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# Patient-reported quality of life in grade 2 and 3 gliomas after surgery, can we do more?<sup>★</sup>

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#### ABSTRACT

Objective: To study the effects of surgery and the explanatory variables for patient-reported health-related quality of life (HRQoL) after brain tumor surgery for astrocytomas and oligodendrogliomas grade 2 and 3.

Methods: Patients operated for an astrocytoma or an oligodendrogliomas, grade 2 or 3, at the Department of Neurosurgery, Uppsala, Sweden, 2016–2021, were included. HRQoL was assessed with RAND-36 preoperatively and 4 months postoperatively. Demographic, tumor, and treatment data were prospectively collected.

Results: Sixty-two patients were included, 34 with an astrocytoma and 28 with an oligodendroglioma. Physical function, role physical, general health, vitality, and social functioning decreased significantly (p-values < 0.01) 4 months after surgery, whereas bodily pain, role emotional, and mental health remained unchanged. In Spearman analyses, younger patients deteriorated more in role physical, females worsened less often in general health but more often in social functioning than males, a higher level of education correlated with a more pronounced drop in social functioning, and a greater extent of resection corresponded to a worsening in physical function post-operatively (p-values < 0.05).

Conclusions: Several HRQoL domains deteriorated after glioma surgery in specific groups of patients, particularly general health, vitality, physical, and social functions. This was only weakly explained by surgical variables. Specific groups of patients may need closer follow-ups and tailored support/rehabilitation to detect and address these HRQoL deteriorations.

#### 1. Introduction

Diffuse gliomas grade 2 and 3 affect young patients and are often detected after new-onset seizures in otherwise asymptomatic patients. With an initial conservative approach, the disease is usually radiologically stable the first years after diagnosis [1], but the tumor inevitably becomes malignant, and the patient eventually dies after 6–7 years [2, 3]. Diffuse gliomas are infiltrative tumors, often located in or near eloquent cortical and subcortical brain areas related to language, sensorimotor, and visual functions [4]. Due to the risk of inflicting neurological injury by surgery in relatively asymptomatic patients, previous management favored a watch-and-wait approach until the glioma became malignant [5]. However, in recent years, there has been a paradigm shift towards early, maximal resection, since a greater extent of resection (EOR) increases survival with several years [3,5–8]. Patients with diffuse gliomas nowadays live around 15 years with optimal management with maximal surgical resection and oncological

treatments [7], but in addition to survival, it is important to maintain a high health-related quality of life (HRQoL). The concept of onco-functional balance takes into account the gain in survival with increased EOR and the concurrent risk of neurological sequelae [9,10]. The use of intraoperative neurophysiology and functional monitoring during awake surgery [7] have led to that brain tumors in eloquent brain areas may be removed with a greater EOR with less injury to the monitored function [11,12]. However, despite the surgical technique, functional preservation cannot always be guaranteed [13] as the monitoring of specific functions is always limited by technical, spatial, and time constraints.

Most glioma research has focused on the length of survival, but to optimize the onco-functional balance, there is a need to better understand the factors responsible for patient-reported outcomes, including HRQoL [14–18]. This research is invaluable for better preoperative patient information, shared decision-making, and to reveal potentially negative effects of surgery in patients who experience no focal

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neurological deficits, but still do not recover well. In the current study, the primary aim was to investigate the reported changes in HRQoL after glioma surgery and the secondary aim was to investigate the explanatory variables for HRQoL improvement/decline.

#### 2. Materials and methods

#### 2.1. Patients

Adult patients ( $\geq$  18 years of age) with a suspected diffuse glioma grade 2 and 3 operated at the Department of Neurosurgery, Uppsala University Hospital, during the period 22 August 2016–1 May 2021 were eligible for inclusion. Out of 123 patients who consented to take part in the study, those 62 with an astrocytoma (IDH mutation without 1p19q co-deletion) or oligodendroglioma (IDH mutation in combination with 1p19q co-deletion), grade 2 or 3, and with both pre- and post-operative HRQoL data were included. Sixty-one patients were excluded, 29 due to another diagnosis (astrocytoma grade 4/glioblastoma (n = 20), ganglioglioma (n = 3), dysembryoplastic neuroepithelial tumor (n = 1), neurocytoma (n = 1), and unclear/other diagnosis than brain tumor (n = 4)), 16 patients due to missing preoperative HRQoL data, and 16 patients due to missing postoperative HRQoL data.

