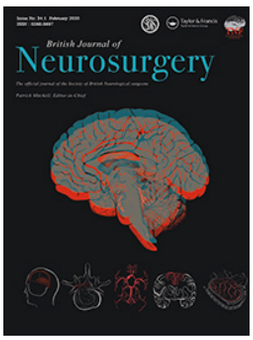

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ORIGINAL ARTICLE

Does preoperative health-related quality of life predict survival in high-grade glioma patients? – a prospective study

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ABSTRACT

Purpose: To explore if preoperative patient-reported health-related quality of life (HRQoL) provides additional prognostic value as a supplement to other preoperatively known clinical factors in patients with high-grade glioma (HGG).

Methods: In a prospective explorative study, 114 patients with high-grade glioma were included. The participants completed the generic HRQoL questionnaire EQ-5D 3L, and the disease-specific questionnaires EORTC QLQ-C30 and EORTC QLQ-BN20 1–3 days before surgery. Operating neurosurgeons scored the patient's preoperative functional level by using Karnofsky Performance Status (KPS). Univariate and multivariate Cox regression analyses were performed to identify HRQoL domains that were associated with survival. Kaplan–Meier survival curves and Log-rank tests were used to visualize differences in survival between groups.

Results: In addition to preoperative KPS and age, the EORTC QLQ-BN20 subdomains 'seizures' (HR 0.98, $p < .006$), 'itchy skin' (HR 1.01, $p < .036$) and 'bladder control' (HR 1.01, $p < .023$) were statistically significant independent predictors of survival in a multivariate cox model.

Conclusions: Our results suggest that in patients with HGG, certain preoperative symptom scales within EORTC QLQ-BN20 may provide additional prognostic information to supplement other clinical prognostic factors. However, further studies are required to validate our findings. Overall the instruments EQ-5D 3L and EORTC QLQ-C30 do not seem to provide much additional valuable prognostic information to already known prognostic factors.

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Brain neoplasms; high-grade glioma; patient-reported outcome measures; prognosis; surgery; quality of life

Introduction

High-grade glioma (HGG) is associated with aggressive tumor growth and poor prognosis despite active and multimodal treatment. Surgery with tumor resection is considered to improve survival,[1–3] but also presents a significant risk of neurological deficits and complications.[4] Thus, potential survival benefits must be weighed against possible risks in a given patient.

Prognostic factors are important for clinical decision making, and several different factors have been identified in HGG patients. Some of the most significant preoperative prognostic factors are age, expected histological diagnosis, comorbidity, and tumor localization.[5–8] In addition, patients functional level, often assessed by health professionals as Karnofsky Performance status (KPS), remains a strong prognostic factor in general cancer patients,[9] including HGG.[10–14] However, while functional status in general cancer patients is often linked to the extent or stage of the disease, this correlation is less established in brain cancer as small lesions in or near functional areas (so-called eloquent areas) may result in severe loss of functions. Another point is that clinician-rated functional status does not capture all facets of functions or health-related quality of life (HRQoL) as viewed by the patients themselves.[15]

Little is known about the potential added clinical value of pretreatment HRQoL as a prognostic factor in HGG patients since baseline HRQoL is usually measured after surgery and before radiotherapy and chemotherapy in oncological studies.[16–20] However, pretreatment HRQoL has been found associated with survival in several other cancer types.[21–24] Also, deterioration in HRQoL 1 month after surgery is found to be independently associated with shorter survival in patients with glioblastoma.[25]

In the present study, we sought to explore preoperative patient-reported HRQoL as a potential predictor for survival in patients with HGG in addition to other preoperatively known prognostic factors.

