Cognitive status and quality of life in patients with suspected versus proven low-grade gliomas
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Article abstract—Background: The preferred management of patients with suspected low-grade gliomas (S-LGG) remains controversial. The benefits of resection or radiotherapy early in the course of the disease have not been proven in terms of survival. Little is known about the effects of early therapy on quality of life (QOL) and cognitive status. The authors compared functional status, QOL, and cognitive status of patients suspected of having a LGG, in whom treatment was deferred, and patients with proven LGG (P-LGG), who underwent early surgery. Methods: The authors recruited 24 patients suspected of having an LGG. These patients were matched with 24 patients with a histologically proven LGG and healthy control subjects for educational level, handedness, age, and gender. The two patient groups were also matched for tumor laterality, use of anticonvulsants, and interval between diagnosis and testing. Functional status was determined in both patient groups. QOL and cognitive status were compared between the three groups. Results: Matching criteria and functional status did not differ significantly between groups. Both patient groups scored worse on QOL scales than healthy control subjects. Unoperated patients with S-LGG scored better on most items than patients with P-LGG. Cognitive status was worse in both groups than in healthy control subjects, but, again, patients with S-LGG performed better than patients with P-LGG. Conclusion: These data suggest that a wait-and-see policy in patients with S-LGG has no negative effect on cognitive performance and QOL.

A recurring dilemma arises when a patient presents with late-onset epilepsy and brain imaging shows a lesion suggestive of a low-grade glioma (LGG). Although several retrospective analyses have suggested a survival benefit in patients with early radiotherapy, these studies are confounded by patient selection. Preliminary results of a large randomized trial indicate that early radiotherapy fails to prolong survival in LGG patients. Also, in the dose range evaluated, a randomized clinical trial failed to demonstrate a dose–response relationship for radiation in LGG patients. The benefits of surgical resection have not been proven either, as retrospective studies show conflicting results. Therefore, deferring intervention and even biopsy may be justified in these patients.

Health-related quality of life (QOL) has become an increasingly important measure in studies of brain tumor patients. Assessment of QOL in glioma patients is particularly relevant, as these patients cannot be cured and nearly all will eventually die of their disease. The effects on QOL of all treatment modalities in patients with glioma have to be balanced against their possible survival benefits. QOL of patients with glioma is often impaired by a decreased general and neurologic performance status and decreased cognitive functioning. Patients with LGG do not have a significantly affected performance status, but they do show serious cognitive impairment. Modern radiotherapy to moderate doses does not lead to significant cognitive impairment within a median of 3 years of treatment, but the results of longer-term studies are yet to be reported. Therefore, cognitive disturbances should probably be attributed to damage by the tumor itself or surgical procedures or to psychological effects.

To our knowledge, no studies have assessed QOL and cognitive performance status (CPS) in patients with suspected but unconfirmed LGG (S-LGG). Uncertainty about the diagnosis may negatively influence CPS and QOL, as has been shown in other patient groups. If this also applies to S-LGG patients, it would be a reason to aim at a definite diagnosis at an early stage. On the other hand, surgical procedures (stereotactic biopsy or resection) necessary to reach this goal may also have a negative impact on CPS and QOL.

The present study was undertaken to determine the CPS and QOL of patients with S-LGG and investigate whether there is a difference in CPS and QOL between S-LGG patients and patients with a proven LGG (P-LGG). We therefore assessed CPS and QOL in 24 S-LGG patients in whom all intervention for the tumor was deferred. These results were com-
pared with data of carefully matched healthy control subjects and with data of patients with P-LGG who underwent subtotal resection or biopsy.

Methods. Patients and control subjects. Patients with S-LGG were recruited from 16 hospitals in the western and central part of the Netherlands. Recruitment of this group took approximately 1 year. The subjects were studied between June 1998 and July 1999. All patients were at least 18 years old and had presented with epileptic seizures without neurologic deficits. All patients showed non-enhancing supratentorial lesions on MRI or CT, without edema or mass effect. Furthermore, none of the patients had radiologic or clinical signs of progression for at least 6 months from the moment of the presumed diagnosis. None of the patients used corticosteroids. All patients gave written informed consent before assessment, and the ethical committee of the University Medical Center Utrecht approved all aspects of the study.