# 2.2. Demography, surgery, postoperative care, adjunct treatments, and follow-up

Demographic and treatment data were collected from the medical records. Co-morbidities were assessed according to the Charlson co-morbidity index (CCI) [19].

The intent of the tumor surgery was maximal, safe resection. Tumor resection was done through craniotomy and was based on microsurgical technique, guided by neuronavigation and intraoperative ultrasound [13]. Intraoperative neurophysiological monitoring of motor function was performed if the tumor was located in proximity to the motor cortex and/or pathways. Awake surgery was done if the tumor was close to eloquent areas related to speech function or other cognitive domains as previously described by our group [20]. Adjunct oncological treatment (radio- and/or chemotherapy) was given to some patients the first months after surgery, based on multidisciplinary conference decisions, in accordance with the European Association of Neuro-Oncology (EANO) guidelines [6]. The patients were followed by a neurosurgeon, speech therapist, and neuropsychologist approximately at 3–5 months postoperatively.

#### 2.3. Radiology

A magnetic resonance imaging (MRI) scan was done prior to surgery and postoperatively within 48 h. A conventional MRI protocol consisting of T2W, T2-FLAIR (in low slice thickness, 1 mm), diffusion sequences, and pre- and post-contrast T1W were acquired, according to our standard glioma imaging practice [21]. Morphological MRI sequences (volumetric T1W, T2W, and T2-FLAIR) were used to assess brain tumor location and radiological features [21]. T2 turbo spin echo or T2-FLAIR images in Vue picture archiving and communication system (PACS) software (version 11.1.0, Carestream Health Inc., Rochester, NY) were used to segment the lesions both pre- and postoperatively with the aid of a semiautomatic method (Livewire Algorithm) [22].

Diffusion tensor imaging (DTI) reconstructions were used to analyze tumor location and eloquence. DTI image acquisition and reconstruction technique has been described in detail in previous studies by our group [20]. The tumors were considered eloquent in case of infiltration of the white matter pathways in the "minimal common brain" (inferior fronto-occipital fascicle (IFOF), arcuate fasciculus (AF), corticospinal tract (CST), and optic radiation (OR)) [23,24].

#### 2.4. Health-related quality of life assessment

RAND-36 is a generic measure for HRQoL. Two versions are available [25], of which RAND-36 Item health survey is a public domain form and SF-36 Item health survey is a copyrighted, commercially distributed form. RAND-36 and SF-36 differ only in minor scoring procedures and both are available in Swedish [25]. RAND-36 includes 36 questions that concern eight different HRQoL domains; physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). The scales range from 0 (worst possible) to 100 (best possible). The RAND-36 questionnaire was filled in within a few weeks to one day prior to surgery and approximately 3–5 months postoperatively. The follow-up time point was chosen as a balance to give a reasonable time for neurological recovery, but not so late that tumor recurrence would have taken place.

#### 2.5. Statistical analysis

Nominal variables were described as numbers or proportions and ordinal or continuous variables were described as medians (interquartile range (IQR)). The difference in the RAND-36 variables pre- and post-operatively surgery was calculated with the Wilcoxon signed-rank test. The RAND-36 variables pre- and postoperatively were also compared depending on if it was the first tumor resection or due to recurrence, with the Mann-Whitney U-test. The explanatory variables (demography, tumor characteristics, and treatments) for the RAND-36 variables that had significantly changed after surgery were analyzed with the Spearman rank correlation test or the Kruskal-Wallis test.

A p-value < 0.05 was considered statistically significant. The statistical analyses were performed in SPSS version 27 (IBM Corp, Armonk, NY, USA).

#### 2.6. Ethics

All procedures performed in the study were in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments. The study was approved by the institutional ethics review board (Dnr 2016/112). Informed consent was obtained prior to participation.

