Brain Lesions Associated with Communication-Related Quality of Life Following Surgical Removal of Primary Left-Hemisphere Tumours

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Abstract

Background. Long-term health-related quality of life (HRQoL) is an important consideration in planning treatment for individuals with brain tumours.

Aim. The current study examined relationships between HRQoL and anatomical location of the lesion in patients 6-24 months post-surgery.

Methods. Following left-hemisphere tumour resection, 37 individuals underwent behavioural testing and MRI. A principal component analysis across 10 HRQoL measures identified two components explaining ~62% of the variance: a communication-related and a mood-related component. Three lesion maps were generated per participant capturing (1) the primary resection, (2) the resection plus residual tumour, oedema, and peri-resection treatment effect (resection+), and (3) residual tumour, oedema, and peri-resection treatment effect alone (residual). Relationships between HRQoL components and lesion maps were examined using voxel-wise lesion symptom-mapping as well as general linear models predicting tract- and voxel-wise disconnection severities.

Results. Communication-related quality of life was significantly associated with lesions comprising both the resection+ and residual tumour in the left medial inferior parietal lobe. Voxel-wise analyses of white matter disconnection severities revealed significant associations between communication-related quality of life and thalamostriatal fibres for the residual tumour lesions. None of the analyses involving mood-related quality of life or the primary resection lesion maps were significant.

Conclusions. The findings highlight the role of the residual tumour, oedema, and peri-resection treatment effects and associated white matter disconnection in communication-related quality of life following treatment.

Key words: brain tumours, surgery, quality of life, aphasia, neuroimaging, white matter

Introduction

Health-related quality of life (HRQoL) refers to "how well a person functions in their life and his or her perceived well-being in physical, mental, and social domains of health" (Hays & Reeve, 2010, p. 198). HRQoL may also be considered as "those aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment" (Ebrahim, 1995, p. 1384). HRQoL can be affected in those with brain tumours; both in the early stages of symptoms and along the diagnosis/treatment journey. Although brain tumour treatment is not yet curative, advances in surgical approaches and adjuvant therapies have improved the 5-year survival rates (Allemani et al., 2018), making long-term HRQoL critical to the treatment planning process. The goal of brain tumour surgery is to maximally remove tumour tissue to improve survival while also preserving brain function and HRQoL. Awake brain surgery, in particular, has made it possible to preserve brain function despite removing tumours near eloquent brain regions (Paldor et al., 2016; Papagno et al., 2012; Sarubbo et al., 2020; Suarez-Meade et al., 2020; Zigiotto et al., 2020). To date, studies examining tumour location and its resection relative to long-term HRQoL are limited.

For individuals with brain tumours, reduced HRQoL is associated with several factors including seizures, neurocognitive deficits, and mood disturbance (Haider et al., 2021; Nassiri et al., 2019; Noll et al., 2017; Teng et al., 2021). In addition, individuals with left-hemisphere brain tumours are at increased risk of developing aphasia (Brownsett et al., 2019; Davie et al., 2009; Satoer et al., 2018), which may further impact HRQoL by limiting social functioning and independence (Santini et al., 2012; Veretennikoff et al., 2017). Communication impairment is often an exclusion criterion in studies of HRQoL in adults with brain tumours (Rimmer et al., 2022), limiting our understanding of HRQoL in these patients. It is therefore important to not

only examine aspects of HRQoL that pertain to activities of daily living, cognition, and anxiety/depression, but also to communication and social interaction.

Current measures of HRQoL employed in clinical trials for brain cancer treatment either fail to address language and communication issues or provide only limited coverage. For example, the EuroQol's group EQ-5D-3L (The EuroQol Group, 1990) and the Sherbrooke Neuro-Oncology Assessment Scale (Goffaux et al., 2009) are generic self-report measures that do not include questions about communication, while others such as the Functional Assessment of Cancer Therapy-Brain (FACT-Br) and European Organization for Research and Treatment of Cancer's Quality of Life Questionnaire (BN20) (Taphoorn et al., 2010) each include only four questions relevant to communication. Using the latter measure, two recent studies reported, respectively, that more than 50 percent of patients treated for gliomas self-reported communication and language-related quality of life (QoL) concerns (Umezaki et al., 2020), and that these subjective reports were significantly associated with poorer neuropsychological function (Gehring et al., 2015).

