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Brain atlas for assessing the impact of tumor location on perioperative quality of life in patients with high-grade glioma: A prospective population-based cohort study

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ABSTRACT

Background: Tumor location is important for surgical decision making. Particular attention is paid to regions that contain sensorimotor and language functions, but it is unknown if these are the most important regions from the patients' perspective.

Objective: To develop an atlas for depicting and assessing the potential importance of tumor location for perioperative health-related quality of life (HRQoL) in patients with newly diagnosed high-grade glioma.

Methods: Patient-reported HRQoL data and semi-automatically segmented preoperative 3D MRI-images were combined in 170 patients. The images were registered to a standardized space where the individual tumors were given the values and color intensity of the corresponding HRQoL. Descriptive brain maps of HRQoL, defined quantitative analyses, and voxel-based lesion symptom mapping comparing patients with tumors in different locations were made.

Results: There was no statistical difference in overall perioperative HRQoL between patients with tumors located in left or right hemisphere, between patients with tumors in different lobes, or between patients with tumors located in non-eloquent, near eloquent, or eloquent areas. Patients with tumors involving the internal capsule, and patients with preoperative motor symptoms and postoperative motor deficits, reported significantly worse overall HRQoL-scores.

Conclusions: The impact of anatomical tumor location on overall perioperative HRQoL seems less than frequently believed, and the distinction between critical and less critical brain regions seems more unclear according to the patients than perhaps when judged by physicians. However, worse HRQoL was found in patients with tumors in motor-related regions, indicating that these areas are crucial also from the patients' perspective.

1. Introduction

Diffuse glioma is the most common primary malignant brain tumor in adults (Ostrom et al., 2017). The surgical aim is to achieve maximal "safe" resection, which is a delicate balance between extensive surgical resections that potentially prolong survival (Jakola et al., 2012; Brown et al., 2016; Stummer et al., 2008) while avoiding postoperative adverse effects including new or worsened neurological deficits (De Witt Hamer et al., 2012). Consequently, tumor location is one of the most important factors for clinical decision making in glioma surgery, and traditionally, brain regions that contain sensorimotor, visual and language functions are considered so-called eloquent or more crucial to

Abbreviations: 3D, three dimensional; EQ-5D, EuroQoL 5D; HGG, high-grade glioma; HRQoL, health related quality of life; KPS, Karnofsky Performance Status; MCID, minimal clinical important difference; MRI, magnetic resonance imaging; VLSM, voxel-based lesion symptom mapping; WHO, World Health Organization

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patient outcomes (Sawaya et al., 1998).

More specifically, neurosurgeons often pay extra attention to cortical regions of the dominant (usually left) hemisphere, including the inferior frontal lobe (Broca), superior temporal lobe (Wernicke), angular gyrus, and the bilateral posterior frontal lobes (motor control of dominant hand) (Sawaya et al., 1998; Sanai et al., 2008; Chang et al., 2008). Surgeons also try to respect the medial occipital lobes (vision) and to some degree the anterior parietal lobes (so-called parietal functions) (Sawaya et al., 1998; Sanai et al., 2008; Chang et al., 2008). In addition, major white matter tracts, including the pyramidal tracts, the superior longitudinal fascicle (with the arcuate fascicle) and the visual tracts are often respected (Sawaya et al., 1998; Essayed et al., 2017; Witwer et al., 2002; Sanai and Berger, 2018; Hervey-Jumper and Berger, 2016). Since maximal safe resection is the treatment goal of surgery, various pre- and intraoperative methods are used to identify these regions in an attempt to minimalize the risk for postoperative neurological deficits and assumed subsequent reduction of quality of life in patients (e.g. functional MRI, Diffusion Tensor Imaging (DTI), navigated transcranial magnetic stimulation (nTMS), neuronavigation, and direct cortical or subcortical stimulation) (De Witt Hamer et al., 2012; Senft et al., 2011; Taylor and Bernstein, 1999; Nadkarni et al., 2015; Frey et al., 2014; Unsgaard et al., 2006). However, methods based on preoperative assessement are limited by intraoperative brain shift and debatable reproducibility (Hill et al., 1998; Weng et al., 2018; Wakana et al., 2007), and intraoperative methods are limited by no agreed set-up, large practice variations, the potential for false stimulation findings, and risk of intraoperative seizures (Szelenyi et al., 2010; Kovac et al., 2016; Borchers et al., 2011). Also, awake surgery requires intraoperative cooperation and is not suitable for all patients. Additionally, not all brain functions are easy to monitor in an intraoperative setting. All together, the evidence for these surgical adjuncts is therefore generally rather low and direct comparisons across methods are largely lacking.

While it is well known that lesions and surgery in the mentioned eloquent areas may cause neurological symptoms and that identification of these areas during surgery may reduce the risk of certain functional deficits (De Witt Hamer et al., 2012; Sawaya et al., 1998) the association between tumor location and patient-reported health-related quality of life (HRQoL) has not been much explored. Presumably, there are no non-functional areas in the brain, and since HRQoL is a complex construct consisting of both physical, psychological and social domains, it may provide valuable information as a supplement to neurological function and functional anatomy (Katzan et al., 2017). Since it is assessed from the patients perspectives, it accounts for the patient's own subjective evaluation of health, which often differs substantially from the judgment of health professionals (Slevin et al., 1988; Fisch et al., 2003; Schiavolin et al., 2018). Thus, HRQoL evaluations are by definition relevant to patients, and more clinically important impairments and changes may potentially be detected.

The relationship between lesion location and HRQoL has been explored in several studies, but with inconsistent results. In most studies with larger study populations no relationship between lesion laterality/affected lobes and HRQoL have been found (Cheng et al., 2010; Brown et al., 2006; Polin et al., 2005; Sundseth et al., 2015), while some studies report worse HRQoL scores in patients with lesions located in specific areas (de Haan et al., 1995; Liu et al., 2009; Hahn et al., 2003; Salo et al., 2002; Mainio et al., 2003; Moon et al., 2004). Possible explanations of these contradictory findings are that different HRQoL instruments have been used, that different study populations have been studied, and that assessments have been done at different time points during a specific disease course. Another likely explanation is that many studies may suffer from variable external validity due to strict inclusion criteria, limited sample sizes, small subgroups, and ill-defined locations. Thus, the risk of false positive and negative findings may be high. Traditionally, the impact of brain tumor location has also been assessed by dichotomizing location into traditional anatomical regions (e.g. lobes, gyri etc) and relating to dichotomous traditional functional outcome (e.g. language problems yes/no, paresis yes/no). This may introduce bias towards functional anatomical regions that are predefined and towards functions that are easy to assess. Therefore, to overcome some of the limitations from previous studies, location-specific maps with descriptive patient-reported data and defined quantitative analyses may be a way to advance.