#### 3. Results

# 3.1. Demography, tumor characteristics, treatments, and acute complications

Sixty-two patients were included, of whom 43 (69%) were male and

**Table 1** Demography, tumor characteristics, and treatments.

| Patients, n (%)                                      | 62 (100%)      |  |  |
|--|----------------|--|--|
| Age, median (IQR)                                    | 41 (34–51)     |  |  |
| Sex (male/female), n (%)                             | 43/19 (69/31%) |  |  |
| Education (elementary/high-school/university), n (%) | 3/38/18 (5/64/ |  |  |
|  | 31)            |  |  |
| Working at time of diagnosis, n (%)                  | 47 (76%)       |  |  |
| Charlson co-morbidity index, median (IQR)            | 0 (0-0)        |  |  |
| Tumor volume (ml), median (IQR)                      | 39 (16-60)     |  |  |
| Tumor eloquence (yes/no), n (%)                      | 52/10 (84/16%) |  |  |
| Tumor lateralization (right/left), n (%)             | 23/39 (37/63%) |  |  |
| New tumor/tumor residual, n (%)                      | 44/18 (71/29%) |  |  |
| Surgery awake/sedated, n (%)                         | 32/30 (52/48%) |  |  |
| Extent of resection (%), median (IQR)                | 88 (77-100)    |  |  |
| Tumor type   |                |  |  |
| Astrocytoma, grade 2, n (%)                          | 20 (32%)       |  |  |
| Astrocytoma, grade 3, n (%)                          | 14 (23%)       |  |  |
| Oligodendroglioma, grade 2, n (%)                    | 21 (34%)       |  |  |
| Oligodendroglioma, grade 3, n (%)                    | 7 (11%)        |  |  |
| Postoperative oncological treatment before RAND-36   | 41 (66%)       |  |  |
| evaluation, n (%)                                    |                |  |  |

the median age was 41 (IQR 34–51) (Table 1). Forty-seven (76%) patients were working or studying at the time of diagnosis, whereas 15 (24%) were on sick leave. The tumor was located in an eloquent area in 52 (84%) cases. Half (52%) of the patients were operated with awake surgery technique and the others with general anesthesia. The diagnosis was astrocytoma grade 2 in 20 (32%) patients, astrocytoma grade 3 in 14 (23%), oligodendroglioma grade 2 in 21 (34%), and oligodendroglioma grade 3 in 7 (11%). Forty-four (71%) patients were operated for the first time due to a newly diagnosed tumor, whereas 18 (29%) were operated due to tumor recurrence after previous surgery. In the latter group, 9 (50%) of 18 patients had previously received oncological treatment (6 with radiotherapy and 3 with radiochemotherapy).

During the first week postoperatively, 26 (42%) patients developed a new neurological symptom. Thirteen (21%) patients exhibited a paresis, 16 (26%) dysphasia, 10 (16%) had a seizure, and 5 (8%) the supplementary motor area (SMA)-syndrome [26] (Table 2). Awake surgery was associated with more postoperative complications (53% vs. 30%, p = 0.06), specifically dysphasia (41% vs. 10%, p = 0.006) and seizures (25% vs. 7%, p = 0.05). Patients with a left- rather than right-sided tumor more often exhibited postoperative dysphasia (38% vs. 4%, p = 0.003), but the complication rate was otherwise not related to tumor lateralization. Five (8%) patients had persistent neurological deficits at follow-up, of whom 2 still suffered from both dysphasia and hemiparesis and 3 with dysphasia alone. Forty-one (66%) patients received adjunct oncological treatment (radio- and/or chemotherapy) before their RAND-36 follow-up assessment.

#### 3.2. Pre- and postoperative health-related quality of life

RAND-36 was preoperatively reported the day before surgery or in the outpatient clinic one month before and was postoperatively reported in median after 4 (IQR 3–5) months. The HRQoL had then deteriorated in different domains (Fig. 1 and Table 3), specifically in PF, RP, GH, VT, and SF, whereas BP, RE, and MH remained stable at follow-up. Patients who were operated due to tumor recurrence had a slightly higher preoperative RP than those with a newly diagnosed tumor, but there were otherwise no significant differences in the pre- and postoperative RAND-36 variables (Fig. 2).

# 3.3. Explanatory variables for a change in pre- and postoperative health-related quality of life

In Spearman analyses, younger patients deteriorated more in RP, females deteriorated less in GH but more in SF than males, patients with a higher level of education deteriorated more in SF, and a greater EOR correlated with a worsening in RP (Table 4). There was no association among CCI, tumor volume, tumor lateralization, tumor location in eloquent areas, awake surgery, postoperative complications, or adjunct oncological treatment in relation to the deterioration in the RAND-36 variables. Furthermore, the type of tumor (origin and grade) was not related to a change in these RAND-36 variables, as assessed with the Kruskal-Wallis test (4 groups; astrocytoma grade 2/3 and oligodendroglioma grade 2/3).