Although lesion analysis methods have been applied for some time to investigate neuropsychological function in tumour patients (Cargnelutti et al., 2020), only two studies have used lesion-symptom mapping (LSM) to examine the relationship between lesion location and HRQoL in individuals with brain tumours. The first by Sagberg and colleagues (2019) found no relationship between lesion location and HRQoL as assessed by the EQ-5D-3L when examined before or in the 4-6 weeks following surgery in patients with high-grade glioma. The second LSM study by Fortin et al. (2021) investigated HRQoL in pre-operative patients with high-grade glioma using the Sherbrooke Neuro-Oncology Assessment Scale (Goffaux et al., 2009) and found positive correlations between temporoparietal regions in the right hemisphere and adverse

HRQoL (Fortin et al., 2021). The authors expressed surprise at the right-hemisphere findings; that is, they expected left-dominant language functions to have a larger impact on HRQoL than right-dominant functions such as visuospatial cognition. However, neither of these studies employed HRQoL measures that included specific questions about language and communication. In the following paragraphs, we refer to similar measures as non-communication specific HRQoL measures.

Other studies examining anatomical predictors of non-communication specific HRQoL outcomes in individuals with brain tumours have focused on the extent of the resection, discrete locations of the tumour, and tumour volume. In the weeks following surgery, the extent of resection does not appear to be a predictor of HRQoL (Jakola et al., 2011), but in the 6-12 months after surgery, gross total resection is associated with better HRQoL (Drewes et al., 2016; Muto et al., 2018). Maximal resection is not always possible, however, if part of the tumour is within eloquent brain regions of speech, motor, and cognitive functions. In those cases, the residual tumour, in addition to tumour growth or effects of surgery and ongoing adjuvant therapy, may contribute to postoperative impairment in cognitive and neurological function that may prevent an individual from returning to work (Muto et al., 2018). These findings highlight the importance of examining not only the resection cavity, but also other lesion variables that might extend beyond the primary tumour when considering the impact on HRQoL.

Studies investigating the role of tumour laterality have reported significant relationships with non-communication specific HRQoL before surgery (Hahn et al., 2003; Mainio et al., 2003; Salo et al., 2002), although these effects do not seem to hold after surgery (Drewes et al., 2016; Mainio et al., 2003; Sagberg et al., 2019; Wettervik et al., 2022). One study reported that individuals with occipital lobe lesions were more likely to experience reduced HRQoL in the

acute postsurgical phase (Jakola et al., 2011), but other studies failed to detect an association between tumour lobe and post-surgical HRQoL (Sagberg et al., 2019; Wettervik et al., 2022). Tumour volume was also not predictive of HRQoL following surgery despite often being associated with neuropsychological impairments (Sagberg et al., 2016, 2019; Wettervik et al., 2022). Measures of tumour laterality, lobe, and volume are relatively coarse measures that do not capture the precise location of the tumour or its resection and thus may not be sensitive to consequences in HRQoL. Detailed analyses of lesion location combined with longer-term measures of HRQoL (> 6 months post surgery) have the potential to reveal some of the neural contributions to HRQoL following brain tumour removal.

The current study aimed to (1) comprehensively characterise HRQoL in individuals 6-24 months following resection of left-hemisphere tumours and (2) examine the relationships between HRQoL and anatomical lesion location in the same cohort. Specifically, HRQoL measures were selected to capture communication, mood, and factors associated with living with a brain tumour. The lesions were delineated according to the primary surgical resection, the resection plus residual tumour, oedema, and peri-resection treatment effect (resection+), and residual tumour, oedema, and peri-resection treatment effect only (residual). The relationships between HRQoL and the lesions were quantified using voxel-wise LSM (VLSM) and white-matter-tract disconnection severity analyses.