We hypothesized that brain regions associated with worse HRQoL could be different from brain regions judged by clinicians as eloquent. Using an explorative novel study approach in this setting, we have developed an atlas for depicting and assessing the potential importance of anatomical tumor location on perioperative generic HRQoL in patients with newly diagnosed high-grade glioma (HGG). In this atlas, semi-automatically segmented 3D MRI images and patient-reported data were merged into a standardized space, and the individual tumors were given the values and color intensity of the corresponding HRQoL. We hereby present the preliminary results from our prospective population-based cohort.

2. Material and methods

2.1. Study population

In this prospective study, HGG-patients ≥18 years that were scheduled for first-time surgical resections or diagnostic biopsies between January 2007 and December 2016 at St. Olavs Hospital, Trondheim, Norway were eligible for inclusion. This department serves a population of approximately 750,000 inhabitants as the single neurosurgical department in a defined geographical catchment region. The tumors were histopathologically classified by a neuropathologist based on the 2007 WHO-classification (Louis et al., 2007), except those who were diagnosed in the second half of 2016 and classified according to the most recent WHO-classification (Louis et al., 2016). Patients with missing preoperative MRIs, and multifocal/multicentric tumors were excluded. Functional MRI and/or diffusion tensor imaging (DTI) were performed preoperatively if deemed helpful. All patients underwent surgery under general anesthesia, and a neuronavigation system integrating preoperative MRIs and intraoperative 3D ultrasound volumes was routinely used (Gronningsaeter et al., 2000). After surgery, the patients were referred to the oncological department for radiation and concomitant and adjuvant chemotherapy according to the Stupp protocol (Stupp et al., 2005).

2.2. Data collection and variables

A HRQoL-questionnaire was completed 1–3 days before scheduled surgery by the patient themselves, or with assistance from family or a nurse. Postoperative follow-up was conducted by a study nurse in a structured telephone interview with the patients at 4–6 weeks. Proxy ratings were used if the patients had severe dysphasia or disabling cognitive symptoms. These are found to be strongly correlated to patient-reported HRQoL (Brown et al., 2005; Sneeuw et al., 2002). To assess HRQoL we used EQ-5D 3 L, which is a generic questionnaire developed by the EuroQol Group (EuroQolGroup, 1990). It is widely used in many health conditions, and validated in the Norwegian population (Nord, 1991). The questionnaire consists of five single dimensions, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels: “no problem”, “slight problem” or “major problem”, which give 243 possible combinations of responses that can be converted to a single global index value. The index value was our primary outcome (i.e. “overall HRQoL”), and range from −0,594 to 1, where 1 corresponds to perfect health, 0 to death, and negative values are considered as worse than death. We have previously demonstrated that the minimal clinically important difference (MCID) for the EQ-5D index value is ± 0.15 in HGG-patients (Sagberg et al., 2014).

Patient and treatment characteristics including comorbidity (Charlson et al., 1987) were collected from electronic medical records in a prospectively maintained tumor registry. Karnofsky Performance Status (KPS) was reported by the operating surgeon on a preoperative questionnaire. Patient-reported new and/or worsened neurological deficits after surgery were registered at follow-up, and postoperative complications within 30 days were classified according to the Landriel classification system (Landriel Ibanez et al., 2011). In addition, eloquence was estimated from preoperative MRI images as suggested by Sawaya et al. (1998). According to this, we defined eloquent brain tumors to be located in motor/sensory cortex, visual or speech center, internal capsule, basal ganglia, hypothalamus/thalamus, brain stem and/or dentate nucleus, while near-eloquent tumors were located near these areas, including the corpus callosum.

2.3. Tumor segmentation

Preoperative 3D MRI images were obtained at admission using a 1.5 or 3 Tesla MRI scanner, including Siemens Skyra 3 T ($n = 60$), Siemens Avanto 1.5 T ($n = 51$), Philips Intera 3 T ($n = 34$), Siemens TrioTim 3 T ($n = 11$), Siemens Prisma 3 T ($n = 7$), GE Signa Hdxt 1.5 T ($n = 2$), Siemens Symphony 1.5 T ($n = 2$), Siemens Biograph 3 T ($n = 2$) or Philips Achieva 1.5 T (n = 1). Two different software packages were used for semi-automatic tumor segmentation: 3D Slicer version 4.3.1-4.5.0 (3D Slicer, Boston, Massachusetts) (Fedorov et al., 2012) and BrainVoyager version 1.2 (Brain Innovation, Maastricht, Netherlands). In a recent study, we found high agreement in intra- and inter-rater reliability using both these packages (Fyllingen et al., 2016). In total 130 MRI-images (77%) were segmented using 3D Slicer. The work-flow for this software has previously described by others (Egger et al., 2013). Remaining images ($n = 40$, 23%) were segmented using BrainVoyager, as described previously (Stensjoen et al., 2015). In both software packages, T1-weighted images were used in contrast-enhancing lesions, and the tumor was defined as the volume of pathological contrast-enhancement and necrotic tissue within the contrast-enhancing borders ($n = 141$). Fluid attenuation inversion recovery (FLAIR) images were used in non-enhancing lesions ($n = 29$). Median slice thickness in the segmented images was 1 mm (range 1 to 10). The segmentations were performed by one of two authors (L.M.S., E.H.F) or a trained medical student, and all segmentations were later verified by either a neurosurgeon (O.S) or a neuroradiologist.