Material and methods

Study design and study population

In this prospective study, consecutive HGG patients ≥18 years who underwent first-time surgery at the Department of

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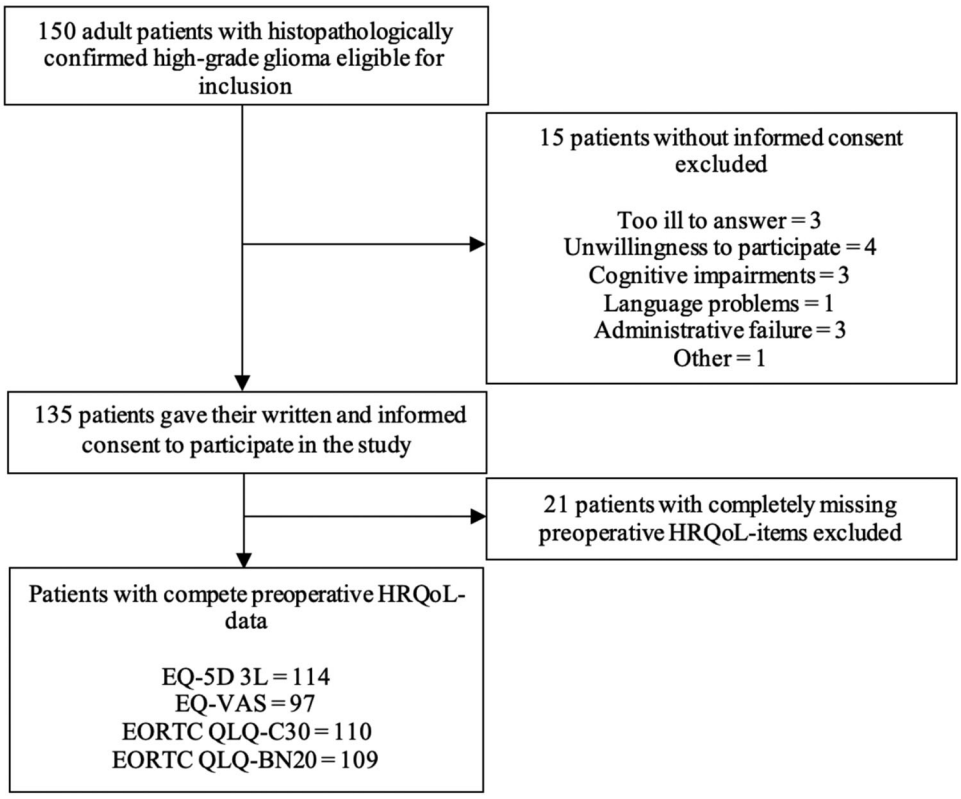

Figure 1. Flow chart of patient inclusion.

Neurosurgery at St. Olavs University Hospital (Trondheim, Norway) from September 2011 to December 2015 were asked to participate. Only histopathological confirmed tumors according to the 2007 WHO classification were included in the analyses.[26]

Data collection and variables

The included patients completed HRQoL-questionnaires 1–3 days prior to surgery, by self-administration or by assistance from family members or a nurse. Three different HRQoL-questionnaires were used; EQ-5D 3L, EORTC QLQ-C30 and EORTC QLQ-BN20.

EQ-5D is a generic questionnaire developed by the EuroQol Group. It consists of two parts, a descriptive system and visual analog scale (VAS). The first part assesses five dimensions; mobility, self-care, activity, pain, and anxiety. The questions have three possible response options of severity; 'no problem', 'slight problem' or 'major problem'.[27] In the second part, the patient ranks its health status from 0–100, where 100 is the best possible health condition, and 0 is the worst imaginable health. The questionnaire has been validated in the Norwegian population and is used for many health conditions.[28,29]

The EORTC QLQ-C30 questionnaire consists of five functional scales; physical functioning, role functioning, cognitive deficits, emotional functioning, and social functioning. In addition, it contains different symptom scales; fatigue, pain, nausea/vomiting, dyspnea, appetite loss, insomnia, constipation, and diarrhea. Lastly, it assesses the financial difficulties and global health (overall HRQoL). EORTC QLQ-C30 is recommended for use in conjunction with EORTC QLQ-BN20 in patients with brain cancer.[30]

The EORTC QLQ BN-20 consists of four multi-item scales, including future uncertainty, visual disorder, motor dysfunction, and communication deficit. Furthermore, it addresses seven specific brain-cancer-related issues, including seizures, headache, drowsiness, itchy skin, hair loss, weakness in legs and bladder control issues.[31]