Materials and Methods

Ethics

This study was performed in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Human Research Ethics Committee at the respective hospitals

(approval numbers: HREC/14/QPAH/367, HREC/15/MH/58) and informed consent was obtained from all individual participants included in the study.

Participants

Forty-seven participants were recruited as part of a larger study examining language outcomes following surgery to remove primary left-hemisphere brain tumours (de Zubicaray et al., submitted). All participants underwent surgery on average nine months (range = 6-24 months) earlier at the Princess Alexandra, Royal Brisbane and Women's, and Royal Melbourne and Melbourne Private Hospitals in Australia. Surgery was conducted by authors SO, RLJ, and KD, respectively, at these sites. All participants were right-handed and native English speakers. Exclusion criteria were non-primary and non-intraparenchymal tumours, history of uncorrected hearing or visual impairment, other neurological or psychiatric conditions, substance abuse, head injury, or metal implants. No data were collected on whether participants received language therapy following surgery.

From this initial cohort of 47 participants, a subset of participants (N = 37; 17 female) were identified as having complete datasets with both HRQoL and brain imaging measures and were included in the current analyses. Tables 1 and 2 provide the demographic, clinical and language assessment data for the included participants. Language performance was assessed using the Comprehensive Aphasia Test (CAT) (Swinburn et al., 2004). The CAT assesses impairment according to a cognitive neuropsychological model of language processing. It has 27 subtests (Table 2) that together provide a cognitive screen and detailed characterisation of language ability (comprehension of spoken and written language, repetition, naming, reading, writing, and spoken and written picture descriptions). In addition, the CAT includes a Disability Questionnaire described in more detail in the *HRQoL assessments* section below. A small

number of the cognitive screening and language subtests (7/27) had missing data due to 1-2 participants being unable to complete the assessment. Raw scores were converted to T-scores and impairment was defined as being below the fifth percentile of a sample of neurologically healthy controls (Swinburn et al., 2004). Twenty-five participants (68%) met the threshold for impairment on at least one subtest, with 17 (46%) impaired on at least two subtests, and 13 (35%) impaired on at least 3 subtests.

Insert Tables 1 and 2 about here

HRQoL assessments

All participants were assessed in a single session, with sessions usually occurring on the same day as image acquisition (median = 0 days, IQR = 4). The HRQoL assessments included: (1) the CAT Disability Questionnaire (Swinburn et al., 2004); (2) the Depression Anxiety Stress Scale (DASS-21) (Osman et al., 2012); and (3) the FACT-Br (Thavarajah et al., 2014; Weitzner et al., 1995). All assessments were completed by the participants, and not a caregiver or proxy.

CAT Disability Questionnaire

The CAT Disability Questionnaire captures the extent of perceived disability and impact of living with aphasia (Swinburn et al., 2004). A *total disability score* was estimated from ratings of talking, understanding, reading, and writing ability (maximum score = 64). A *total impact score* was estimated from ratings of intrusion, self-image, and emotional consequences (maximum score = 60). Higher scores indicate greater disability/impact. The scores are based on responses to 31 questions rated on a 5-point scale from 0-4. Example questions from the talking subtest include: *"how easy is it for you to talk to the person closest to you?"* and "*how easy is it*

to talk if you are stressed or under pressure?" (Swinburn et al., 2004). A rating of 0 corresponds to talking with no problem, and a rating of 4 indicates a complete inability to talk.

DASS-21

The DASS-21 measures distress experienced in the past week along three dimensions: depression, anxiety, and stress (Osman et al., 2012). Each dimension has an associated score; higher scores indicate more severe distress (maximum score = 21 for each dimension). The scores are based on responses to 21 statements rated on a 4-point scale (never, sometimes, often, and almost always). Sample statements include: *"I felt that I had nothing to look forward to"* and "*I tended to over-react to situations"*.

