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Clinical Study

Surgical strategies in low-grade gliomas and implications for long-term quality of life

Asgeir S. Jakola^{a,b,c,d,*}, Geirmund Unsgård^{a,c,d}, Kristin S. Myrmed^e, Roar Kloster^f, Sverre H. Torp^g,
Lisa M. Sagberg^d, Sigurd Lindal^e, Ole Solheim^{a,c,d}

^a Department of Neurosurgery, St. Olav's University Hospital, N-7006 Trondheim, Norway

^b MI Lab, Norwegian University of Science and Technology, Trondheim, Norway

^c Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway

^d National Centre for Ultrasound and Image Guided Therapy, Trondheim, Norway

^e Department of Pathology, University Hospital of Northern Norway, Tromsø, Norway

^f Department of Ophthalmology and Neurosurgery, University Hospital of Northern Norway, Tromsø, Norway

^g Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway

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ABSTRACT

Reports on long-term health related quality of life (HRQL) after surgery for World Health Organization grade II diffuse low-grade gliomas (LGG) are rare. We aimed to compare long-term HRQL in two hospital cohorts with different surgical strategies. Biopsy and watchful waiting was favored in one hospital, while early resections guided with three-dimensional (3D) ultrasound was favored in the other. With a population-based approach 153 patients with histologically verified LGG treated from 1998–2009 were included. Patients still alive were contacted for HRQL assessment ($n = 91$) using generic (EQ-5D; EuroQol Group, Rotterdam, The Netherlands) and disease specific (EORTC QLQ-C30 and BN20; EORTC Quality of Life Department, Brussels, Belgium) questionnaires. Results on HRQL were available in 79 patients (87%), 25 from the hospital that favored biopsy and 54 from the hospital that favored early resection. Among living patients there was no difference in EQ-5D index scores ($p = 0.426$). When imputing scores defined as death (zero) in patients dead at follow-up, a clinically relevant difference in EQ-5D score was observed in favor of early resections ($p = 0.022$, mean difference 0.16, 95% confidence interval 0.02–0.29). In EORTC questionnaires pain, depression and concern about disruption in family life were more common with a strategy of initial biopsy only ($p = 0.043$, $p = 0.032$ and $p = 0.045$ respectively). In long-term survivors an aggressive surgical approach using intraoperative 3D ultrasound image guidance in LGG does not lower HRQL compared to a more conservative surgical approach. This finding further weakens a possible role for watchful waiting in LGG.

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1. Introduction

Surgical treatment of diffuse World Health Organization (WHO) grade II low-grade gliomas (LGG) varies greatly between centers [1]. We recently published a population-based comparative study on surgical management in LGG [2]. A significant survival benefit was demonstrated if treated at a centre favoring early surgical resection as opposed to biopsy and watchful waiting. Most authors now argue in favor of early resections [2–5]. However, the balance between improving survival by extensive resection and inducing deficits is delicate. One may worry that an aggressive surgical

strategy, although leading to improved survival, may be offset by significantly reducing the patient's health related quality of life (HRQL) [6]. Patient reported HRQL may be a key to an unbiased assessment of patient symptoms and functions, a prerequisite to settling the controversy concerning surgical management.

We aimed to study possible differences in long-term overall HRQL between parallel cohorts with supratentorial LGG treated at two centers with different surgical strategies and to explore various domains in the relevant questionnaires.

2. Methods

The background and details concerning patient selection and the regional differences in surgical practice have been described

* Corresponding author. Tel.: +47 7257 5567.

E-mail address: asgeir.s.jakola@ntnu.no (A.S. Jakola).

thoroughly in a previous publication [2]. Briefly, in a socialized health care system with a regional referral practice, two neurosurgical centers that were exclusive providers in adjacent regions were compared. One hospital favored initial biopsy and watchful waiting. The other hospital favored early resection guided with a three-dimensional (3D) ultrasound based neuronavigation system (SonoWand; SonoWand AS, Trondheim, Norway).

2.1. Histopathological review

The review process has been described in detail in a previous publication [2]. Adults ≥ 18 years with histologically verified supratentorial WHO grade I and II tumors diagnosed between 1998 and 2009 were screened. A blinded histopathological review was performed and the only inclusion criterion was histopathological verification of a diffuse grade II glioma (that is, LGG) [7]. There were no exclusion criteria.

2.2. Study variables

Patient and treatment characteristics were retrospectively retrieved from medical records. Anatomical location was divided into non-eloquent, intermediate and eloquent [8]. To register and adjust for validated prognostic factors we used the Pignatti score [9].