 Table 2

 Acute postoperative neurological symptoms.

| Postoperative neurological symptoms, n (%) | 26 (42%) |
|--|----------|
| Paresis, n (%)                             | 13 (21%) |
| Dysphasia, n (%)                           | 16 (26%) |
| Seizure, n (%)                             | 10 (16%) |
| SMA-syndrome, n (%)                        | 5 (8%)   |

SMA = Supplementary motor area.

Some patients exhibited multiple, concurrent acute neurological symptoms postoperatively.

#### 4. Discussion

In this study, including 62 patients with grade 2–3 gliomas, there was a decline in several RAND-36 domains the first months after surgery, particularly PF, RP, GH, VT, and SF, but not in BP, RE, and MH. The immediate time before and after surgery is very complex, including preoperative anxiety, postoperative recovery, receiving the definite diagnosis, and possibly adjunct oncological treatments. Surgical variables were only weakly associated with the HRQoL deterioration. Optimizing surgical techniques and intraoperative monitoring to improve oncological outcomes and preserve vital functions are very important for survival and preservation of neurological functions, but may only be one of many aspects for how the patients perceive their early HRQoL. An early and thorough follow-up program in combination with tailored rehabilitation/support could be important to better detect and address these patient-reported outcomes.

# 4.1. Pre- and postoperative health-related quality of life after glioma surgery

In this study, HRQoL deteriorated 4 months after surgery in several domains. There is only a limited number of studies looking at HRQoL in association to glioma surgery. In contrast to our findings, two previous studies found that HRQoL remains stable in most domains for grade 2 gliomas the first year after surgery, according to EQ-5D measurements [27,28]. The conflicting results could be explained by that we studied diffuse gliomas, including both grade 2 and 3 tumors, as opposed to grade 2 alone. The rationale to group grade 2 and 3 tumors together was that they share similar preoperative radiological features and the same preoperative assessment and follow-up program including language assessment/neuropsychology as a part of our protocol. However, one important difference is that more aggressive adjunct oncological treatment is given for grade 3 tumors [6]. In one of the previous HRQoL studies, patients with grade 2 and grade 3-4 glioma patients exhibited similar HRQoL at 1 month postoperatively, but those with grade 3-4 deteriorated at 6 months [27]. Hence, a higher grade could explain worse HRQoL outcome in our patients as evaluated 3-5 months postoperatively. However, there was no association between tumor type/grade and HRQoL deterioration in our patient cohort and the deterioration at 6 months in the previous study [27] was more likely explained by grade 4 tumors. Furthermore, both our and the previous [27,28] HRQoL studies were small (n < 150) and heterogeneity in tumor characteristics, surgery, adjunct oncological treatment, and rehabilitation could contribute to the different outcomes.

Specifically, the patients deteriorated in physical and social functions, whereas pain and mental health remained stable in this study. These tumors are often near eloquent areas of speech, motor, and cognitive functions [4], which make physical and social functions susceptible to decline, both from the disease and surgical interventions. Particularly RP deteriorated, corresponding to worse performance at work and everyday life, which is in line with previous studies reporting a low rate of return to work [29]. BP did not deteriorate after surgery in our patient cohort, in line with previous studies [27,28]. This was expected, considering that the surgical wounds were small and that surgery rather alleviates eventual painful mass effect from the tumor. Furthermore, there was no deterioration in RE and MH after surgery, which was also in line with previous studies [27,28]. However, the overall MH score was low around 60-70 pre- and postoperatively and it is possible that although preoperative anxiety was relieved after surgery, it was replaced with anxiety and depression from receiving the definite diagnosis [27].

Despite the deterioration in many RAND-36 domains after surgery, those patients who were operated due to tumor recurrence reported a similar to slightly better HRQoL than those with a newly diagnosed tumor. This indicates that HRQoL recovers in the long-term, but it could reflect a selection bias of patients with tumor recurrence and a preserved

### Pre- and postoperative HRQoL (median)

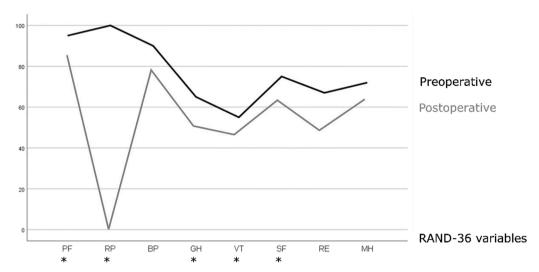


Fig. 1. Pre- and postoperative health-related quality of life for lower grade glioma. BP = Bodily pain. GH = General health. HRQoL = Health-related quality of life. IQR = Interquartile range. MH = Mental health. PF = physical function. RE = Role emotional. RP = Role physical. SF = Social function. VT = Vitality. Asterisk (\*) indicates statistical significance.