Patients with P-LGG were recruited from a database of 200 patients with histologically proven supratentorial LGG from the “Vrije Universiteit” Medical Center (Amsterdam, the Netherlands). All patients had also presented with epileptic seizures, and none of them had neurologic deficits. They had undergone biopsy or resection at least 6 months previously and had been without progression since then. None of them had been treated with radiotherapy. They were selected to match S-LGG patients on tumor laterality, handedness, educational level, number of years of full-time education, interval between diagnosis and testing, gender, and age. Healthy control patients were recruited from a database of the University of Maastricht (the Netherlands; MAAS study; CPS data)\(^{17}\) and the Netherlands Organization for Applied Scientific Research (TNO; Medical Outcomes Study [MOS] SF-36 Short Form Health Survey QOL data). They were matched with the patients for handedness (CPS data only), educational level, gender, and age.

Performance status. Functional impairment was assessed with the Karnofsky Performance Status (KPS)\(^{18}\) and the Barthel Index.\(^{19}\) Neurologic functioning of patients was rated by means of the Neuropsychologic Functional Status Scale (NFSS).\(^{20}\)

Quality of life. The QOL was assessed with the MOS SF-36 Short-Form Health Survey, which has been translated into the Dutch language.\(^{21,22}\) It is a self-report questionnaire, composed of 36 items, organized into eight multi-item scales assessing physical functioning, physical role functioning, emotional role functioning, pain, vitality, social functioning, mental health, and general health perceptions. A supplementary questionnaire module, the Brain Cancer Module 20 (BCM20), was employed to assess brain tumor-specific QOL issues. The BCM20 contains four multi-item scales assessing visual disorder, communication deficit, motor dysfunction, and uncertainty about the future and seven single items about headache, seizures, drowsiness, hair loss, itching, weakness of the legs, and difficulty in bladder control.\(^{23}\) To assess the self-perceived level of cognitive functioning, we used the Cognitive Functioning Scale (CFS), a six-item scale reflecting problem solving, concentration, confusion, forgetfulness, sustained attention, and slowness.\(^{21}\) The summary “cognitive complaints” score of this scale was used for statistical analysis. Filling in of all questionnaires took \(\approx 45\) minutes.

Cognitive performance status. A neuropsychological test battery was administered to each patient by trained psychometricians, who were supervised by a neuropsychologist. This test battery consisted of the following tests: Visual Verbal Learning Test,\(^{24}\) Working Memory Task,\(^{25}\) Letter–Digit Substitution Test,\(^{26}\) Categoric Word Fluency,\(^{27}\) Concept Shifting Test,\(^{28}\) Stroop Color Word Test,\(^{29}\) and Working Memory Task.\(^{25}\) Summary measures were calculated to detect possible deficits in the domains of attention and concentration, visual–verbal memory, executive function, and psychomotor function. Administration of these tests, which were administered in a fixed order for each patient, took an average of 90 minutes. Because of missing data, 21 subjects of the S-LGG group and 23 subjects of the healthy control group were used in the final analysis of the CPS data.

Statistical analysis. All statistical analyses were carried out with the Statistical Package for the Social Sciences (SPSS version 9.0 for Windows). All tests were two sided, and significance was accepted at the 5% level. Statistical analysis of the matching criteria was done with \(\chi^2\) tests (sex, handedness), Fisher’s exact test (tumor location, anticonvulsants), analysis of variance (ANOVA; age, years of full-time education, interval between diagnosis and testing), and Kruskal–Wallis \(H\) test (educational level). Statistical analysis of tumor diameter, KPS, Barthel Index, and NFSS was done with Mann–Whitney \(U\) tests.

