Neurosurgical patterns of care for diffuse low-grade gliomas in Sweden between 2005 and 2015

Louise Carstam, Anja Smits, Peter Milos, Alba Corell, Roger Henriksson, Jiri Bartek Jr, and Asgeir Store Jakola

Department of Neurosurgery, Sahlgrenska University Hospital, Gothenburg, Sweden (L.C., A.C., A.S.I.); Institute of Neuroscience and Physiology, University of Gothenburg, Sahlgrenska Academy, Sweden (L.C., A.S., A.S.J.); Department of Neuroscience, Neurology, Uppsala University, University Hospital, Sweden (A.S.); Department of Neurosurgery, Linköping University Hospital, Sweden (P.M.); Regional Cancer Centre Stockholm Gotland, Stockholm, Sweden (R.H.); Department of Radiation Sciences & Oncology, University of Umeå, Sweden (R.H.); Department of Neurosurgery, Karolinska University Hospital, Stockholm, Sweden (J.B.); Department of Neuroscience and Department of Medicine, Karolinska Institutet, Stockholm, Sweden (J.B.); Department of Neurosurgery, Copenhagen University Hospital Rigshospitalet, Denmark (J.B.); Department of Neurosurgery, St. Olavs University Hospital HF Trondheim, Norway (A.S.J.)

Corresponding Author: Louise Carstam, MD, Primary affiliation: Department of Neurosurgery, Blå Stråket 5, Sahlgrenska University Hospital, 41345 Gothenburg, Sweden. Secondary affiliation: Institute of Neuroscience and Physiology, University of Gothenburg, Sahlgrenska Academy, Box 430, 405 30 Göteborg, Sweden (louisecarstam@hotmail.com).

Abstract

Background. In the last decade, increasing evidence has evolved for early and maximal safe resection of diffuse low-grade gliomas (LGGs) regarding survival. However, changes in clinical practice are known to occur slowly and we do not know if the scientific evidence has yet resulted in changes in neurosurgical patterns of care.

Methods. The Swedish Brain Tumor Registry was used to identify all patients with a first-time histopathological diagnosis of LGG between 2005 and 2015. For analysis of surgical treatment patterns, we subdivided assessed time periods into 2005-2008, 2009-2012, and 2013-2015. Population-based data on patient and disease characteristics, surgical management, and outcomes were extracted.

Results. A total of 548 patients with diffuse World Health Organization grade II gliomas were identified: 142 diagnosed during 2005-2008, 244 during 2009-2012, and 162 during 2013-2015. Resection as opposed to biopsy was performed in 64.3% during 2005-2008, 74.2% during 2009-2012, and 74.1% during 2013-2015 (P = .08). There was no difference among the 3 periods regarding overall survival (P = .11). However, post hoc analysis of data from the 4 (out of 6) centers that covered all 3 time periods demonstrated a resection rate of 64.3% during 2005-2008, 77.4% during 2009-2012, and 75.4% during 2013-2015 (P = .02) and longer survival of patients diagnosed 2009 and onward (P = .04).

Conclusion. In this nationwide, population-based study we observed a shift over time in favor of LGG resection. Further, a positive correlation between the more active surgical strategy and longer survival is shown, although no causality can be claimed because of possible confounding factors.

Key words
diffuse low-grade glioma | glioma/surgery | neurosurgery | patterns of care | treatment outcome
larger observational surgical series relatively uncommon, while surgical trials using randomization of patients are unlikely to be performed because of questionable clinical equipoise.6,7

In lack of consensus, the surgical management of LGG has previously varied among centers.6,8 Currently, the argument frequently favors a more active surgical approach encouraged by growing evidence for the favorable impact of early and maximal safe resection on clinical outcome.6,9–12

To what extent today’s scientific evidence favoring maximal safe resection has resulted in changes of clinical practice remains unknown, but changes in clinical practice are known to occur slowly.13 To address this issue, a nationwide observational, registry-based study of current practice is attractive because registries are equipped to monitor rare diseases. Further, surgical registry-based studies may capture trends in disease characteristics in addition to surgical effectiveness and risks.

The primary aim of this nationwide registry-based study was to explore trends in surgical treatment of LGG patients in Sweden during the last decade (2005-2015). The secondary aims were (i) to investigate differences in patient and disease characteristics in relation to surgical strategy, and (ii) to investigate clinical outcomes over time following different surgical strategies.