Prior to surgery, preoperative KPS was scored by the operating neurosurgeon. KPS is a widely used and well-known functional scale that ranges from 100 (normal physical function, no complaints or evidence of disease) to 0 (death). The scale has been validated and is reliable for use in clinical practice and treatment.[32–34] Clinical data (i.e. preoperative symptoms, histopathology, and comorbidity) was registered from electronic medical records. To categorize the patients' comorbidity, we used the American Society of Anesthesiologists (ASA) status that was routinely scored by an anesthesiologist.[35] Tumor volumes were calculated by a neurosurgeon from preoperative MRI-images by using an ellipsoid volume model formula ($4\pi r^3/3$).[36] Eloquent tumor location was graded as suggested by Sawaya *et. al.*[37] Survival time was calculated from the time of surgery to death, and the patients were followed until death or 31.12.2017 (minimum 2 years).

Statistical analysis

Data analyses were done using SPSS Statistics version 24.0. Shapiro–Wilk normality tests and QQ-plots were used to test for normal distributions. Medians and interquartile ranges (IQR) are presented due to skewed data. For calculating the HRQoL scales and scores, the instructions for each questionnaire were followed. The EQ-5D scores were converted into an index value, that range from −0.594 to 1 (negative values = worse than death, 0 = death, 1 = perfect health).[38] Answers in the EORTC-questionnaires were linearly transformed to a 0 to 100 scale, where higher scores in the functional scales represents a high level of functioning, and higher scores in the symptom scales represents a higher symptom burden.[31]

Cox regression analyses were performed to explore if different continuous scales and total scores of the HRQoL-questionnaires, as well as other known prognostic factors, were associated with survival. First, all variables were tested as univariates. Univariates with $p < .10$ were then tested in a multivariate analysis where the significance level was set to $p \leq .05$. To screen for multicollinearity, bivariate Pearson correlation analyses were done among significant variables from the univariate analyses, and the predecided cutoff level was $r < 0.75$. The proportionality assumption was checked using log minus log plots. Hazard ratios (HR) along with 95% two-sided confidence intervals (95% CI) and p-values are reported. Kaplan–Meier survival curves were used to visualize differences in survival between groups. Using SamplePower, a sample size calculation was carried out for KPS based on a HR of 0.66 from a previous study.[12] According to this, minimum 93 participants were required for 80% power.

Ethics and approvals

The data collection was approved by the Regional Ethical Committee (REC) for Health Region Mid-Norway (REC-number 2011/974). All the included patients signed an informed consent.

Results

Study population and baseline characteristics

As shown in Figure 1, 150 patients with HGG underwent surgery during the inclusion period, and a total of 114 patients were included in the analyses.

Table 1 summarizes the baseline characteristics in included patients. One hundred and five patients (92%) had died at the end of follow up. The median patient age at diagnosis was 64 years, and 68% were men. The majority of patients (78%) were functionally independent preoperatively with a preoperative KPS $\geq$ 70. Of the histopathologic subtypes, glioblastoma was most frequent (84%). From hospital records, preoperative cognitive deficit was the most frequently reported preoperative symptom and was documented in 49% of patients.

Table 1. Baseline characteristics.

Characteristic	Value (%)
Median age in years, IQR	64, 56–71
Male	78 (68)
Preoperative KPS	
≥70	89 (78)
<70	25 (22)
Preoperative symptoms[a]	
Headache	42 (37)
Seizures	36 (32)
Nausea	16 (14)
Ataxia	41 (36)
Dysphasia	38 (33)
Cranial nerve deficits	3 (3)
Visual disturbances	8 (7)
Cognitive deficits	56 (49)
ASA score	
1–2	77 (68)
≥3	37 (32)
Preoperative use of corticosteroids	88 (77)
Histopathology	
WHO grade III	18 (16)
WHO grade IV	96 (84)
Eloquent location[b]	49 (43)
Median preoperative tumor volume in cm^3, IQR	25, 13-54

ASA: American Society of Anesthesiologists; IQR: Interquartile Range; KPS: Karnofsky Performance Status; WHO: World Health Organization.
[a]Some patients had occurrence of multiple symptoms.
[b]Eloquent location according to Sawaya grading.