2.3. Follow-up

All patients were followed until death or until 11 April 2011. Patients still alive were requested by mail to participate in the HRQL part of the study. Non-responders received one reminder by mail. Patients not responding after one reminder by mail were contacted by telephone for an interview.

2.4. HRQL

2.4.1. The EuroQol 5D

EQ-5D (EuroQol Group, Rotterdam, The Netherlands) is a generic and preference-weighted measure of HRQL that is validated in the Norwegian population [10,11]. Five dimensions of HRQL are scored: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with three possible answers to each dimension. This results in 243 different possible health states which are transformed into an index value [12]. EQ-5D index values range from -0.594 to 1 , where 1 corresponds to perfect health. With this scoring of the EQ-5D index, a common but perhaps controversial meaning of the value of zero is suggested, since zero equals death. Negative values are considered to be worse than death. We used an unconventional approach with imputing zero in all patients who were dead at end of follow-up since the index value could be interpreted with this approach. Although potentially controversial this approach could enable researchers to weigh a patient's HRQL against survival in one single measure. A visual analogue scale (EQ-VAS) where patients rate their current health state on a line ranging from 0 to 100 (worst to best imaginable health) forms the second part of the EuroQol questionnaire.

2.4.2. EORTC QLQ-c30

QLQ-C30 (EORTC Quality of Life Department, Brussels, Belgium) consists of cancer specific functional and symptom scales in addition to a scale on overall health and HRQL [13]. Possible answers range from 1 – 4 , where 1 is described as “not at all”, 2 as “a little”, 3 as “quite a bit”, and 4 as “very much”. This applies for all but two questions on global health status where the scale ranges from 1 – 7 . All domains are converted to a score (0 – 100). The questionnaire consists of one global HRQL scale, five functional scales (physical,

role, emotional, cognitive and social) and nine symptom scales/items (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial). A high score represents a high global HRQL and level of functioning, but in the symptom scales/items a higher score indicates more symptoms.

2.4.3. EORTC QLQ-BN20

This questionnaire is specifically designed for brain cancer patients [14]. Possible answers range from 1 – 4 , where 1 is described as “not at all”, 2 as “a little”, 3 as “quite a bit”, and 4 as “very much”. The QLQ-BN20 (EORTC Quality of Life Department) consists of four domains (future uncertainty, visual disorder, motor dysfunction, and communication deficit). Scores in the domains are converted to a scale (0 – 100) where higher score represents worse HRQL. The questionnaire also consists of seven single items (headache, seizures, drowsiness, hair loss, itchy skin, weakness of legs, and bladder control).

2.5. Statistical analysis

All analyses were done with Predictive Analytics SoftWare (SPSS, Chicago, IL, USA), version 18.0. End-points were analyzed with respect to regional treatment policy and not actual treatment (that is, direct regional comparisons including patients treated with resection at hospital favoring biopsy and *vice versa*) unless otherwise specified. Central tendencies are presented as mean $\pm$ standard deviation, or median $\pm$ interquartile range when data was skewed. Independent samples *t*-test was used for comparisons of means. For descriptive presentation of the questions in the EORTC questionnaires we dichotomized the items (“not at all” and “a little” against “quite a bit” and “very much”). However, when we analyzed categorical data with the chi-square test we used the original score and not the dichotomized values. We explored all HRQL subscales. Statistical significance level was set to $p < 0.05$, and not adjusted for multiple analyses since we were especially interested in any detrimental effects of surgery that could be hidden by a more conservative analytic strategy. All tests were two-sided.

2.6. Handling of missing HRQL data

For missing values within multi-item domains in the EORTC questionnaires we imputed the mean for that patient in the missing item if at least half of the items were present. In cases where the mean would be in the middle of scores, we consequently chose the score representing more symptoms or lower function. In multi-item domains with more than half missing we simply kept it as missing ($n = 2$, “future uncertainty” and “global HRQL”). For missing single-items we simply kept them as missing. In total there were seven imputations in the QLQ-C30 questionnaire and three in the BN20 questionnaire. One patient who otherwise scored well on HRQL (EQ-5D index value 1.0) forgot to fill out the entire BN20 module, thus there were 78 respondents in this module, as we registered that questionnaire as missing. The QLQ-C30 ($n = 79$) and BN20 ($n = 78$) each had four missing single values that were not imputed.

In addition one entire questionnaire and one single domain were missing in the EQ-5D (six domains in total). In these cases we imputed the values based on the EORTC questionnaires. Also, five missing EQ-VAS were found from responders ($n = 79$) and imputed based on EQ-5D domains and global function in QLQ-C30 questionnaire.

2.7. Ethics and approvals

The study protocol was approved by the Regional Ethical Committee for Health Region Mid-Norway (reference 2010-3231) and

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