Materials and Methods

The Registry

The Swedish Brain Tumor Registry (SBTR) is a regionally based registry covering data from 1999 and onward of adult patients diagnosed with brain tumors. The Swedish health care system is divided into 6 regions that each provide neurosurgical care to patients with tumors in the central nervous system. All regions report data to the SBTR, but the level of coverage from the different regions has varied somewhat over time. In our study, a minimum registration rate of 80% was required to be included in the analysis at any given year for each region to provide representative population-based data. Registration rate was defined as the percentage of diagnoses in the SBTR that corresponds to diagnoses reported to the compulsory National Cancer Registry. For this reason, in the case of 1 region, only data from 2012-2013 were used, while only data from 2009 and onward were used in the case of another region. For the remaining 4 regions, data inclusion covered the entire time period from 2005 to 2015. There have been revisions of the SBTR during the study period, with the latest revision in 2015, and consequently some variables are missing for certain time periods. For further details of the SBTR, see Asklund et al.14

We analyzed data for adults (≥ 18 years) with a first-time diagnosis of supratentorial hemispheric diffuse LGG, defined as WHO grade II astrocytoma, oligoastrocytoma or oligodendroglioma according to the 2007 WHO classification of brain tumors.1 Patients with radiologically suspected LGG only were not included in the present study.

Definition of Variables

In Table 1, the definitions of variables according to the SBTR are provided.

The total number of patients was divided over 3 consecutive time periods (2005-2008, 2009-2012, 2013-2015) with the aim of creating balanced group sizes but also taking into account 2 landmark papers that could influence surgical management during these time periods. In 2008, Smith and colleagues showed that extent of resection of LGGs affected overall survival. In 2012, a comparison between 2 Norwegian centers, 1 favoring early resection and the other favoring biopsy only, showed a large and significant survival benefit for the former.12,15 In addition, we assumed there was a natural delay between the appearance of scientific evidence and subsequent changes in clinical practice, justifying the 3 time periods of 2005-2008, 2009-2012, and 2013-2015. Importantly, these time periods were selected prior to data analysis to avoid data-driven analysis.

Statistics

All analyses were performed with SPSS, version 21.0 (Chicago, IL, USA) or newer. Statistical significance level was set to \( P < .05 \). All tests are 2 sided. Central tendencies are presented as means ± standard deviation, or median and interquartile range if skewed. Categorical data were analyzed with the Pearson chi-square test. Comparisons of continuous variables between time periods were analyzed using analysis of variance when normally distributed or Kruskal-Wallis test if skewed. Overall survival is presented as Kaplan-Meier curves and compared using the log-rank test. For all statistical tests, the date of diagnosis was defined as the date of surgery.

Ethics Statement

This study was approved by the regional ethical committee in Västra Götaland region (Dnr: 702–16).

Results

Demographic Data

A total number of 548 patients with LGGs were included, 142 patients (26% of total in entire study period) diagnosed during the time period 2005-2008, 244 patients diagnosed during 2009-2012 (44% of total in entire study period), and 162 patients (30% of total in entire study period) diagnosed during 2013-2015.

Temporal Trends

Crude incidence was calculated for the 3 time periods using population data from Statistics Sweden (Swedish public authority on statistics, www.scb.se, accessed February 20, 2018). The incidence as calculated from our cases was 0.78/100 000 in 2005-2008, 0.94/100 000 in 2009-2012, and 0.79/100 000 in 2013-2015.
Patient, tumor, and treatment characteristics are presented in detail in Table 2.

As shown, the more recently treated patients more often had intracranial pressure (ICP)-related preoperative symptoms, lower performance status, and longer time intervals between radiological diagnosis and surgery. In addition, oligodendroglial histology was more frequent. Postoperative complications were more frequent in more recent time periods, but hospital stay in neurosurgical departments was shorter and patients were less often selected for immediate postoperative adjuvant oncological treatment. Tumor resection (as opposed to biopsy) in the different time periods was performed in 64.3% in 2005-2008, 74.2% in 2009-2012, and 74.1% in 2013-2015 (P = .08). There was no survival difference between time periods (Fig. 1).

Sensitivity Analysis

To rule out that the results were caused by practice differences among different regions, we performed a sensitivity analysis leaving out the 2 regions that had not provided complete data covering all 3 time periods. As illustrated in Supplementary Table 1, the sensitivity analysis did not significantly alter the main findings presented in Table 2. However, in this analysis we found that resection was preferred over biopsy in 90/140 patients (64.3%) in 2005-2008, 151/191 patients (77.4%) in 2009-2012, and 92/122 patients (75.4%) in 2013-2015 (P = .02).