Known prognostic factors only

The results of the Cox regression analyses are displayed in Table 2. In the first model, the known prognostic factors KPS, age, tumor volume, ASA score (≥3 vs <2) and WHO tumor grade (grade IV vs. III) were tested. In this model, KPS ($p < .001$), age ($p = .002$) and tumor volume ($p = .03$) were statistically significant in univariate analyses. The correlation between these variables was $r < 0.75$. A multivariate analysis was available in 105 patients (92%) and showed that KPS ($p = .002$) and age ($p = .014$) were significantly associated with survival. The HR indicates that the relative hazard of dying decreases by 2% (95% CI = 0.96–0.99) for each level increase in KPS, and for every 1-year increase in age, the relative hazard of dying increases by 3% (95% CI = 1.01–1.05).

Known prognostic factors and HRQoL

In the next model, HRQoL variables were added to the already significant known prognostic factors from the first model. As shown in Table 2, the EORTC QLQ-BN20 symptom scales 'seizures' ($p = .024$), 'itchy skin' ($p = .003$), 'hair loss' ($p = .085$) and 'bladder control' ($p < .001$) were significant in the univariate analyses. The EQ-5D index value and subdomains, or main items of the EORTC QLQ-C30 were not associated with survival. There was no correlation between the significant variables from the univariate analyses ($r < 0.75$). In the multivariate model which included 99 patients (88%), lower KPS ($p = .004$), increasing age ($p = .025$), absence of seizures ($p = .006$), more problems with itchy skin ($p = .036$) and more problems with bladder control ($p = .023$) were associated with shorter survival. In this analysis, the HR indicates that the relative hazard of dying decreases by 3% (95% CI = 0.96–0.99) for each level increase in KPS, and for every 1-year increase in age, the relative hazard of dying increases by 3% (95% CI = 1.00–1.05). Further on, the HR in the EORTC QLQ-BN20 domains indicates that the relative hazard of dying decreases 2% for every unit increase of reported seizures (95% CI = 0.97–0.99). The relative hazard of dying increases by 1% for every unit increase of reported itchy skin (95% CI = 1.00–1.02) and bladder control issues (95% CI = 1.01–1.02). Preoperative tumor volume and the EORTC QLQ-BN20 symptom 'hair loss' were not significant as prognostic factors of survival in the multivariate model.

In post-hoc tests, there was no correlation between bladder control problems and preoperative tumor volume ($r = 0.07$, $p = .471$), or between bladder control problems and frontal tumor location ($r = 0.25$, $p = .11$).

Survival curves

The Kaplan–Meier survival curves (Figure 2) indicate a prolonged survival in patients with higher preoperative KPS compared to those with lower KPS, and in patients with age <64 (median split). Median survival time for patients with KPS <70 was significantly shorter than in patients with KPS ≥ 70 (241 vs. 336 days, log-rank $p < .001$), while median survival time for patients ≥64 years was significantly shorter than in patients

Table 2. Univariate and multivariate cox regression analyses for survival.