2.4. Registration to a standardized space

The segmented MRI images were further brought into the Montreal Neurological Institute (MNI) space, which is a standardized frame of reference defined by the ICBM-152 brain template (Fonov et al., 2011; Fonov et al., 2009). This atlas is the average of 152 young normal brains and is available at http://nist.mni.mcgill.ca/. The segmented images were spatially aligned with the average brain by intensity-based image registration using the Advanced Neuroimaging Tools (ANT) registration toolkit (Avants et al., 2008) as part of the Nipype framework (Gorgolewski et al., 2011). First, the individual images were pre-processed (bias field correction (Tustison et al., 2010), intensity normalization and resampling to 1 mm^3), and skull-stripped to exclude non-brain structures using the brain mask included with the ICBM-152 template. Each image volume was then registered to the template using affine and non-linear registration. During non-linear registration, the segmented tumors were used to mask out the tumor region from the estimation of the non-linear transformation. The resulting transformations were then applied to the individual tumor segmentations in order to bring all the tumors into a common space. Two engineers performed the data processing (D.H.I, I.R), and the pipeline can be downloaded at https://github.com/Danielhiversen/NeuroImageRegistration. The individual tumors were further given the intensity of the corresponding preoperative EQ-5D index value, and the postoperative change value. All files were then converted and imported into the CustusX platform (Askeland et al., 2016), were the colors and thresholds finally were defined. Tumor locations were defined by using imported atlases of lobes (Collins et al., 1999) and white matter tracts (Thiebaut de Schotten et al., 2011). Lobes were classified according to where the center of gravity in each tumor was located, while tumors that overlapped with any part of specific white matter tracts were classified as involvement of these tracts.

2.5. Statistical analyses

The EQ-5D index values were calculated according to the EuroQol scoring manual, using the UK time trade off (TTO) value set (Dolan, 1997). The calculations were impossible in seven patients due to missing values in one or two subdomains, and these patients were thereby included in subdomain analyses only. In the postoperative map, the median change score was calculated in each voxel and values < MCID ± 0.15 were considered as “unchanged”.

Both descriptive and defined quantitative analyses were done using SPSS Statistics version 23.0 (IBM, Armonk, New York). Q-Q plots were used to test for normal distribution of data. Mean ± SD was used if data were normally distributed while median and range was used if data were skewed and/or had significant outliers. For defined quantitative analyses, independent samples *t*-test, Mann-Whitney *U* test, Kruskal Wallis H-test, Pearson Chi-Square, and/or Fishers Exact test were used to compare differences between groups. The statistical significance level was set to $P \leq .05$, and all tests were two-sided. In a power analyses for two independent samples, 41 patients in each group were required ($\alpha = 0.05$, $1–\beta = 0.8$). Due to the use of non-parametric tests, 15% were added, resulting in a total need of 47 patients in each group. Mean differences and SD were obtained from a prior study (Sagberg et al., 2014). For voxel-based lesion symptom mapping (VLSM), the NiiStat toolbox for Matlab (www.nitrc.org/projects/niistat) was used. Only voxels where at least ten patients had tumor were included in the analysis. Age and lesion volume were included as nuisance variables in the analysis. As our data were not normally distributed, the data were de-skewed using the square transform included in NiiStat. Voxelwise statistical significance was determined by voxel-based permutation thresholding (1000 permutations).

2.6. Ethics and approvals

All patients provided written, informed consent prior to enrollment into the study. Data collection was approved by the Regional Ethical Committee for Health Region Central-Norway, and adhered to guidelines of the Helsinki Declaration.

3. Results

3.1. Study population

A flow-chart of the inclusion process is shown in Fig. 1. In total, 170 (60%) of 285 eligible patients provided informed consent, filled out the HRQoL-questionnaire and were included in the study. There were no significant differences in age ($P = .12$), tumor volume ($P = .20$) or KPS ($P = .17$) between included and excluded patients at baseline. Patients with biopsy only were excluded from postoperative analyses and follow-up data was available in 112 patients (82% of all resections). Median follow up time was 36 days (range 24 to 70).

3.2. Baseline and treatment characteristics

Baseline and treatment characteristics are presented in Table 1. As seen, 79% were functionally independent before surgery (i.e. KPS ≥70). The most common preoperative symptoms were cognitive symptoms (42%), headache (38%), balance/coordination problems

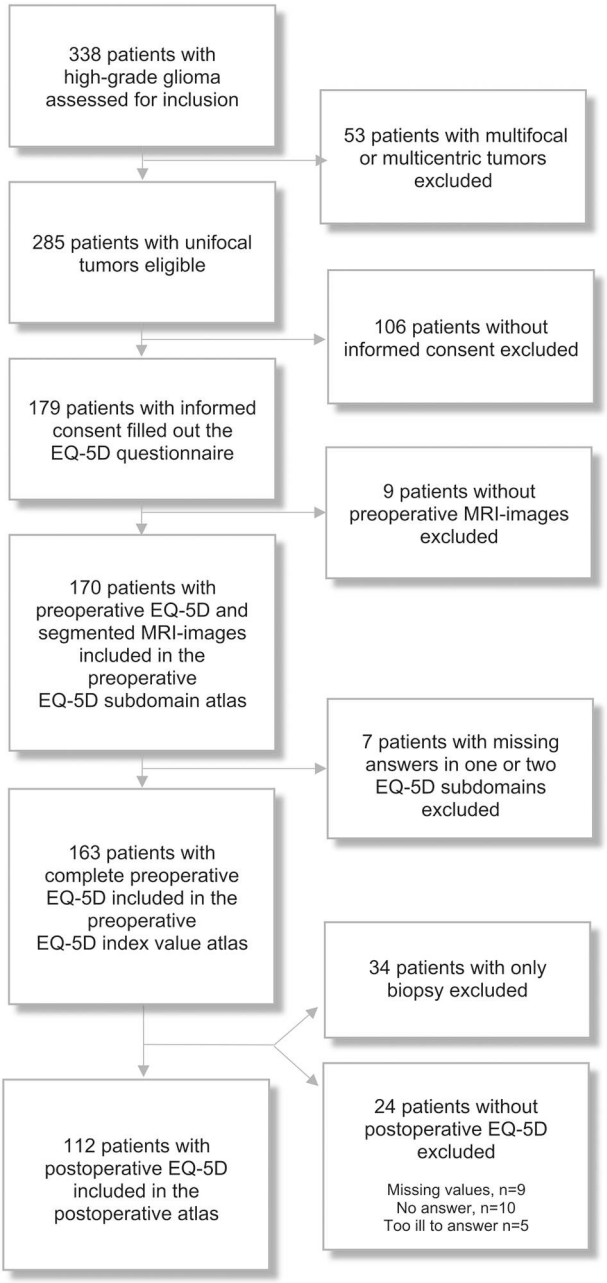

Fig. 1. Flow chart of the inclusion process.

(34%), epileptic seizures (33%), and language problems (32%). Among the 112 patients who underwent resections, moderate or severe complications occurred in 12 patients (11%), while 26 (23%) reported new or worsened neurological deficits after surgery.