Based on the findings in the sensitivity analysis, we also analyzed survival in the 4 centers contributing data during the entire study period. As shown in Fig. 2, this

| Table 1 Definitions of Variables |
|----------------------------------|
| **Variable**                     | **Definition**                          |
| Age                              | Years at time of diagnosis              |
| Sex                              | Male or female                          |
| Symptoms at Diagnosis            | • Asymptomatic (yes/no)                 |
|                                  | • Focal deficit (yes/no)                |
|                                  | • Seizure (yes/no)                      |
|                                  | • ICP related (yes/no; exemplified with H/A and cognitive deficit) |
| Performance Status*              | 0-4                                      |
| Date of Imaging Diagnosis        | dd.mm.yyyy                               |
| Main Location According to ICD   | C71.1 (frontal), C71.2 (temporal), C71.3 (parietal), C71.4 (occipital), C71.8 (corpus callosum or overlapping sites), C71.9 (not specified) |
| Laterality                       | Left/right/bilateral                    |
| Multifocal                       | Yes/no                                   |
| Largest Diameter of Tumor        | < 4 cm                                   |
|                                  | 4-6 cm                                   |
|                                  | > 6 cm                                   |
| MRI Preop                        | Yes/No                                   |
| Type of Surgery                  | Biopsy or resection                      |
| Date of Surgery                  | dd.mm.yyyy                               |
| Type of Resection (Surgeon Impression or Image Based) | Partial or radical resection |
| Complication Within 30 Days      | Yes/No                                   |
| New Focal Deficit Within 30 Days | Yes/No                                   |
| New Seizure Within 30 Days       | Yes/No                                   |
| Any Infection Within 30 Days     | Yes/No                                   |
| Any VTE Within 30 Days           | Yes/No                                   |
| Any Hematoma Within 30 Days      | Yes/No                                   |
| Complication Leading to Reoperation Within 30 Days | Yes/No                                   |
| Date of Discharge from Neurosurgical Department | dd.mm.yyyy |
| Histopathology                   | SNOMED codes                             |
|                                  | Astrocytoma: 94 003, 94 203, 94 113, 94 103 |
|                                  | Oligoastrocytoma: 93 823b                |
|                                  | Oligodendroglioma: 94 503                |
| Planned oncological treatment    | Yes/No                                   |

**Abbreviations:** H/A, headache; ICD, International Classification of Diseases; ICP, intracranial pressure; MRI, magnetic resonance imaging; preop, preoperatively; SNOMED, Systemized Nomenclature of Medicine-Clinical Terms; VTE, venous thromboembolism; WHO, World Health Organization.

*Performance status according to WHO.

For oligoastrocytoma WHO grade II and oligoastrocytoma grade III, the SNOMED code is similar (92 823).
Table 2  Baseline Characteristics and Factors Related to Surgical Treatment