	Univariate		Multivariate	
Variable	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Model with known prognostic factors only[a]				
KPS (ordinal)	0.97 (0.95–0.99)	**<.001**	0.98 (0.96–0.99)	**.002**
Age (continuous)	1.03 (1.01–1.05)	**.002**	1.03 (1.01–1.05)	**.014**
Tumor volume (continuous)	1.00 (1.00–1.01)	**.030**	1.00 (0.99–1.01)	.17
ASA (≥3 vs <2)	1.40 (0.93–2.11)	.11		
Histopathology (grade IV vs III)	1.27 (0.72–2.26)	.39		
Model with known prognostic factors and HRQoL[b]				
KPS (ordinal)	0.97 (0.95–0.99)	**<.001**	0.97 (0.96–0.99)	**.004**
Age (continuous)	1.03 (1.01–1.05)	**.002**	1.03 (1.00–1.05)	**.025**
Tumor volume (continuous)	1.00 (1.00–1.01)	**.030**	1.00 (0.99–1.01)	.54
EQ-5D 3L index value	0.99 (0.52–1.86)	.96		
Mobility	1.26 (0.90–1.77)	.17		
Self-care	1.49 (0.90–2.46)	.11		
Activity	1.10 (0.84–1.44)	.53		
Pain	1.06 (0.77–1.44)	.71		
Anxiety	1.09 (0.81–1.44)	.57		
EQ-VAS[c]	0.99 (0.98–1.00)	.12		
EORTC QLQ-C30				
Physical function	0.99 (0.98–1.00)	.41		
Role function	1.00 (0.99–1.01)	.80		
Emotional function	1.00 (0.99–1.01)	.48		
Cognitive function	0.99 (0.98–1.00)	.16		
Social function	1.00 (0.99–1.01)	.59		
Fatigue	1.00 (0.99–1.01)	.86		
Nausea/vomiting	1.01 (0.99–1.02)	.37		
Pain	1.00 (0.94–1.01)	.94		
Dyspnea	1.01 (0.99–1.02)	.30		
Insomnia	1.00 (0.99–1.01)	.45		
Appetite loss	1.00 (0.99–1.01)	.74		
Constipation	1.00 (0.99–1.01)	.69		
Diarrhea	1.00 (0.99–1.01)	.58		
Financial difficulties	0.99 (0.98–1.01)	.49		
Global health (Overall QoL)	0.99 (0.98–1.00)	.18		
EORTC QLQ-BN20				
Future uncertainty	1.00 (0.99–1.01)	.87		
Visual disorder	1.01 (0.99–1.02)	.14		
Motor dysfunction	1.01 (0.99–1.02)	.34		
Communication deficits	1.01 (0.99–1.02)	.21		
Headache	1.00 (0.99–1.01)	.75		
Seizures	0.98 (0.97–0.99)	**.024**	0.98 (0.97–0.99)	**.006**
Drowsiness	1.00 (0.99–1.01)	.92		
Itchy skin	1.02 (1.01–1.03)	**.003**	1.01 (1.00–1.02)	**.036**
Hair loss	1.02 (0.99–1.04)	**.085**	1.00 (0.97–1.02)	.96
Weakness in legs	1.00 (0.99–1.01)	.43		
Bladder control	1.02 (1.00–1.03)	**<.001**	1.01 (1.00–1.02)	**.023**

Significant values are marked in bold.
[a]$n = 105$ (9 censored).
[b]$n = 99$ (9 censored, 6 missing *EORTC QLQ-BN20* items).
[c]$n = 97$ (9 censored, 8 missing *EQ-VAS* items).

<64 years (248 vs. 383 days, log-rank $p < .002$). Kaplan–Meier curves of the HRQoL domains that were significantly associated with survival in the multivariate Cox model are shown in Figure 2. As seen, patients with absence from seizures ($n = 12$) had a shorter survival than those with seizures, and median survival time for patients without seizures was significantly shorter (316 days vs. 549 days, log-rank $p = .003$). In a post-hoc analysis, we found that patients with seizures had smaller tumors than those without (16.8 ml vs 25.7 ml), but the finding was not significant ($p = .22$, Mann–Whitney *U* test). Patients reporting itchy skin issues ($n = 17$) lived shorter than those without itchy skin issues, and median survival time for patients with itchy skin was significantly shorter (307 vs. 337 days, log-rank $p = .042$). Patients reporting bladder control issues ($n = 26$) lived shorter than patients without this problem (median survival 218 vs. 375 days, log-rank $p < .001$).