FACT-Br

The FACT-Br is a measure of HRQoL that combines the original FACT-General with a subscale for individuals with brain tumours (Thavarajah et al., 2014; Weitzner et al., 1995). The FACT-Br assesses HRQoL along five dimensions, each with an associated score: physical (maximum = 28), social/family (maximum = 28), emotional (maximum = 24), and functional - well-being (maximum = 28), in addition to disease-specific concerns (maximum = 92). Higher scores indicate higher HRQoL. Altogether, participants rate 50 statements based on their experience over the past week. Responses are on a 5-point scale (not at all, a little bit, somewhat, quite a bit, very much). Examples of the disease-specific concerns statements include: *"I have had seizures (convulsions)"*, and *"I have difficulty expressing my thoughts"*.

In total, ten scores were provided by the HRQoL assessments. To reduce the dimensionality of the data, we conducted a principal component analysis (PCA) across all ten scores in Jamovi (R Core Team, 2021; The jamovi project, 2022). The Kaiser-Meyer-Olkin measure verified the sampling adequacy for the analysis (Kaiser-Meyer-Olkin = .796), and all

Kaiser-Meyer-Olkin values for individual items were > .695, well above the acceptable limit of .5. Bartlett's test of sphericity was also significant, $\chi^2 = (45) = 231$, $p < .001$, indicating that correlations between measures were sufficiently large for PCA. The analysis used varimax as the rotation method and a Kaiser criterion eigenvalue threshold of 1 to determine the initial number of components. The components were further evaluated such that only components with four or more moderate to high loadings (i.e., > .6) were considered reliable (Guadagnoli & Velicer, 1988) and included in subsequent analyses. The measures loaded on each component were reviewed to identify the primary construct captured by a given component. The components were also examined with respect to time post-surgery and World Health Organization (WHO) grade.

Image acquisition

Imaging was conducted at the Princess Alexandra, Royal Brisbane and Women's, and Royal Melbourne and Melbourne Private Hospitals, Australia on 3 Tesla Skyra, Trio, or Prisma Siemens Scanners (Erlangen, Germany) 6-24 months post surgery. At all sites, 3D FLAIR and post-gadolinium contrast MPRAGE 3D T1-weighted images were acquired using the parameters provided in Table 3.

Insert Table 3 about here

Lesion maps

The FLAIR images were coregistered to the T1-weighted images using Statistical Parametric Mapping software (SPM12; Wellcome Department of Cognitive Neurology, London, UK). Lesions were manually traced on the T1-weighted and FLAIR images using MRIcroGL software (v6; https://www.nitrc.org/projects/mricrogl/) in axial orientation and cross-checked by

authors SB, KLM and GZ, who were blind to the participant's behavioural/ HRQoL measures and adjunctive therapy. Two lesion maps were generated per participant: one representing the primary *resection* (dark on T1) and one representing the resected area plus voxels with hyperintense FLAIR and gadolinium-enhanced signal from residual tumour and/or oedema and peri-treatment effects (*resection+).* The resection+ map was a binary map and did not differentiate between the residual tumour, oedema, or peri-treatment effects. The structural images and resection+ maps were then normalised into MNI space with the Clinical Toolbox in SPM12 using enantiomorphic normalization and a lesion-mask cost function (Brett et al., 2001; Nachev et al., 2008; Rorden et al., 2012). A 3mm full-width half-maximum Gaussian kernel was used to smooth the resection maps, and these maps were also normalised into MNI space using the transformations derived for the resection+ maps. Finally, *residual* lesion maps were generated by exclusively masking the resection and resection+ lesion maps.