3.3. Preoperative HRQoL

Axial images of the brain with preoperative overall HRQoL, tumor volume and tumor distribution in patients with complete preoperative EQ-5D questionnaires are presented in Fig. 2 and Video 1. Some "hotspots" with worse HRQoL are seen in the right primary sensorimotor cortex, in the basal ganglia, and near the anatomical Wernicke's area, arcuate fasciculus and the left hippocampus/amygdala. However, there are few tumors in some of these locations, making the data less powerful.

There were no statistically significant differences in preoperative EQ-5D index values between patients with tumors in left or right

Table 1
Patient characteristics at baseline (N = 170) and treatment characteristics after resection (N = 112).

Patient characteristics at baseline (N = 170)	
Age in years, mean (SD)	61 (± 12)
Female, *n* (%)	62 (37)
Preoperative Karnofsky Performance Status, *n* (%)	
≥80	101 (59)
70	33 (19)
≤60	36 (21)
Charlson Comorbidity Index, *n* (%)	
≥2	17 (10)
Preoperative symptoms, *n* (%)[a]	
Headache	65 (38)
Seizures	56 (33)
Cognitive symptoms	71 (42)
Nausea	17 (10)
Balance/coordination problems	57 (34)
Visual disturbances	16 (9)
Language problems	54 (32)
Motor symptoms	45 (26)
Preoperative tumor volume in mL, median (range)	34.5 (0.1 to 210.1)
Histopathology, *n* (%)	
Glioblastoma	133 (78)
Anaplastic astrocytoma or anaplastic oligodendroglioma	33 (19)
Unspecified high-grade glioma	4 (2)
Biopsy only, *n* (%)	34 (20)
Treatment characteristics after resection (N = 112)	
Gross total resection, *n* (%)[b]	35 (31)
Moderate or severe postoperative complications within 30 days, *n* (%)[c]	12 (11)
Postoperative new or worsened neurological deficits at follow up, *n* (%)[d]	26 (23)
Initiation of adjuvant treatment within 30 days, *n* (%)	
Radiotherapy	97 (87)
Chemotherapy	83 (74)

[a] Many patients had multiple symptoms.
[b] Based on postoperative MRI < 48 h. N = 111 since one patient lacked an early postoperative MRI.
[c] Grade II-III complications according to the Landriel classification system.
[d] Some patients had several deficits. N = 111 since one patient lacked patient-reported deficits at follow up.

hemisphere, between tumors with the tumor center located in different lobes, or between patients with tumors located in non-eloquent, near eloquent or eloquent regions (Table 2). Using an additional white matter tract atlas (Hammers et al., 2003), no difference in HRQoL between tumors in the central lobe (i.e. pre- and postcentral gyrus) compared to other locations were observed (mean rank 69.17 vs. 83.9, P = .18). Further, there was no significant difference for affection of specific white matter tracts, except for patients with tumors involving the internal capsule who reported significantly worse HRQoL scores compared to patients without internal capsule involvement (mean rank 90.35 vs. 68.4, P = .004). When using VLSM methods to validate our findings, no voxels survived the significance level (unthresholded maps are presented in appendix (Fig. A1). The relationship between preoperative symptoms as registered from the medical journals and preoperative overall HRQoL was also explored. Significantly worse HRQoL-scores were only found in patients with balance/coordination problems (mean rank 70.69 vs. 87.61, P = .03) and motor symptoms (mean rank 62.24 vs. 88.86, P = .002) compared to patients without these symptoms.

As seen in Fig. 2, different tumor volumes are at diagnose rather evenly distributed in the brain. However, tumors in the right hemisphere were statistically larger (35.5 mL vs. 29.7 mL, P = .03) and tumors in the central lobe were significantly smaller compared to other locations (median 15.2 mL vs. 36.5 mL, P = .01). There was no correlation between preoperative tumor volume and preoperative EQ-5D