|                     | 2005-2008 n = 142 | 2009-2012 n = 244 | 2013-2015 n = 162 | P-Value |
|---------------------|-------------------|-------------------|-------------------|---------|
| **Age, Mean (SD)**  | 47.0 (15.7)       | 47.0 (14.4)       | 45.2 (15.2)       | .43     |
| **Female, n (%)**   | 73 (51.4)         | 108 (44.3)        | 64 (39.5)         | .12     |
| **Tumor Size, n (%)** | N = 116         | N = 241           | N = 126           | .73     |
| < 4 cm              | 51 (44.0)         | 96 (39.8)         | 47 (37.3)         |         |
| 4-6 cm              | 46 (39.7)         | 95 (39.4)         | 50 (39.7)         |         |
| > 6 cm              | 19 (16.4)         | 50 (20.7)         | 29 (23.0)         |         |
| **MRI Preop, n (%)** | 132 (93.6)        | 236 (96.7)        | 157 (96.9)        | .25     |
| **Main Lobe Involved, n (%)** | 66 (46.5) | 127 (52.0)        | 94 (58.0)         | .19     |
| **Frontal**         | 46 (39.7)         | 95 (39.4)         | 50 (39.7)         |         |
| **Temporal**        | 19 (16.4)         | 50 (20.7)         | 29 (23.0)         |         |
| **Parietal**        | 23 (17.8)         | 46 (18.9)         | 34 (21.0)         | .51     |
| **Occipital**       | 10 (7.8)          | 46 (18.9)         | 34 (21.0)         |         |
| **Overlapping Sites** | 5 (3.5)         | 10 (4.1)          | 5 (3.1)           |         |
| **Not Specified**   | 10 (7.0)          | 14 (5.7)          | 8 (4.9)           |         |
| **Laterality, n (%)** | N = 138         | N = 242           | N = 160           | .19     |
| **Left**            | 72 (52.2)         | 120 (49.6)        | 85 (53.1)         |         |
| **Right**           | 65 (47.1)         | 110 (45.5)        | 66 (41.3)         |         |
| **Bilateral**       | 1 (0.7)           | 12 (5.0)          | 9 (5.6)           |         |
| **Multifocal, n (%)** | 15 (10.6)       | 20 (8.2)          | 23 (14.2)         | .16     |
| **Asymptomatic, n (%)** | N = 141        | N = 243           | N = 157           | .66     |
| **Focal Deficit, n (%)** | 44 (31.7)      | 92 (38.0)         | 64 (41.8)         | .19     |
| **Seizures, n (%)** | 79 (58.1)         | 160 (66.1)        | 99 (64.7)         | .84     |
| **ICP Related, n (%)** | 26 (22.8)       | 51 (21.1)         | 49 (32.0)         | .04     |
| **Performance status, n (%)** | N = 140      | N = 238           | N = 157           | .03     |
| 0                   | 88 (62.9)         | 143 (60.1)        | 69 (43.9)         |         |
| 1                   | 28 (20.0)         | 62 (26.1)         | 48 (30.6)         |         |
| 2                   | 17 (12.1)         | 25 (10.5)         | 31 (19.7)         |         |
| 3                   | 5 (3.6)           | 6 (2.5)           | 6 (3.8)           |         |
| 4                   | 2 (1.4)           | 2 (0.8)           | 3 (1.9)           |         |
| **Weeks from Imaging to Surgery, Median (IQR)** | 4 (2-8)        | 4 (2-12)          | 7 (3-15)          | .002    |
| **Surgery Performed, n (%)** | N = 140       | N = 244           | N = 158           | .08     |
| **Biopsy**          | 50 (35.7)         | 63 (25.8)         | 41 (25.9)         |         |
| **Resection**       | 90 (64.3)         | 181 (74.2)        | 117 (74.1)        |         |
| **Radical Resection**, n (%) | N = 90       | N = 181           | N = 117           | .02     |
| **Histopathology, n (%)** | 90 (63.4)    | 112 (45.9)        | 71 (43.8)         | .001    |
| Astrocytoma         | 35 (24.6)         | 19 (7.8)          | 22 (13.6)         |         |
| Oligoastrocytoma    | 17 (12.0)         | 113 (46.3)        | 69 (42.6)         |         |
| Oligodendroglioma   | 23 (16.2)         | 64 (26.2)         | 46 (28.4)         | .03     |
| Postop Complication, n (%) | 16 (17.8)     | 38 (16.5)         | 34 (21.0)         | .51     |
| Postop New Neurological Deficit, n (%) | N = 90       | N = 231           | N = 162           |         |
post-hoc analysis demonstrates that survival improved in the 2 recent time periods. This improvement in survival over time was observed without any increase of patients selected for immediate adjuvant oncological therapy. To exclude the impact of lead-time bias due to upfront surgery, we also analyzed survival from the time point of radiological diagnosis but this did not alter the results (data not shown, log-rank $P = .02$).

**Biopsy Only vs Resection**

We also explored differences between patients who had undergone a biopsy ($n = 154$) compared with those who had undergone a resection ($n = 388$) without stratification into different time periods. The result of this analysis is presented in detail in Table 3. To summarize, patients undergoing biopsy were older, more often had bilateral or multifocal LGGs, and more seldom frontal or temporal tumor location, more focal deficits, and lower performance status. In the biopsy group there were also more astrocytomas, fewer complications, shorter hospital stays in neurosurgical units, and impaired 1-year survival. Survival analysis comparing biopsy and resection showed a median survival of 4.5 years (95% confidence interval 2.2-6.8) following biopsy while median survival was not reached for the group with resection ($P < .001$) (Fig. 3).