VLSM analyses

The normalised and binarized resection, resection+, and residual lesion maps were entered into separate VLSM analyses using the CLIMB (CLSM v2.55; https://www.nitrc.org/projects/clsm/; Ivanova et al., 2020) extension of the original VLSM software (Bates et al., 2003; Ivanova et al., 2021; Wilson et al., 2010). Specifically, we performed univariate LSM using a linear regression with a voxel lesion value as the dependent variable, HRQoL principal component scores as the independent variable, and age, sex, education in years, time post-surgery, WHO grade (1-4), and lesion volume as covariates. As analyses were conducted on binary lesion maps, we did not include scanner as a covariate. Only voxels where at least five participants had damage were included in the analysis. We employed univariate LSM because (1) unlike stroke lesions that demonstrate significant spatial

autocorrelation which violates the assumptions of univariate approaches, post-surgical lesions are typically more randomly distributed in the brain (Xu et al., 2018); (2) they are generally more accurate and robust at detecting and localizing a single target with a low false positive rate than multivariate approaches, and (3) they require smaller sample sizes (Ivanova et al., 2021; Sperber & Karnath, 2018). Correction for multiple comparisons was performed via nonparametric permutation-based cluster-size thresholding with a voxel-wise threshold of $p < .001$ as it provides a good balance between a sparse, spatially differentiated solution and robust results (Ivanova et al., 2021).

Tract-wise disconnection analyses

To identify affected white matter fibre pathways associated with each participant's resection, resection+, and residual lesion maps, we performed tract-wise analysis using the Lesion Quantification Toolkit (Griffis et al., 2021). Specifically, we estimated disconnection severities for six major dorsal and ventral language tracts from the Human Connectome Project's population-averaged streamline tractography atlas (HCP-842): the arcuate fasciculus, frontal aslant tract, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, uncinate fasciculus, and superior longitudinal fasciculus-III (SLF-III) (Dick et al., 2014; Forkel & Catani, 2018; Yeh et al., 2018). Each lesion map was embedded into the HCP-842 atlas as a region-of-interest to identify the percentage of disconnected streamlines, resulting in an explicit measure of disconnection for each tract. We conducted linear regressions in Jamovi (R Core Team, 2021; The jamovi project, 2022) with the percentage of disconnected streamlines in each tract as the dependent variable and HRQoL principal component scores as the independent variable, comparing them with a null model that included sex as a factor and age, education, WHO grade,

time post-surgery and lesion volume as covariates. We applied a Bonferroni correction for multiple comparisons across the six tracts, resulting in a critical *p* value of .0083.

Voxel-wise disconnection analyses

To identify voxel-wise disconnection severities associated with each participant's resection, resection+, and residual lesion maps, we calculated tract density image volumes using the Lesion Quantification Toolkit (Griffis et al., 2021). These volumes were converted into a voxel-wise percent disconnection severity map, where the voxel values correspond to the percentage of streamlines contained within each voxel that are expected to be disconnected by each participants' lesion. The disconnection severity maps were entered into voxel-based morphometry analyses in SPM12 with age, sex, education in years, time post-surgery, WHO grade, and lesion volume specified as covariates. We thresholded the results using a voxel-wise threshold of $p < .001$ and a spatial cluster extent threshold of $p < .05$ (FWE corrected via the Bonferroni procedure).

Results

HRQoL

Table 4 shows descriptive statistics for the HRQoL measures. On the CAT Disability Questionnaire, participants' perceived disability (mean 11.76) and impact (mean 13.22) scores both corresponded to the 65th percentile, compared to a normative sample of people with aphasia (Swinburn et al., 2004). The 65th percentile indicates better than average perceived disability and impact associated with living with aphasia.

On the DASS-21, participants on average reported sub-clinical levels of depression (mean 3.89), mild levels of anxiety (mean 3.35), and sub-clinical levels of stress (mean 6.54). However, the levels of distress across all three dimensions (depression, anxiety, stress) ranged

from sub-clinical to extremely severe. Specifically, ten participants (27%) reported depression above subclinical levels, 16 (43%) participants reported anxiety above subclinical levels, and 5 participants (14%) reported stress above subclinical levels.