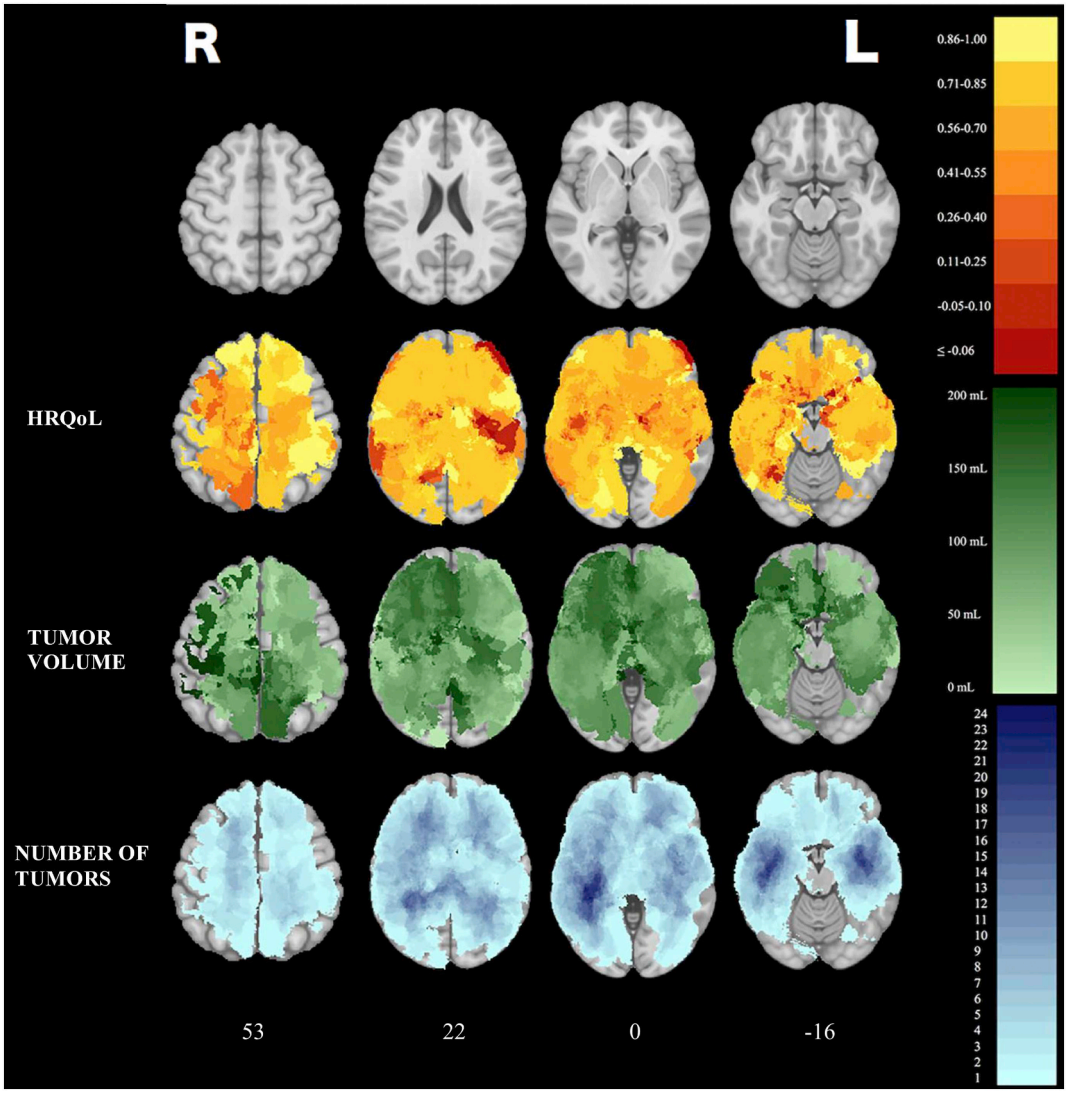

Fig. 2. Median preoperative EQ-5D index values in each voxel = yellow-red. Median preoperative tumor volume in each voxel = green. Number of tumors in each voxel = blue. Scalar bars for each volume are shown at the right, and z-coordinates at the bottom. $N = 163$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

index values (r_s − 0.073, $P = .36$) or postoperative change in EQ-5D index values (r_s − 0.046, $P = .59$).

For subitems of HRQoL, the most frequently reported preoperative problems were for “activity”, “pain/discomfort” and “anxiety/depression” (Fig. 3). Statistically, laterality (right vs. left), involvement of specific lobes, and eloquence was not related to “mobility”, “activity”, “pain/discomfort” or “anxiety/depression” (Appendix, Tables A1–A5). Tumor laterality and eloquence were not related to preoperative “self-care”, while lobes were significantly related ($P = .04$). In a post-hoc analysis we found that patients with tumors located in the right frontal lobe reported significantly more problems with “self-care” than patients with tumors located in other regions (32% vs. 16%, $P = .03$), and that patients with tumors in the left temporal lobe reported significantly less problems (3% vs. 23%, $P = .007$). Patients with tumor involvement in the left uncinate fasciculus reported less problems with “mobility” (17% vs. 40%, $P = .02$) while patients with tumors in the right uncinate fasciculus reported less problems with “activity” (31% vs. 55%, $P = .02$), and more problems with “anxiety/depression” (71% vs. 49%, $P = .03$). Further, patients with tumor involvement in the internal capsule reported more problems with “mobility” (53% vs. 25%, $P < .001$), self-care (28% vs. 13%, $P = .01$) and “activity” (64% vs. 42%, $P = .006$), and patients with tumor involvement in the right cingulum had more problems with “activity” (63% vs. 45%, $P = .04$).

3.4. Postoperative changes

Clinically important change in HRQoL after surgery was assessed in patients who underwent surgical resection (Fig. 4, Video 2). Based on the maps, it could seem like patients with tumors in or near the sensorimotor cortex or harbouring deeper lesions affecting the pyramidal tracts, the superior longitudinal fasciculus or the basal ganglia more often reported change in HRQoL after surgery. However, statistically, laterality, location in specific lobes, grading of eloquence, or tumor locations overlapping specific white matter tracts were not predictive factors of deterioration in HRQoL after surgery (Table 3). In post-hoc analyses, deterioration in HRQoL was not more common in patients with tumors in the central lobe (14% vs. 13%, $P = .85$), but patients with new or worsened motor deficits after surgery more frequently reported deterioration in HRQoL as compared to other patients (62% vs 25%, $P = .001$).

Table 2
Preoperative EQ-5D index values versus tumor location, $N = 163$.

	n (%)	Mean rank	Median	χ^2	*U*	df	*P*
Laterality					3082.5		0.45
Left	86	84.66	0.80				
Right	77	79.03	0.73				
Lobes				9.08		8	0.34
Frontal left	32 (20)	75.59	0.71				
Frontal right	31 (19)	79.15	0.73				
Temporal left	35 (21)	92.97	0.80				
Temporal right	28 (17)	83.52	0.80				
Parietal left	15 (9)	89.30	0.74				
Parietal right	12 (7)	86.21	0.73				
Occipital right	1 (1)	95.00	0.80				
Deep central left	4 (2)	67.00	0.62				
Deep central right	5 (3)	32.80	0.52				
Grading of eloquence				2.98		2	0.23
Non eloquent	42 (26)	84.26	0.78				
Near eloquent	54 (33)	89.24	0.73				
Eloquent	67 (41)	74.75	0.73				
White matter tract involvement[a]							
Arcuate fasciculus left					2112.0		0.78
Yes	31 (19)	84.13	0.74				
No	132 (81)	81.50	0.73				
Arcuate fasciculus right					2182.0		0.68
Yes	36 (22)	79.11	0.73				
No	127 (78)	82.82	0.73				
Cingulum left					2779.0		0.55
Yes	44 (27)	85.66	0.78				
No	119 (73)	80.65	0.73				
Cingulum right					2441.0		0.35
Yes	46 (28)	76.57	0.73				
No	117 (72)	84.14	0.73				
Fornix and/or corpus callosum					3297.5		0.74
Yes	97 (60)	82.99	0.76				
No	66 (40)	80.54	0.73				
Uncinate left					2073.0		0.57
Yes	29 (18)	86.48	0.80				
No	134 (82)	81.03	0.73				
Uncinate right					1916.5		0.72
Yes	27 (17)	84.98	0.80				
No	136 (83)	81.41	0.73				
Optic radiations					1975.0		0.61
Yes	32 (20)	78.22	0.78				
No	131 (80)	82.92	0.73				
Inferior longitudinal fasciculus left					1300.5		0.98
Yes	18 (11)	81.75	0.76				
No	145 (89)	82.03	0.73				
Inferior longitudinal fasciculus right					1115.5		0.19
Yes	19 (12)	68.71	0.62				
No	144 (88)	83.75	0.73				
Internal capsule					2288.0		**0.004**
Yes	62 (38)	68.40	0.69				
No	101 (62)	90.35	0.80				

χ^2 = Chi-square (Kruskal Wallis H test).
df = Degrees of freedom.
P = P-value. Bolded text indicates statistical significance.
U = Mann-Whitney *U* test.
[a] Overlap with tumor and white matter atlas data.