**Table 3**RAND 36 variables before and after surgery.

|                        |              | 0.            |   |             |
|------------------------|--------------|---------------|---|-------------|
| RAND 36<br>variables   | Preoperative | Postoperative | Paired difference Δ<br>(postoperative-<br>preoperative) | p-<br>value |
| PF, median<br>(IQR)    | 95 (85–100)  | 85 (75–95)    | (-)5 ((-)15–5)  | 0.003       |
| RP, median<br>(IQR)    | 100 (25–100) | 0 (0–75)      | (-)25 ((-)100–0)  | 0.001       |
| BP, median<br>(IQR)    | 90 (58–100)  | 78 (45–100)   | 0 ((-)23–10)  | 0.18        |
| GH,<br>median<br>(IQR) | 65 (50–80)   | 50 (45–65)    | (-)10 ((-)20–5)   | 0.002       |
| VT, median<br>(IQR)    | 55 (40–70)   | 45 (35–65)    | (-)5 ((-)20–5)  | 0.01        |
| SF, median<br>(IQR)    | 75 (63–100)  | 63 (38–88)    | (-)13 ((-)25–0)   | 0.001       |
| RE, median<br>(IQR)    | 67 (0–100)   | 50 (0–100)    | 0 ((-)33–33)  | 0.57        |
| MH,<br>median<br>(IQR) | 72 (48–84)   | 64 (56–84)    | 0 ((-)12–8)   | 0.52        |

$$\begin{split} BP &= Bodily\ pain.\ GH = General\ health.\ IQR = Interquartile\ range.\ MH = Mental\ health.\ PF = physical\ function.\ RE = Role\ emotional.\ RP = Role\ physical.\ SF = Social\ function.\ VT = Vitality.\ Bold\ and\ italics\ indicate\ statistical\ significance. \end{split}$$

HRQoL who were considered for repeated surgery. A previous larger study has rather indicated that those who have lived with a grade 1–2 glioma for several years exhibit an impaired HRQoL in most domains compared to healthy controls, but still similar to other malignancies [16]. Another explanation for the relatively high preoperative HRQoL in the patients with tumor recurrence is a response-shift, i.e. a better outcome than previously would have been reported due to adaption to the new life circumstances [30]. Furthermore, all patients experience a life-changing situation at the diagnosis and uncertainty about the overall survival. However, in case of a second operation, patients with tumor recurrence know they can survive with sufficient HRQoL.

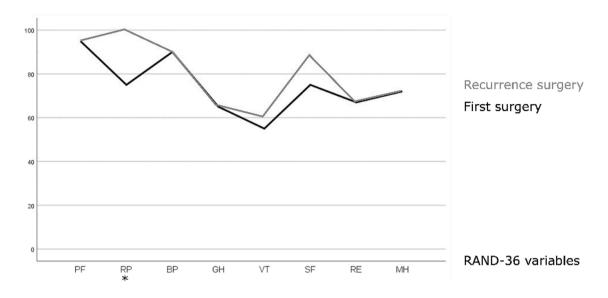
4.2. Explanatory variables for deterioration in health-related quality of life after glioma surgery

In this study, younger patients deteriorated more in RP, females worsened less often in GH but more often in SF than males, a higher level of education correlated with a more pronounced drop in SF, and a greater EOR corresponded to a worsening in PF postoperatively. However, these associations were generally weak, particularly considering multiple statistical comparisons.

The association with younger age and a deterioration in RP could be confounded by that these patients were more often operated with a greater EOR (r=-0.30, p=0.02). The more aggressive surgical approach in these patients is explained by the benefit of improving survival is often worth the immediate neurological deterioration in the acute phase thanks to a greater capacity for plasticity still leading to long-term recovery [20]. Furthermore, females tended to do better in GH, but worse in SF than males. The underlying cause is not clear, but possibly due to a combination of differences in socio-economy and biology between the sexes [31]. The association with a higher level of education and a greater deterioration in SF postoperatively might be explained by that these patients previously performed higher-order, complex tasks, which could no longer be done due to cognitive decline.