On the FACT-Br, the average scores of physical, social/family, emotional, and functional well-being all fell within 1 SD of a large (N = 1075) sample of the general adult population in the USA (Brucker et al., 2005), with a wide range across subjects. Normative data are not provided for the disease-specific subscale of the FACT-Br, however, a range of scores were observed (mean = 68.83, range = 36–86).

Insert Table 4 about here

A PCA across all ten HRQoL scores revealed that three components accounted for 79.5% of the variance in the data (PC1 = 33.2%; PC2 = 28.7%; PC3 = 17.6%). Table 5 provides the loadings for the principal components. The first component loaded primarily with communication-related QoL measures, with higher scores indicating lower communication-related QoL. The second component primarily loaded with mood-related QoL measures, with higher scores indicating lower mood-related QoL. The third component only had two suprathreshold loadings and was not considered reliable for inclusion in subsequent analyses.

Insert Table 5 about here

Neither communication nor mood-related QoL components were significantly associated with time post-surgery (communication-related QoL: r = .25, p = .135; mood-related QoL: r =

.06, p = .705) or WHO grade (communication-related QoL: $t(35) = -1.85$, p = .073; mood-related QoL: $t(35) = 1.84$, p = .075). Only communication-related QoL was significantly correlated with age, with older age associated with poorer QoL, r = .42, p = .01 (mood-related QoL, r = -.29, p = .087). To determine the relationships between aphasia and both PCA measures of QoL, we performed analyses of covariance (ANCOVAs). We operationally defined aphasia as impairment on two or more subtests on the CAT; we chose this cut-off as it approximated a median split with 17/37 (46%) patients meeting the cut-off. We included age, time post-surgery, and WHO grade as covariates. The presence of aphasia was associated with significantly poorer communication-related QoL, $F(1,32) = 9.513$, p =.004, $\eta^2 = 0.182$, but not mood-related QoL, $F(1,32) = 0.012$, p =.913, $\eta^2 = 0.000$.

Voxel-wise LSM

Figure 1 shows the spatial topography of the resection, resection+, and residual lesions. All figures follow neurological convention where the left hemisphere of the brain appears on the left side of the image. For resection lesions, the mean volume was 13.8 ml (SD = 15.8), and maximum overlap was in the left superior medial frontal region (n = 6). For resection+ lesions, the mean volume was 50.8 ml (SD = 54.4), and maximum overlap was in the left posterior temporoparietal region (n = 9). For the residual (n = 8) lesions, the mean volume was 37.1 ml (46.8), and maximum overlap was also in the left posterior temporoparietal region.