4. Discussion

Using an explorative novel study approach in this setting, we developed an atlas for depicting and assessing the potential importance of tumor location for generic perioperative HRQoL in patients with newly diagnosed HGG. We found that patient-reported overall HRQoL is rather evenly distributed across different tumor locations in the brain. Anatomical "hotspots" were most often seen in regions with few lesions, suggesting that these might reflect outliers. We found no statistical difference in overall perioperative HRQoL between patients with tumors in various lobes, in so-called eloquent areas, or in various voxels. From the patients' perspective, there is no "dominant" hemisphere, and except for the internal capsule, involvement of other major white matter tracts was not associated with worse preoperative overall HRQoL. Even though patients with preoperative motor symptoms reported lower preoperative HRQoL, and although acquired motor deficits were associated with worsened HRQoL after surgery, from preoperative MRI images we failed to identify specific neuroanatomical regions that were predictive of perioperative deterioration of overall HRQoL. The distinction between critical and less critical brain regions seems thereby more unclear according to the patients than when judged by physicians.

The relationship between lesion laterality/ affected lobes and HRQoL has been explored in several studies, but with considerably less detail and with inconsistent results. In accordance with our findings most studies with larger study populations have not found differences in HRQoL between patients with lesions in different regions. Cheng et al. used a disease-specific HRQoL questionnaire in 92 patients with glioma, and did not find preoperative differences between patients with tumors in the left or right hemisphere, or among tumors located in different lobes (Cheng et al., 2010). Similar findings have also been reported for postoperative HRQoL in a large oncological study (Brown et al., 2006), and in an even larger neurosurgical sample where the relation between tumor location and pre- and postoperative KPS was investigated (Polin et al., 2005). In contrast, a weak association between right-sided stroke and lower HRQoL has been found in 441 patients at 6 month follow up. However, in patients with high-grade gliomas such long-term HRQoL are difficult to assess due to the progressive disease, multimodal treatment and short life span. Also, functional reorganization and the effects of rehabilitation are probably smaller. Interestingly, in a small study of 65 patients with low-grade gliomas, patients with left-sided tumors had worse physical well-being than patients with right-sided tumors (Liu et al., 2009). Another small study also found more depressive symptoms and memory problems in patients with tumors in the left hemisphere (Hahn et al., 2003). Conversely, worse preoperative HRQoL have also been found in right-sided tumors, especially within the subdomains "pain", "social isolation", "emotion" (Salo et al., 2002) and "anxiety" (Mainio et al., 2003). Patients with strokes in the subcortical gray matter are also found to have lower HRQoL (Moon et al., 2004).

Assuming that a certain symptom burden usually is needed before being diagnosed with a brain tumor, and assuming that burden or symptoms increase with tumor volume, a difference in tumor volume between brain regions at diagnosis might indirectly reflect how important the region is to the patient. Accordingly, we detected right-sided tumors to be significantly larger than tumors in the left hemisphere, and tumors in the central lobe to be smaller. This might be interpreted as an indirect sign of the left hemisphere being dominant and supports the impression that motor functions are more critical. However, deficits relating to motivation, cognition or emotions are often more difficult to detect by patients than conventional neurologic deficits such as language deficits.

We found more preoperative problems in some EQ-5D subdomains for several specific locations. These were reported from patients with tumors in motor and limbic related regions, especially if they were

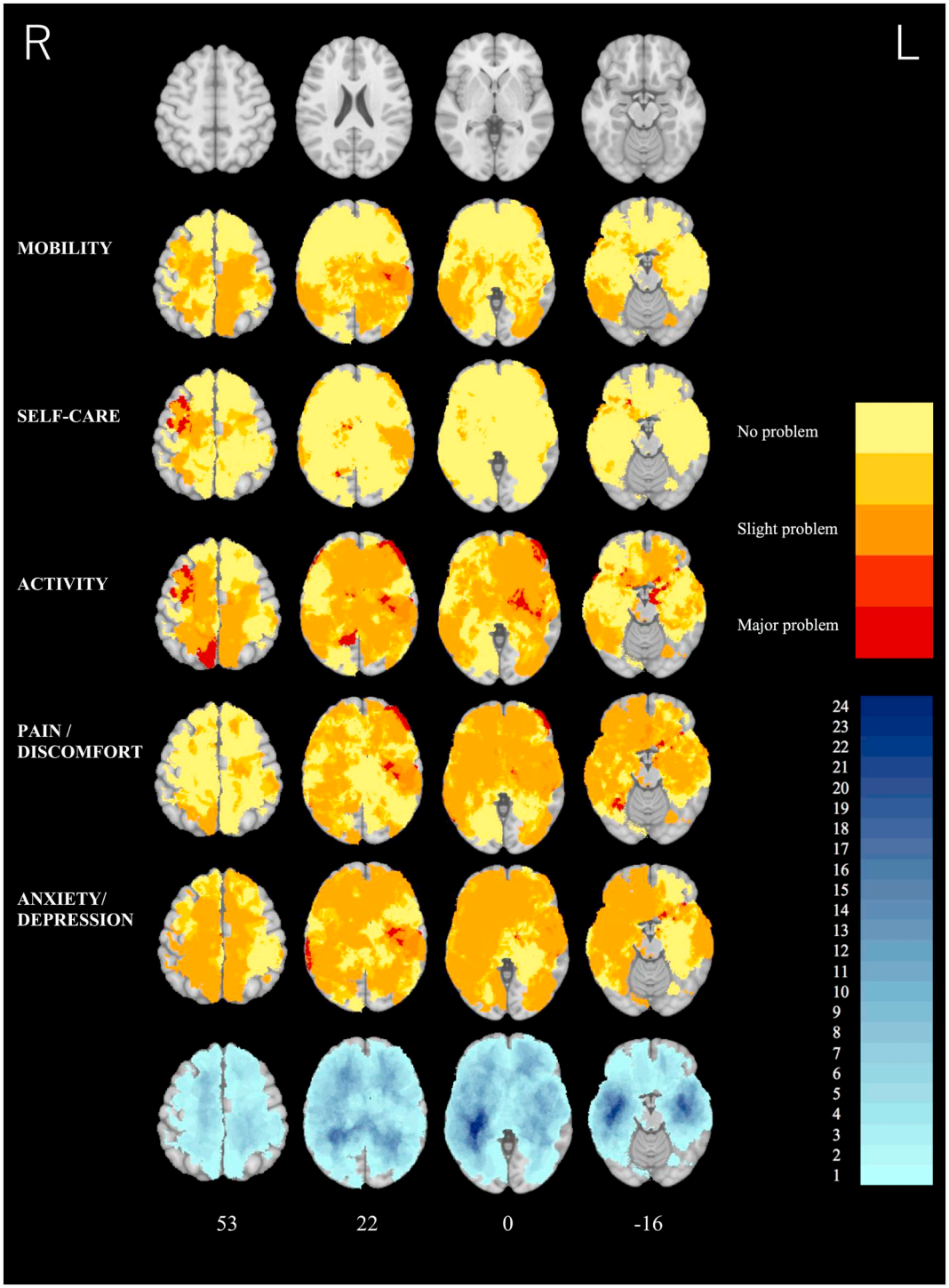

Fig. 3. Median preoperative problems in EQ-5D index subdomains in each voxel = yellow-red. Number of tumors in each voxel = blue. Scalar bars for each volume are shown at the right, and z-coordinates at the bottom. $N = 170$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