In addition, a greater EOR was associated with a deterioration in RP. This could be explained by a corresponding increased risk of complications. However, in a recent study on grade 3-4 gliomas, postoperative deficits rather than tumor location and size was shown to impact on postoperative HRQoL [32]. Although postoperative neurological deficits were common (42%) in our study, most patients (81%) recovered from them and early complications were not associated with a HRQoL deterioration. Particularly those operated with awake surgery were preoperatively prepared for the risk of early, transient neurological symptoms, in order to increase EOR and improve oncological outcomes. Furthermore, left-sided tumors, eloquent location, and greater tumor size correlated with a lower EOR, but not with worse HRQoL. In contrast, some previous studies indicate that occipital lesions [28], hemispheric laterality (contradictory, worse if lesion in the right [33] or left [34]) and increased tumor size [33] correlate with HRQoL. The conflicting results are likely explained by small and heterogeneous patient populations. However, it is obvious that tumor size and proximity to

### Preoperative HRQoL (median)



### Postoperative HRQoL (median)

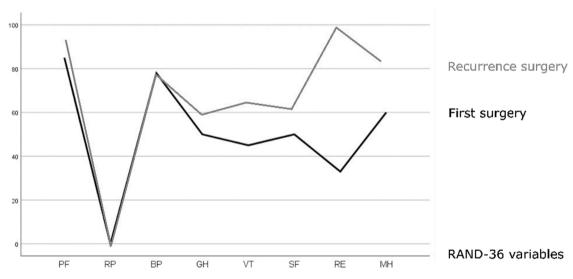


Fig. 2. Differences in pre- and postoperative health-related quality of life for patients with first surgery and recurrence surgery for lower grade glioma. BP = Bodily pain. GH = General health. HRQoL = Health-related quality of life. IQR = Interquartile range. MH = Mental health. PF = physical function. RE = Role emotional. RP = Role physical. SF = Social function. VT = Vitality. Asterisk (\*) indicates statistical significance.

eloquent brain areas influence the need for monitoring of neurological functions such as speech and motor pathways and also affect EOR.

Altogether, HRQoL deterioration was common in many domains after surgery, but this only correlated weakly with tumor characteristics and surgical factors. Surgery can be optimized to improve the onco-functional balance with radiological imaging and intraoperative monitoring techniques to avoid gross neurological deficits to achieve a satisfactory result from a neurosurgeon's perspective. However, our results highlight that these patients still do not recover well in the early course. The time before and after surgery is very complex, in which the patients receive surgical and oncological treatments and are given a lifechanging diagnosis. Compared to the preoperative stage these patients experience a clear impairment in many aspects of their life and in most cases they do not receive enough help/support. This is partly due to the limitations of a standard neurological examination which may not

reveal any deficits, although they often suffer from mood/anxiety disorders and higher-order cognitive/language disturbances [35]. There was no consistent data on the level of active rehabilitation for our patients received, but it was likely very limited especially before the oncological treatment. Considering the heterogeneity in glioma patients and their clinical course, HRQoL deterioration and recovery may be difficult to predict. Our results indicate that younger age, female sex and those with total resection may need different type of rehabilitation/support. Hence, we think there is great room for improvement in research and clinical care with closer follow-ups including cognition, language, mood, and general HRQoL to detect these patient-reported deteriorations and to guide further rehabilitation in the early post-operative period [36].

Table 4
Explanatory variables for changes in RAND 36 variables after surgery –
Spearman rank correlation analysis.

|  | ΔPF<br>(r) | ΔRP<br>(r)         | ΔGH<br>(r) | ΔVT<br>(r) | ΔSF<br>(r)         |
|--|------------|--------------------|------------|------------|--------------------|
| Age  | 0.02       | $0.26^{a}$         | 0.02       | -0.03      | 0.00               |
| Sex <sup>1</sup>                             | 0.17       | 0.03               | $0.32^{a}$ | -0.06      | -0.26 <sup>a</sup> |
| CCI  | -0.24      | -0.03              | 0.00       | -0.00      | 0.01               |
| Education <sup>2</sup>                       | -0.04      | 0.06               | -0.10      | -0.14      | -0.28 <sup>a</sup> |
| Eloquence <sup>3</sup>                       | 0.16       | 0.22               | -0.05      | -0.04      | -0.12              |
| Tumor lateralization <sup>4</sup>            | 0.02       | -0.03              | 0.03       | 0.18       | -0.01              |
| Tumor recurrence <sup>5</sup>                | 0.00       | -0.11              | 0.14       | 0.17       | 0.04               |
| Tumor volume                                 | 0.08       | 0.24               | -0.06      | -0.03      | 0.15               |
| Awake surgery <sup>6</sup>                   | -0.00      | 0.05               | 0.14       | 0.25       | 0.11               |
| Extent of resection                          | -0.07      | -0.25 <sup>a</sup> | 0.06       | -0.09      | -0.04              |
| Postoperative complication <sup>7</sup>      | -0.07      | 0.09               | 0.06       | 0.01       | 0.07               |
| Oncological treatment before                 | 0.14       | 0.21               | 0.12       | 0.10       | 0.15               |
| follow-up RAND-36<br>assessment <sup>8</sup> |            |                    |            |            |                    |