Discussion

In this prospective explorative study, we investigated the potential importance of pretreatment patient-reported HRQoL measured with EQ-5D 3L and the EORTC questionnaires QLQ-C30 and QLQ-BN20 as predictors for survival in patients with HGG in combination with already known prognostic factors that are available in a preoperative setting. In a multivariate Cox regression model, we found the EORTC QLQ-BN20 domains 'seizures', 'itchy skin' and 'bladder control' to be significantly associated with survival, in addition to functional status measured with KPS and patients age. Patients without preoperative seizures had shorter survival than patients with seizures, and patients reporting problems with itchy skin and bladder control had shorter survival than patients without these problems. However, rather few patients reported problems in these domains, making the findings uncertain. The EQ-5D index value and subdomains, or

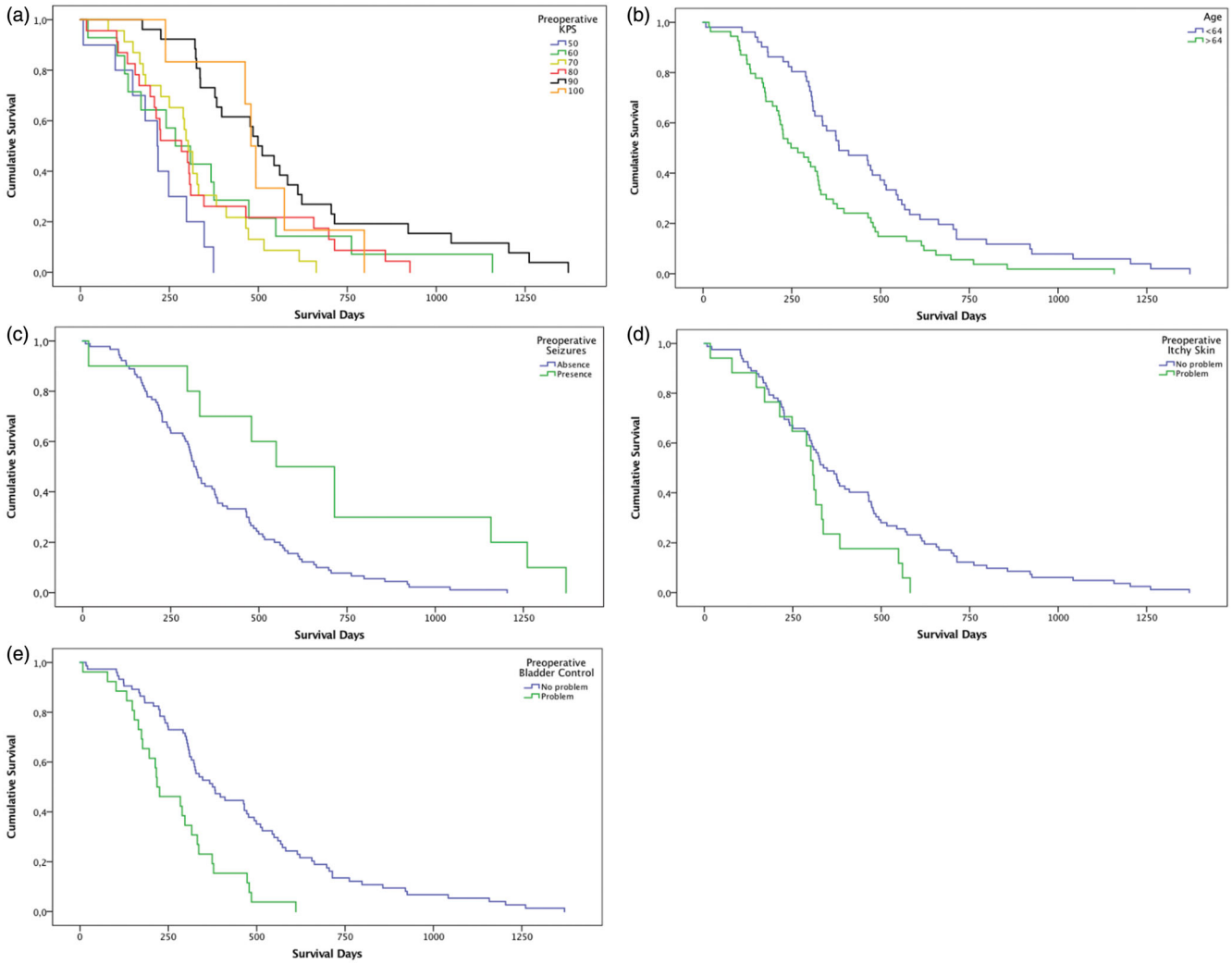

Figure 2. Kaplan–Meier survival curves. (a) Shows the differences in survival days between patients with preoperative KPS ranging from 50 to 100. (b) Shows the differences in survival days between patients with age <64 years and ≥64 years. (c) Shows the differences in survival days in patients with absence of seizures compared to those with presence of seizures. (d) Shows the differences in survival days in patients who have no problems with itchy skin compared to those reporting itchy skin problems. (e) Shows the differences in survival days in patients who have no problems with bladder control compared to those reporting bladder control problems.

main items of the EORTC QLQ-C30 questionnaire were not significantly associated with survival in either univariate or multivariate Cox regression analyses. This indicates that these HRQoL questionnaires may add little prognostic information to already known factors in a preoperative setting.

Age and KPS are strong prognostic factors for survival in patients with HGG, but since KPS does not reflect the patient's self-perceived symptoms, it may miss valuable information. Thus, patient-reported HRQoL may potentially be more important since the patient itself considers his or her own health condition and subjective ailments. Several oncological studies have investigated the potential importance of HRQoL for survival, but with baseline assessments recorded after surgery and with inconsistent results. Using the EORTC questionnaires QLQ-C30 and QLQ-BN20 in patients with HGG, Mauer *et al.* did not find any HRQoL domains to predict survival.[19,20] Other studies using the Functional Assessment of Cancer Therapy-Brain (FACT-Br) questionnaire have found 'fatigue' to predict survival in HGG patients,[16] while 'living with a spouse' and 'FACT-G sum score' have been found to predict survival in patients with anaplastic astrocytoma and brain metastases undergoing radiotherapy.[17]