located in the right hemisphere. Since the frontal lobe includes the primary motor cortex, and the internal capsule consists of motor pathways, more problems reported from patients in the objective subdomains seem logical. The cingulum area is related to motor control and cognition (Paus, 2001), pain and emotion (Vogt, 2005), and other symptoms like nausea (Napadow et al., 2013). This may explain activity problems among patients with tumors in this tract. Further, although the uncinate fasciculus is poorly understood, several others have found an association between this pathway and anxiety, apathy and depression (Hollocks et al., 2015; Phan et al., 2009), which is in agreement with our findings.

The association between clinician-rated eloquence and HRQoL-changes is difficult to explore due to patient selection, and since surgeons carefully attempt to avoid inflicting damage to these areas to preserve neurological function. Also, judging which brain regions that are eloquent based on structural preoperative MRI-images is difficult. In a large validation study of a grading system for arteriovenous malformations, eloquence scores varied between 28% and 60% in different

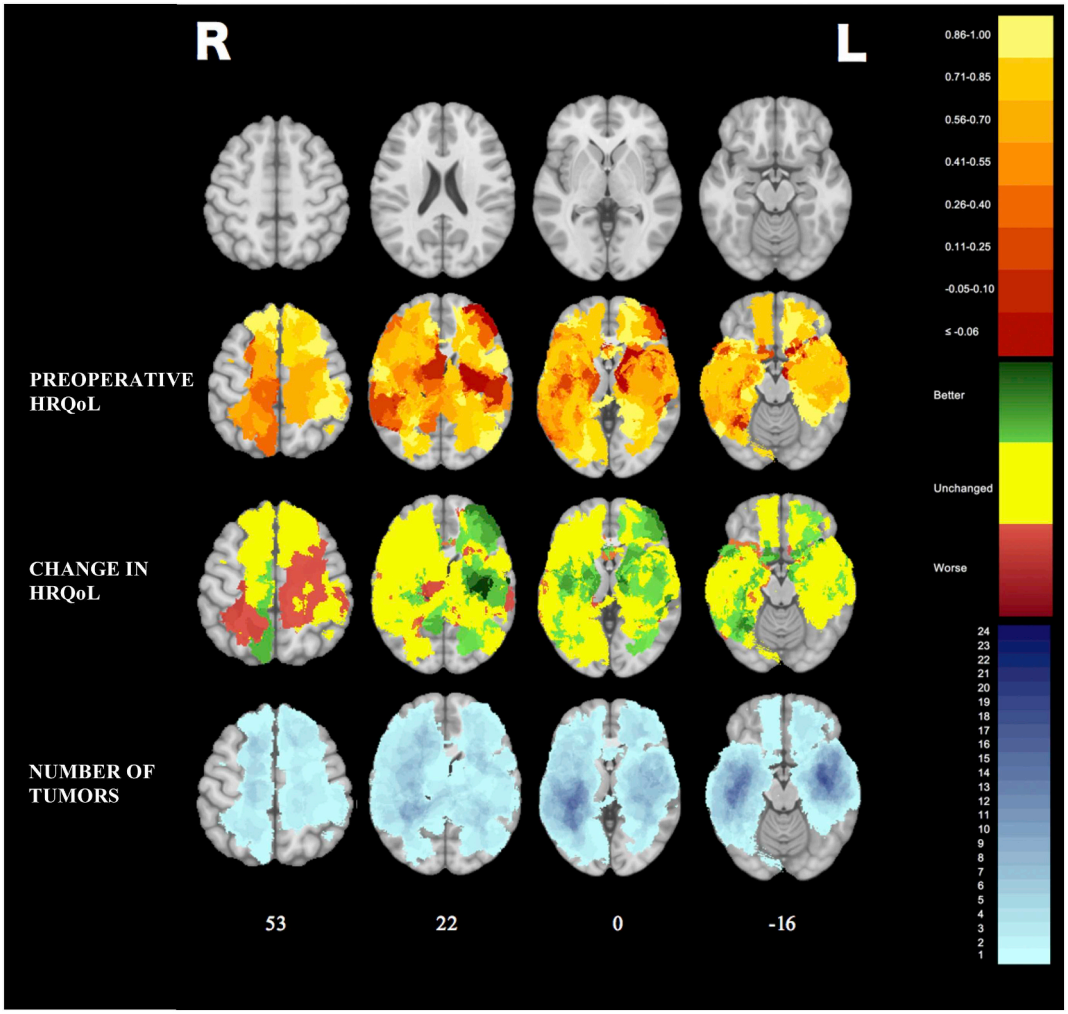

Fig. 4. Median preoperative EQ-5D index values in each voxel = yellow-red. Median postoperative change in EQ-5D index value in each voxel = red-yellow-green (values ≤ ± 0.15 are considered as unchanged). Number of tumors in each voxel = blue. Scalar bars for each volume are shown at the right, and z-coordinates at the bottom. $N = 112$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

centers (Kim et al., 2015). Thus, so-called eloquence assessments are rather imprecise and subjective. Still, even though we did not find any statistical difference in HRQoL between patients with tumors in eloquent, near eloquent or non-eloquent regions, the worse HRQoL scores in patients with preoperative balance/coordination problems and motor deficits, in patients with tumors involving the internal capsule, and in patients with new or worsened motor deficits after surgery together indicate that motor deficits have a particularly profound impact on several aspects of overall HRQoL as measured with EQ-5D, including the subdomains “mobility”, “self-care”, and “usual activities”. From the maps, it also seems like tumors located near motor and sensory cortex had more deterioration in HRQoL after surgery. Thus, although surgeons and their patients may not necessarily agree on what are the most crucial or eloquent brain regions, they seem to agree that motor control is important. Preservation of motor functions may therefore be more critical than other functions with respect to overall HRQoL. The lack of motor control is perhaps more readily acknowledged by both the patients and their surgeons than for example personality changes or milder cognitive deficits, at least in the perioperative phase of the disease. Admittedly, assessment of other brain regions containing functions like language or higher executive functions are more difficult to assess in practice due to the inter-individual variation and the complex and controversial localization of such functions.