 $<sup>^1\</sup>text{Male}=0, \text{ Female}=1. \ ^2\text{Considered} \text{ ordinal}; \text{ Elementary school}=0, \text{ High-school}=1, \text{ University}=2. \ ^3\text{No}=0, \text{ Yes}=1. \ ^4\text{Right hemisphere}=0, \text{ Left hemisphere}=1. \ ^5\text{No}=0, \text{ Yes}=1. \ ^6\text{No}=0, \text{ Yes}=1. \ ^7\text{No}=0, \text{ Yes}=1. \ ^8\text{No}=0, \text{ Yes}=1. \ ^6\text{No}=0, \text{ Yes}=1. \$ 

#### 4.3. Limitations

First, glioma patients are typically heterogeneous and so was this study population. Although the tumors shared a similar molecular pattern, oligodendrogliomas/astrocytomas and grade 2/3 tumors are still not the same. The patients were also at different stages in their disease, as some were newly diagnosed with a glioma and others were operated due to tumor recurrence. The surgery also differed regarding monitoring, such as awake vs asleep surgery. Second, many patients (67%) had received oncological treatment before the follow-up. Radioand chemotherapy could worsen HRQoL [37], but having such a treatment did not correlate with a deterioration in any of the RAND-36 variables. However, this association may be confounded by that the decision to initiate oncological treatment depends on many variables such as patient age, clinical status, and tumor type/grade. Third, this study focused on early postoperative HRQoL within the first months. This captured the early phase after some time for neurological recovery, which was evident by the attenuation in postoperative neurological symptoms, and before tumor recurrence had taken place. However, recovery from glioma surgery may take longer time than 3-5 months. Our findings illustrated that HRQoL deterioration is evident in the early course and more can be done to attenuate this, but it is obvious that longitudinal follow-up assessments over a longer period of time is necessary to further improve the understanding of the HRQoL dynamics. Fourth, this was a single-center study and represents only a subset of the grade 2 and 3 glioma patients in our catchment area. Fifth, due to gradual adaptation to new life circumstances after the glioma diagnosis, differences in time of evaluation in relation to time from diagnosis could have resulted in some response-shift. A previous study indicates that this shift is limited, at least the first months postoperatively [30].

#### 5. Conclusions

Health-related quality of life deteriorated in several domains following surgery for grade 2–3 gliomas, particularly in physical and social functions. However, this deterioration only weakly correlated with tumor and surgical variables. Despite the good surgical results and neurological status, the patients experienced a clear impairment in their quality of life. This highlights a need for more active rehabilitation/support to better detect and address groups of patients which are susceptible to deterioration in quality of life in the early postoperative phase. There is an existing gap in the assistance of these patients after

the neurosurgical and before oncological phase, with room for improvement both in research and clinical care with closer follow-ups to better detect these patient-reported deteriorations. A more extensive comprehension of the patients-perceived quality of life may further guide a more active rehabilitation in the early postoperative period.

#### CRediT authorship contribution statement

**Teodor Svedung Wettervik**: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Marcus Ersson**: Methodology, Writing – review & editing. **Mats Ryttlefors**: Resources, Writing – review & editing. **Francesco Latini**: Conceptualization, Methodology, Writing – review & editing. **Maria Zetterling**: Conceptualization, Resources, Supervision, Writing – review & editing.

#### **Declaration of interest**

None.

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 $<sup>^{\</sup>rm a}p\text{-value}<0.05,\ ^{\rm b}p\text{-value}<0.01,\ ^{\rm c}p\text{-value}<0.001.$  Bold and italics indicate statistical significance.

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