The prognostic value of pretreatment HRQoL scores has been investigated in several other disease states, including in a study by Efficace *et al.* were baseline pretreatment HRQoL was explored as a prognostic factor in patients with lung cancer.[21] In this study, EORTC QLQ-C30 with a lung cancer module were used, and patients with 'pain' and 'dysphasia' had an increased likelihood of shorter survival. Other malignancies where domains in the EORTC QLQ-C30 questionnaire have shown to be independent prognostic factors for survival includes head and neck ('physical functioning', 'dyspnea', 'insomnia', 'appetite loss'),[22] liver ('physical functioning', 'role function', 'appetite loss')[23] and ovarian cancer ('cognitive functioning', 'global QoL').[24] Also, Quinten et. al. have reported 'physical functioning', 'pain' and 'appetite loss' to be prognostic factors for survival in general cancer types.[39] None of the above studies report similar results as in our study, indicating that there are either random false-positive findings, differences between the pre- and postoperative setting, or differences between our patient populations. Moreover, different questionnaires were used in the studies making direct comparisons difficult.

Even though a third of the patients in our study had preoperative seizures according to medical records, only a small

proportion reported presence of seizures. However, only symptoms experienced during the last week are to be reported in the EORTC questionnaire, and many patients with seizures had received antiepileptic drugs at this time point. Also, seizures are most common in patients with anaplastic gliomas[40,41] and low-grade gliomas.[42] Given this, patients who reported seizures might have more slow-growing tumors and therefore live longer. Patients who present with seizures alone may also have smaller tumors, i.e. are diagnosed before symptoms of mass effect occur, and seizures might, therefore, be an indirect marker of limited disease at the time of diagnosis. However, we found no significant difference in tumor volume between patients with and without seizures, and the multivariate model was adjusted for tumor volume.

Only a few patients reported itchy skin before surgery in our study, and additional research of preoperative HRQoL data is necessary to confirm this finding as truly significant. Itchy skin is usually not related to the disease before surgery, but may increase after surgery due to hair shaving before surgery or as a side effect of post-treatment with temozolomide.[43] Additionally, itchy skin is an adverse effect to corticosteroids, which may be more often prescribed and at a larger dose in patients with significant preoperative radiological edema. Still, the biological plausibility of 'itchy skin' as a predictor for survival can be questioned.