Considerable obliquity of distribution was present in all groups for most of the QOL variables. This obliquity also seemed to account for the inequality of variances among the groups for several QOL variables. Transformations were not helpful to overcome this problem. Therefore, the QOL scales were treated independently and analyzed by means of nonparametric tests. In case of the MOS SF-36, Kruskal–Wallis \(H\) tests were performed to assess whether there were overall differences between patients and control subjects. We used post hoc Mann–Whitney \(U\) tests with Bonferroni adjustment to determine which of the three groups differed from each other. In case of the BCM, we used Mann–Whitney \(U\) tests to demonstrate possible differences between both patient groups. Performances of the patient groups on the CFS (i.e., summary “cognitive complaints” scores) were compared with a one-way univariate ANOVA.

For analysis of the CPS data, all test scores were rescaled to obtain \(z\) scores (standard equivalents) by using the means and the standard deviations of a matched control group as norm scores. The advantage of the use of means and standard deviations of control subjects to obtain \(z\) scores, instead of ratings of the general population, is that the control subjects in our study were matched for demographic characteristics of the patient groups (i.e., sex distribution, handedness, age at test, and educational level). The four summary functional domain scores for each subject were calculated by averaging the \(z\) scores for a similar domain. A multivariate ANOVA was performed, with the four functional domain scores serving as dependent variables and group (i.e., S-LGG patients, P-LGG patients, and healthy control subjects) as independent variables. In case of a significant multivariate effect, univariate analyses were performed to examine overall group
differences for a specific functional domain. These were followed by t-tests with Bonferroni adjustment to determine differences between the three groups.

To investigate possible relationships between cognitive impairment and tumor size, Spearman correlation coefficients were used to correlate individual CPS and QOL data and tumor diameter. Bonferroni corrections were applied to adjust for multiple testing.

Results. Demographic and clinical characteristics. Matching criteria did not differ significantly between the two patient groups. Moreover, we found no significant differences in performance on the KPS, Barthel Index, and NFSS between the two patient groups. High scores for the KPS, Barthel Index, and NFSS were found in both groups, indicating that patients were functionally independent, were able to carry on normal activity, and showed only minor signs or symptoms of disease. Seventeen patients with P-LGG had undergone (sub-)total resection (71%) and six patients stereotactic biopsy (25%); data on the type of operation were not available in one patient. The histologic diagnosis was low-grade astrocytoma (WHO classification) in all patients. Tumor diameter on the latest MR or CT scan before surgery (P-LGG patients) or before testing (S-LGG patients) did not differ significantly between the two groups. Data on tumor diameter were not available in three S-LGG and two P-LGG patients. Eight patients with P-LGG noticed a change in the pattern or frequency of seizures after biopsy or resection. In four of them, seizure frequency decreased; in two of them, there was an increase; and in the other two, the type of seizures changed. At the time of testing, 19 of 24 S-LGG patients (79%) and 15 of 24 P-LGG patients (63%) were using anticonvulsants. The interval between diagnosis and testing did not differ significantly between the two groups (S-LGG patients, 4.4 ± 4.5 years; P-LGG patients, 5.5 ± 4.5 years). Since the end of the study, two patients with S-LGG have been operated on because of clinical deterioration in combination with an enhancing and mass-occupying lesion on MRI; the histologic diagnosis was anaplastic astrocytoma in both.

The table shows the demographic, clinical, and radiographic characteristics of the two patient groups. The two healthy control groups did not differ significantly from the two patient groups on the matching criteria (QOL healthy control subjects: 13 male, mean age 42.8 ± 12.1 years [range 19 to 71 years], mean educational level 4.0; CPS healthy control subjects, 13 male, mean age 42.8 ± 11.6 years [range 25 to 71 years], mean educational level 4.5, 22 right-handed).