Since the aim of HGG treatment is improved survival without jeopardizing quality of life, potential factors influencing HRQoL should be of particular interest. Compared to a functional status with only one physical component like KPS, HRQoL is a multidimensional construct that also includes physical, psychological and social aspects. It is assessed from the patients' perspective, which often differs from the clinicians' (Slevin et al., 1988). Thereby, it potentially represents a less biased way of reporting and ensures relevance for the patients. Although our intention was to explore the patients *overall* HRQoL, we acknowledge that EQ-5D is not sensitive enough to capture all symptoms and facets of the disease. Thus, using a questionnaire focusing on specific symptoms (e.g. language functions) may have yielded different results. However, in our experience such extensive questionnaires are frequently too burdensome and results in much missing data and consequently selection bias, and is therefore often not applicable in an unselected HGG population (Sagberg et al., 2016). A simple generic questionnaire like EQ-5D is thereby a compromise between external validity and sensitivity while maintaining the patients' perspectives on HRQoL. Although it is a coarse measure, we believe it captures the most significant problems caused by HGG. We have earlier found the questionnaire to be responsive for deterioration after glioma surgery (Sagberg et al., 2014), it reflects the disease course over time (Sagberg et al., 2016), and postoperative deterioration is associated with shorter survival (Jakola et al., 2011).

Further development of our novel study approach with more patients and perhaps other patient-reported measures and/or neuropsychological evaluations is a way to advance if aiming to assess true

Table 3
Crosstabulation of postoperative deterioration in EQ-5D index values and tumor location, $N = 112$.

	Postoperative deterioration (≥MCID)				
	Yes, *n* (%)	No, *n* (%)	χ^2 or F	df	*P*
Laterality			0.30	1	0.58
Left	14 (23)	47 (77)			
Right	14 (28)	37 (73)			
Lobes			5.40		0.60
Frontal left	6 (26)	17 (74)			
Frontal right	4 (19)	17 (81)			
Temporal left	7 (26)	20 (74)			
Temporal right	6 (29)	15 (71)			
Parietal left	1 (13)	7 (88)			
Parietal right	4 (57)	3 (43)			
Deep central left	0 (0)	3 (100)			
Deep central right	0 (0)	2 (100)			
Grading of eloquence			0.70	2	0.70
Non eloquent	8 (23)	27 (77)			
Near eloquent	10 (30)	23 (70)			
Eloquent	10 (23)	34 (77)			
White matter tract involvement[a]					
Arcuate fasciculus left			2.92	1	0.09
Yes	2 (10)	18 (90)			
No	26 (28)	66 (72)			
Arcuate fasciculus right			0.08	1	0.78
Yes	6 (27)	16 (73)			
No	22 (24)	68 (76)			
Cingulum left			0.08	1	0.78
Yes	5 (23)	17 (77)			
No	23 (26)	67 (74)			
Cingulum right			0.02	1	0.90
Yes	7 (26)	20 (74)			
No	21 (25)	64 (75)			
Fornix and/or corpus callosum			0.98	1	0.32
Yes	18 (29)	45 (71)			
No	10 (20)	39 (80)			
Uncinate left			0.49	1	0.49
Yes	4 (19)	17 (81)			
No	24 (26)	67 (74)			
Uncinate right					1.00
Yes	4 (24)	13 (77)			
No	24 (25)	71 (75)			
Optic radiations			0.02	1	0.89
Yes	6 (26)	17 (74)			
No	22 (25)	67 (75)			
Inferior longitudinal fasciculus left					0.76
Yes	3 (19)	13 (81)			
No	25 (26)	71 (74)			
Inferior longitudinal fasciculus right					0.52
Yes	5 (33)	10 (67)			
No	23 (24)	74 (76)			
Internal capsule			0.06	1	0.81
Yes	8 (24)	26 (77)			
No	20 (26)	58 (75)			

χ^2 = Pearsons chi-square.
MCID = Minimal Clinically Important Difference ≥ 0.15.
F = Fishers Exact test.
df = Degrees of freedom.
P = *P*-value. Bolded text indicates statistical significance.
[a] Overlap with tumor and white matter atlas data.

eloquent regions or functions as seen by the patients. Evidence-based tools based on such maps could be useful to guide and support clinical decision-making.

4.1. Strengths and limitations

HGG is a heterogeneous disease, and a major strength in the present study is the population-based sample. However, detailed studies on the impact of tumor location require a considerable sample size, and our findings are therefore presented as preliminary. Admittedly, our sample size is still rather large in this setting, and our negative statistical findings are validated by using VLSM-methods that take the distribution of data into account. Further, although the reliability of our segmentations is found to be acceptable (Fyllingen et al., 2016), finding the exact pathological border of a tumor during segmentation is an impossible task due to the diffuse growth pattern of glioma. Not only the focal tumor volume, but also the effect of edema, the anatomical and functional variability, and possible remote effects may influence the HRQoL in different brain regions. On the other hand, functional reorganization and brain plasticity is probably limited due to the fast-growing biology. In addition, the registration to the average brain, and the use of imported atlases of lobes and white matter tracts may contribute to inaccuracy. However, detailed assessment of all major functional regions and all white matter tracts is impossible on the individual level. Other limitations are the possibility of false negative findings in regions with few or none tumors (e.g. visual cortex), and the risk of false positive findings when making multiple tests. Finally, of 112 patients, 25 (22%) had the best possible score at baseline, indicating a ceiling effect (McHorney and Tarlov, 1995), which could conceal potential improvements after surgery.

5. Conclusions

In this ongoing registry-based project we found that median patient-reported HRQoL is rather evenly distributed across different tumor locations in the brain. The impact of anatomical tumor location on overall perioperative HRQoL therefore seems lower than frequently believed. However, worse HRQoL was found in patients with tumors in motor related regions, indicating that these areas are crucial also from the patients' perspective. Evidence-based tools based on maps could be a useful adjunct to physician-rated experience-based eloquence assessments to guide and support clinical decision-making in neurosurgery.

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Statement

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Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2019.101658.

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