**Discussion**

In this nationwide registry-based study spanning from 2005 to 2015, we demonstrated a trend, albeit nonsignificant, toward more resections during the more recent time periods. Interestingly, the analysis that included only centers contributing data for all time periods showed that surgical resection was more common from 2009 and onward.
Another notable finding was a conspicuous increase over time in the proportion of LGGs with oligodendroglial histology. If this indeed represents a true increase, and not just an artifact in classification, it would naturally influence survival. A similar shift in classification in favor of oligodendroglial tumors at the expense of pure astrocytic tumors has, however, been described previously in other studies, albeit mostly earlier than in our material. Because the histological tumor classification used in the SBTR, as in the abovementioned studies, is based solely on histological appearance without incorporation of the molecular tumor status, the classification is vulnerable to interobserver variability. Also, no central review of pathology was possible in this registry-based study. Altogether, we believe it is unlikely that the observed increase in oligodendroglial tumors reflects a true shift in histological subtypes in a population-based cohort like the one presented in this study. A more plausible explanation is that an increased awareness of oligodendroglial tumors, because of their favorable therapeutic response and prognosis, is lying behind this classification drift.

The secondary aim of this study was to explore survival, and we found no statistically significant differences in survival among the 3 time periods. However, post hoc analysis of data from the 4 centers that provided data from the entire study period revealed an improvement in survival during the most recent period. We think that the increased survival during recent years is unlikely to be explained by lead-time bias due to earlier radiological diagnosis (more widespread MRI) since there was no observed increase of asymptomatic patients (eg, incidental LGG) in the later time period. Thus, although no causality can be claimed from an observational study, we believe that the longer survival may reflect the observed change in surgical strategy in the corresponding time periods, consonant with the literature indicating that surgical resection improves survival.

Apart from survival, functional outcome is another very important factor of risk-benefit of LGG surgery. The observed postoperative neurological deficits in approximately 20% of all patients may seem unacceptable, but it should be noted that the SBTR neither discriminates immediate transient deficits from permanent ones, nor minor from major deficits. In light of this, the results on postoperative outcome presented here may well be comparable to the literature, in which the frequency of “any deficit” at early assessment was reported 30.3%. Nevertheless, the occurrence of postoperative neurological deficits is an obvious risk of a more active surgical attitude and this important aspect needs to be studied in greater detail by methods directly evaluating function (eg, neuropsychology, functional tests) and patient-reported outcomes.

Not surprisingly, we demonstrate that the selection of patients for either biopsy or resection is not random, bearing in mind that not all patients are suitable for major surgery. Hence, case series comparing the impact of surgical treatment on outcome are seemingly studies of selection bias rather than of treatment effectiveness. Accordingly, we found an accumulation of negative preoperative prognostic factors in the group of patients selected for biopsy. In the biopsy group, there were also 78% astrocytomas compared to 39% in the resection group, although this...
| Differences Between Patients Undergoing Initial Biopsy or Resection (n = 542, 6 Cases Missing) |
|---------------------------------------------------------------|
| Biopsy (N = 154) | Resection (N = 388) | P-Value |
| Age, Mean (SD) | 53.0 (14.9) | 44.0 (14.2) | <.001 |
| Female, n (%) | 76 (49.4) | 168 (43.3) | .20 |
| Year of Treatment, Median (IQR) | 2010 (2008-2013) | 2011 (2009-2013) | .09 |
| Tumor Size, n (%) | N = 130 | N = 349 | .10 |
| < 4 cm | 59 (45.4) | 134 (38.4) | .10 |
| 4-6 cm | 41 (31.5) | 148 (42.4) |
| > 6 cm | 30 (23.1) | 67 (19.2) |
| Main Lobe Involved, n (%) | | | <.001 |
| Frontal | 63 (40.9) | 219 (56.4) |
| Temporal | 29 (18.8) | 94 (24.2) |
| Parietal | 24 (15.6) | 47 (12.1) |
| Occipital | 8 (5.2) | 12 (3.1) |
| Overlapping Sites | 8 (5.2) | 6 (1.6) |
| Laterality, n (%) | N = 149 | N = 385 | <.001 |
| Left | 77 (51.7) | 195 (50.6) |
| Right | 58 (38.9) | 182 (47.3) |
| Bilateral | 14 (9.4) | 8 (2.1) |
| Multifocal, n (%) | N = 349 | 23 (5.9) | N = 387 | <.001 |
| Bilateral OR Multifocal, n (%) | 38 (24.7) | 25 (6.5) | N = 387 | <.001 |
| Asymptomatic, n (%) | 7 (5.0) | 29 (7.8) | N = 374 | .27 |
| Focal Deficit, n (%) | 76 (50.0) | 123 (32.7) | N = 376 | <.001 |
| Seizures, n (%) | 86 (61.0) | 246 (67.6) | N = 364 | .16 |
| ICP-Related Symptoms, n (%) | 34 (24.3) | 90 (24.8) | N = 363 | .91 |
| Performance Status, n (%) | N = 149 | N = 380 | .001 |
| 0 | 67 (45.0) | 229 (60.3) |
| 1 | 44 (29.5) | 93 (24.5) |
| 2 | 24 (16.1) | 48 (12.6) |
| 3 | 11 (7.4) | 6 (1.6) |
| 4 | 3 (2.0) | 4 (1.1) |
| Weeks from Imaging to Surgery, Median (IQR) | 4 (2.8-75) | 5 (3-12) | N = 384 | .10 |
| Histopathology, n (%) | | | <.001 |
| Astrocytoma | 120 (77.9) | 152 (39.2) |
| Oligoastrocytoma | 11 (7.1) | 171 (44.1) |
| Oligodendroglioma | 23 (14.9) | 65 (16.8) |
| Postop Complication, n (%) | 14 (9.1) | 117 (30.2) | <.001 |
| Postop New Neurological Deficit, n (%) | 8 (6.2) | 78 (22.5) | N = 347 | <.001 |
| Postop New Seizure, n (%) | 1 (0.8) | 10 (2.9) | N = 346 | .17 |
| Postop Infection, n (%) | 3 (2.1) | 11 (3.0) | N = 361 | .57 |
| Postop VTE, n (%) | 3 (2.1) | 7 (1.9) | N = 361 | .89 |
difference may be somewhat influenced by the more common resections in recent time periods during which LGGs were more frequently classified as oligodendrogliomas. While the 30-day mortality was similar in the 2 groups, a marked difference was observed in 1-year mortality: 26.8% following biopsy and 5.4% following resection. Thus, 1-year mortality was almost 5 times higher in the biopsy group but, as argued previously, this probably related to the multiple negative preoperative prognostic factors in this group.