We also found 'bladder control' to be an independent predictor of survival. Even though 'bladder control', KPS and age were not statistically correlated, we can speculate that patients with bladder control issues are often older, more comorbid, or may have a lower overall functional level than patients without such problems. Other studies have found an association between the EORTC domain 'bladder control' and KPS. Yavas et. al found it to be significantly related to both disease progression and KPS in HGG patients who have undergone surgery and were treated with radiotherapy.[44] Osoba *et al.* found that patients with newly diagnosed HGG had fewer problems with bladder control if the KPS was ranging between 80 and 100.[45] Bladder control issues may also be more common in patients with cognitive deficits. In addition, lower urinary tract dysfunction among patients with tumors located in the frontal lobe has been reported,[46] and the bladder symptoms may perhaps be a surrogate factor for larger tumors. However, we did not find any correlation between bladder control, tumor location and tumor size in our material.

Although deterioration in EQ-5D index value after surgery has been found to predict survival in patients with glioblastoma,[25] we found no association between the preoperative EQ-5D index value or the main items of the EORTC QLQ-C30 questionnaire and survival in our study. However, changes in HRQoL from before surgery may give more information about the prognosis since early changes in HRQoL may reflect both the outcome after surgery and the aggressiveness of the disease. It is also known that surgery-induced deficits are associated with poorer prognosis and reduce the likelihood of receiving multimodal adjuvant therapy.[4] Still, deterioration on HRQoL following surgery is not known preoperatively and cannot be used for surgical decision making.

Although we did not find patient-reported HRQoL assessed with EQ-5D 3L, EORTC QLQ-C30 and EORTC QLQ-BN20 to add strong or likely clinically valuable prognostic information in addition to other known prognostic factors, a preoperative (pre-treatment) baseline may still be valuable to later assess the impact of treatment. Since early deterioration in HRQoL may reflect the aggressiveness of the disease, postoperative changes in different HRQoL domains from before surgery may give more prognostic information than the preoperative status.

Strengths and limitations

We assume that the generalizability of our findings is good, as we have a population-based sample and a rather large sample size with relatively little missing data. However, due to multiple testing in small subgroups, both false positive and false negative findings may be an issue. Also, in HRQoL studies, missing data is the most severe methodological problem since it may produce selection bias and not reflect the true situation.[47] Although a complete case analysis is often not recommended, we chose to exclude patients with missing HRQoL forms or missing items since correct imputations would have been difficult. Thus, patients with the highest symptom burden might have been excluded. Use of proxy ratings are considered as a good alternative, and were therefore used when eligible.[48]

Although our focus was to assess the possible added value provided by patient-reported HRQoL in comparison with other variables that are known preoperatively, we chose to include tumor grade in the regression analyses, even though this information is not confirmed in a preoperative setting. Still, the histopathological diagnose is often suspected based on the MRI appearance. A 'guessed' radiological diagnose would have been a more appropriate variable.

Generic HRQoL tools may fail to detect prognostic factors in primary brain tumors since the general impairment seen in other cancer patients is rarely present, and particularly not at the time of diagnosis. However, in the present study, we also used a brain-cancer specific questionnaire, and even though such tools do not correlate with survival in the early phase of the disease, they are still important when assessing the impact of cancer treatments.

Conclusion

In conclusion, our results suggest that certain symptom scales within patient-reported HRQoL might be independent prognostic factors in patients with HGG, including the presence of seizures, problems with itchy skin and bladder control problems. However, the findings are based on explorative analyses and rather small subgroups. Further studies are therefore required to validate our findings. Overall, HRQoL assessed with EQ-5D 3L, EORTC QLQ-C30 and EORTC QLQ-BN20 seem to add little prognostic information to already known prognostic factors in HGG patients undergoing first-time surgery.

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Disclosure statement

The authors declare that they have no conflict of interest.

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