Quality of life. Kruskal–Wallis U tests showed overall group differences for the domains of general health perceptions (p < 0.05), vitality (p < 0.005), social functioning (p < 0.05), and mental health (p < 0.05) of the MOS-SF 36. Post hoc Mann–Whitney U tests with Bonferroni adjustment indicated that patients with P-LGG scored worse than normal control subjects on all four scales (i.e., general

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**Table Characteristics of patients with suspected (S-LGG) and proven (P-LGG) low-grade glioma**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>S-LGG patients</th>
<th>P-LGG patients</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of persons</td>
<td>24</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>10/14</td>
<td>15/9</td>
<td>NS*</td>
</tr>
<tr>
<td>Age at test, y; mean ± SD (range)</td>
<td>42.8 ± 12.1 (18–71)</td>
<td>38.2 ± 10.6 (20–55)</td>
<td>NS‡</td>
</tr>
<tr>
<td>Handedness, R/L</td>
<td>21/3</td>
<td>22/2</td>
<td>NS*‡</td>
</tr>
<tr>
<td>Tumor location, R/L</td>
<td>11/13</td>
<td>11/13</td>
<td>NS†</td>
</tr>
<tr>
<td>Frontal</td>
<td>10</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Temporal</td>
<td>10</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Parietal</td>
<td>3</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Occipital</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Midline</td>
<td>—</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Tumor diameter, cm</td>
<td>4.24 ± 2.32 (n = 21)</td>
<td>3.59 ± 1.59 (n = 22)</td>
<td>NS†</td>
</tr>
<tr>
<td>Treatment, stereotactic biopsy/surgery/unknown</td>
<td>—</td>
<td>6/17/1</td>
<td>—</td>
</tr>
<tr>
<td>Educational level¶</td>
<td>5.0</td>
<td>3.5</td>
<td>NS§</td>
</tr>
<tr>
<td>Education, y</td>
<td>12.5 ± 3.6</td>
<td>12.9 ± 4.0</td>
<td>NS‡</td>
</tr>
<tr>
<td>Anticonvulsants, N/Y</td>
<td>5/19</td>
<td>9/15</td>
<td>NS†</td>
</tr>
<tr>
<td>Diagnosis to test interval, y; mean ± SD</td>
<td>4.4 ± 4.5</td>
<td>5.5 ± 3.7</td>
<td>NS‡</td>
</tr>
<tr>
<td>Barthel Index, mean ± SD</td>
<td>20.0 ± 0.2</td>
<td>19.9 ± 0.4</td>
<td>NS§</td>
</tr>
<tr>
<td>Neurologic Functional Status Scale, mean ± SD</td>
<td>1.0 ± 0.0</td>
<td>1.0 ± 0.0</td>
<td>NS§</td>
</tr>
<tr>
<td>Karnofsky Performance Scale, mean ± SD</td>
<td>92.5 ± 9.0</td>
<td>88.7 ± 9.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

* x² test. † Fisher’s exact test. ‡ Analysis of variance. § Kruskal–Wallis H test. ¶ Mann–Whitney U test.  
* Educational level was measured by a Dutch scoring system ranging from unfinished primary education (level 1) to university education (level 8).
health perceptions, \( p < 0.05 \); vitality, \( p < 0.01 \); social functioning, \( p < 0.05 \); mental health, \( p < 0.05 \). Patients with S-LGG scored worse on the general health perceptions domain than normal control subjects \( (p < 0.05) \). With the exception of the physical functioning domain, we found a consistent tendency for patients with P-LGG to score lower on all domains than S-LGG patients, as illustrated in figure 1A. The difference was significant only for the vitality domain. BCM20 data show the same tendency of better scores for patients with S-LGG (figure 1B). Mann–Whitney \( U \) tests showed worse scores for patients with P-LGG than for those with S-LGG on the scale motor dysfunction \( (p < 0.001) \) and the single item measuring difficulty in bladder control \( (p < 0.05) \). We found no significant difference in the score for the dimension future uncertainty between both groups. The CFS data are shown in figure 1C. ANOVA revealed no significant differences between the total sum scores of both patient groups \( (S\text{-LGG}, 18.87 \pm 12.61; P\text{-LGG}, 22.11 \pm 5.57) \). We found no correlation between tumor diameter and the scores on the different QOL subscales.

