall and disease-specific survival for adults with primary brain tumors does not exceed 2% during the first 15 years of observation.[43] Progression-free survival was also not assessable due to the nonstandardized imaging and follow-up routines.

Some caution should be used when interpreting the outcomes other than survival in this study due to nonstandardized follow-up and multiple testing performed post hoc. Another potential bias is the possibility of sampling error in brain tumor histopathology. Studies comparing the diagnostic accuracy of biopsy vs resection have reached conflicting results.[44,45] Although sampling error may perhaps be higher with smaller amount of tissue collected, navigated biopsies are usually more targeted toward contrast enhancing regions or metabolic hot spots than specimens from open resections. Altogether, this is an unavoidable drawback and potential criticism to any study comparing resection and biopsy. With balanced baseline data and similar incidence rates in both regions, it seems unlikely that the regional survival difference reflects the diagnostic accuracies of the 2 procedures.

The presence of gemistocytic astrocytomas or gliomatosis cerebri could also influence survival, but these and other subentities should presumably be equally distributed between geographical regions. Occasional patients in both regions, such as elderly patients with considerable comorbidities, may have been followed up with a wait-and-scan approach without histopathological confirmation. It may therefore be argued that the threshold for biopsy could differ between institutions and result in recruiting more patients with worse prognosis from one center. However, in Norway the incidence of LGG diagnosed from imaging only is low and stable around 0.1 per 100 000/year.[33] Thus, it seems unlikely that skewed patient recruitment could explain our findings.

For patients in Norway with LGG, treatment at a hospital that generally favored early surgical resection was associated with better overall survival than treatment at a hospital that favored biopsy and watchful waiting. This significantly strengthens the data in support of early resection in newly diagnosed LGG.

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Author Contributions: Dr Jakola had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Jakola, Solheim.
Acquisition of data: Jakola, Myrmel, Torp, Lindal.
Analysis and interpretation of data: Jakola, Myrmel, Kloster, Torp, Lindal, Unsgård, Solheim.
Drafting of the manuscript: Jakola.
Critical revision of the manuscript for important intellectual content: Jakola, Myrmel, Kloster, Torp, Lindal, Unsgård, Solheim.
Statistical analysis: Jakola, Solheim.
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Study supervision: Myrmel, Kloster, Torp, Lindal, Unsgård, Solheim.

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