There have been limited data on patterns of surgical care of LGGs during the recent decade; however, some data from earlier time periods can be used for comparison.

In a large North American registry-based study of astrocytomas (1999-2010), no consistent change over time in surgical strategy could be seen when measured as the likelihood for undergoing gross total resection (GTR).26 In a similar study based on the same registry (The Surveillance, Epidemiology, and End Results program), the survival and surgical care for patients with oligodendrogliomas was analyzed over time (1999-2012).27 The survival benefit over time observed in WHO grade III oligodendrogliomas was not seen for WHO grade II oligodendrogliomas. The pattern of surgical practice for WHO grade II oligodendrogliomas was largely unaltered during 1999-2008, but thereafter the proportion of GTRs decreased. The discordance between these studies and our study might be due to their somewhat earlier time setting. There is also a difference in categorization of surgical strategy whereby biopsies only are not separated from subtotal resections, when in fact the latter may often be synonymous with what the surgeon perceives as maximal safe resection.

**Limitations of this Study**

Our study has several limitations related to the observational design. In the SBTR, only tumors verified by histology are included. Thus, the true incidence of LGGs in the different regions is unknown. Radiological suspicion of an LGG does not automatically warrant surgical intervention, as this decision may depend on severe comorbidity, old age, critically located tumors or patients’ specific wishes. Another limitation is the lack of molecular data on the tumor subtypes, as a result of the older WHO classification that was used during the inclusion period. To reduce interobserver variability, a central review of pathology would be optimal, although this was not feasible in this registry-based study.

At the time of the study, the SBTR still lacked more detailed information on the type and the date of postoperative adjuvant treatment. As a result, we considered only whether patients were “high risk” and thus selected for immediate oncological treatment (a decision typically made at the first multidisciplinary team conference when histopathological diagnosis was available), but we cannot...
account for the type of treatment in terms of radiotherapy, chemotherapy or combined radiochemotherapy. However, the national guidelines concerning adjuvant treatment were not changed until after the inclusion period as a result of the study by Buckner et al from 2016. In sum, this argues against a significant impact of adjuvant therapy on the survival benefit observed in the present study.

Further shortcomings of this study include the variability of registration coverage over time and across regions, which we addressed in the post-hoc analysis. Strengths include the population-based data acquired through standardized, consecutive, and prospective reporting.

Conclusion

The approach to surgical management of LGGs in Sweden during the past decade seems to have drifted in favor of more active strategy, even for patients with lower performance status and presumably more complex tumors. This more active surgical strategy may be related to the observed improved survival during recent years.

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