Cognitive performance status. The multivariate ANOVA showed an overall difference between the groups \( (F [2.65] = 2.51, p < 0.05) \). Univariate analysis indicated group differences for psychomotor functioning \( (F [2.65] = 7.47, p < 0.005) \). No significant group differences were found for the other three functional domains. Post hoc \( t \) tests with Bonferroni adjustment showed that patients...
Figure 2. Mean z scores for patients with proven (P-LGG; filled columns) and suspected (S-LGG; hatched columns) low-grade glioma on the four cognitive domains compared with the scores of a matched group of healthy control subjects. The mean z scores of the healthy control subjects (open columns) were rescaled to zero for all four domains to visualize the relative performance of the two patient groups (mean and SEM; higher score means better performance). *Lower score for P-LGG patients compared with healthy control subjects and S-LGG patients.

Discussion. This study demonstrates that patients with P- or S-LGG have a worse QOL and cognitive status than healthy control subjects and that patients with LGG who underwent resection or biopsy are worse on these measures than patients with S-LGG who were managed conservatively. Patients with S-LGG show significantly better scores for the QOL domains vitality, motor dysfunction, and difficulty in bladder control than patients with P-LGG. Psychomotor functioning was significantly worse for patients with P-LGG.

QOL has become an increasingly important measure in glioma studies. The measurement of QOL in recent studies, however, was more or less restricted to the patient’s functional status or cognitive functioning. Nowadays, it is generally accepted that a more comprehensive set of measures reflecting health status, CPS, and QOL is needed for a more complete assessment. This is again illustrated by our study: Despite an excellent performance status and the absence of neurologic deficits, both groups demonstrate deficits in CPS as well as a reduction in perceived QOL, when measured with an extensive battery of validated tools.

Neuropsychological assessment showed a significantly worse performance on the domain of psychomotor functioning for P-LGG patients, although they had fewer cognitive symptoms on the self-rating CPS. This discrepancy between subjective complaints and objective test results has been described before and indicates that P-LGG patients may not be aware of their cognitive deficits.

The results of our study may have been biased by the selection of patients. Initial treatment of patients with LGG depends on the local neurologist’s and neurosurgeon’s view about the benefit of early, aggressive treatment, the clinical status of the patient, the site and extent of the lesion, and the patient’s preferences. Presumably, patients with more extensive neurologic deficits or nondominant lesions will more frequently undergo early treatment. All our patients presented with epileptic seizures but were otherwise clinically normal. We found no significant difference in the number of patients taking anticonvulsants between both groups. The patients in our study were matched on tumor laterality, but the groups were too small to use tumor location as a supplementary matching criterion. Tumor size, however, did not differ significantly between the two groups and was not correlated to performance on the QOL or CPS subscales. Furthermore, patients who cannot deal with uncertainty about their diagnosis may insist on early treatment. Premorbid patient characteristics determine, among other factors, the capability of patients to deal with this uncertainty. Therefore, age and educational level, which are a relatively accurate indication of premorbid functioning level, were used as matching criteria.

We do not know whether the decreased QOL and cognitive dysfunctioning of patients with P-LGG should be attributed to the surgical procedures. Previous reports at least have not shown clear benefits of the surgical approach in terms of survival time or progression-free interval. Hope of improving epilepsy may be another reason to operate on patients with LGG. In our group of P-LGG patients, however, epilepsy improved in 4 of 24 patients (17%) after the operation but got worse in at least 2 other patients (8%).

Another reason for operation could be that knowing the definite diagnosis would diminish feelings of uncertainty about the future. Patients with glioma are faced with uncertainty about several issues such as length of survival and anxiety about neurologic impairment with disability. Uncertainty about the future, however, did not differ between the two patient groups in our study. Therefore, we conclude that a definite diagnosis does not lead to a large reduction of these feelings.

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