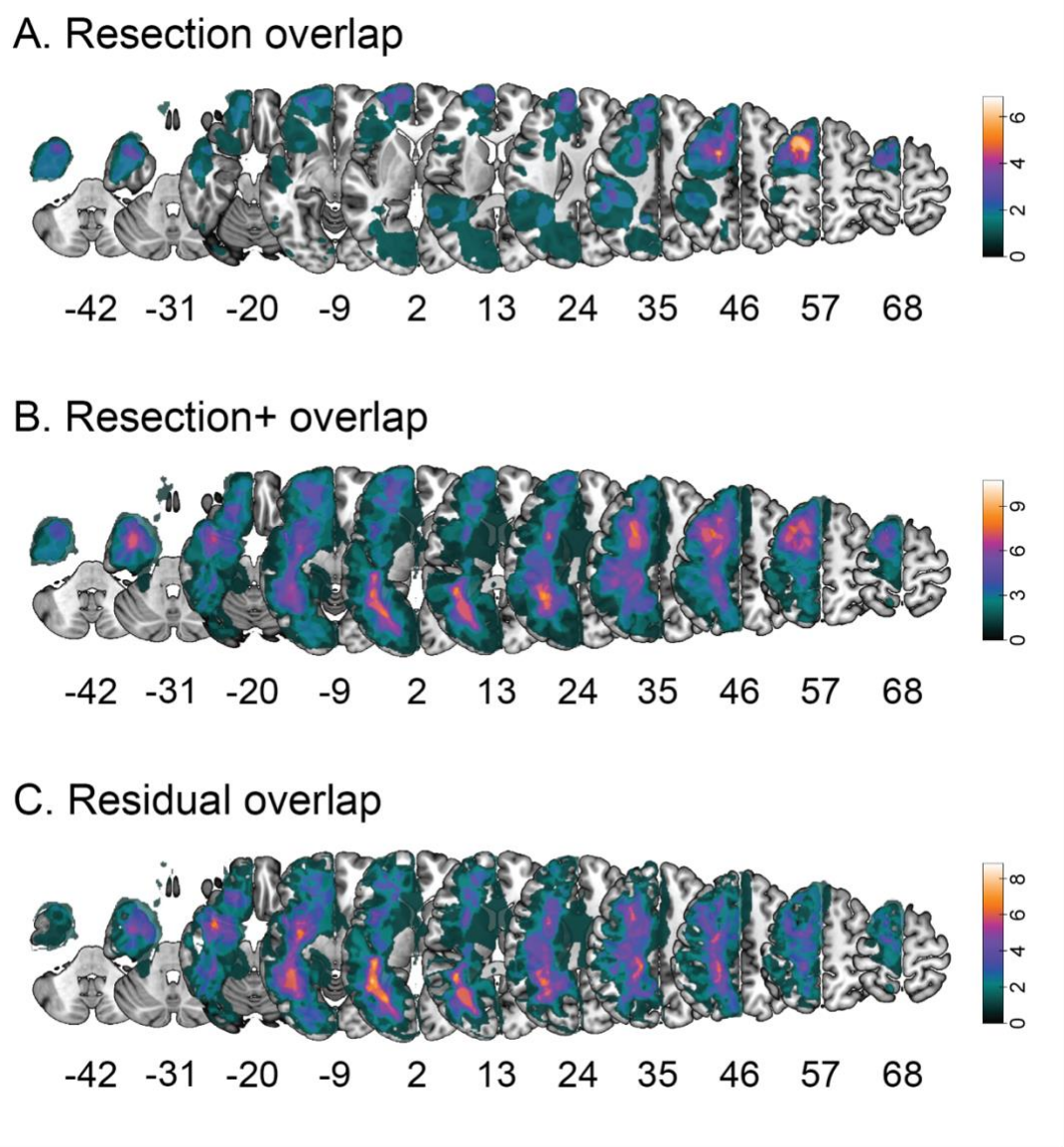

Figure 1. Spatial topography of (A) the primary resection, (B) the primary resection plus voxels with hyperintense FLAIR and gadolinium-enhanced signal from residual tumour, oedema, and peri-treatment effect (resection+), and (C) residual lesions generated by exclusively masking the resection and resection+ lesion maps. The topography is overlaid on axial slices of the MNI152 template provided with MRIcroGL software. Colour bars indicate number of participants with overlapping lesions in a given voxel.

The VLSM analyses performed on the resection lesion maps did not reveal any significant clusters for either HRQoL component score. The VLSM analyses performed on the resection+ lesion maps showed that the communication-related QoL component, but not the mood-related QoL component, was significantly associated with a cluster in the left medial inferior parietal lobe covering portions of the precuneus and angular gyrus as well as deep white matter (peak maxima = [-27, -54, 26], cluster volume = 893, t_{max} = 4.61, $p_{corrected}$ = .016; see Figure 2A). Similarly, the VLSM analyses conducted on the residual lesion maps identified a significant association for the communication-related QoL component, but not the mood-related QoL component, with a cluster in the left medial inferior parietal lobe encompassing portions of the precuneus in addition to deep white matter (peak maxima = [-18, -55, 20], cluster volume = 105, t_{max} = 4.30, $p_{corrected}$ = .039; see Figure 2B).

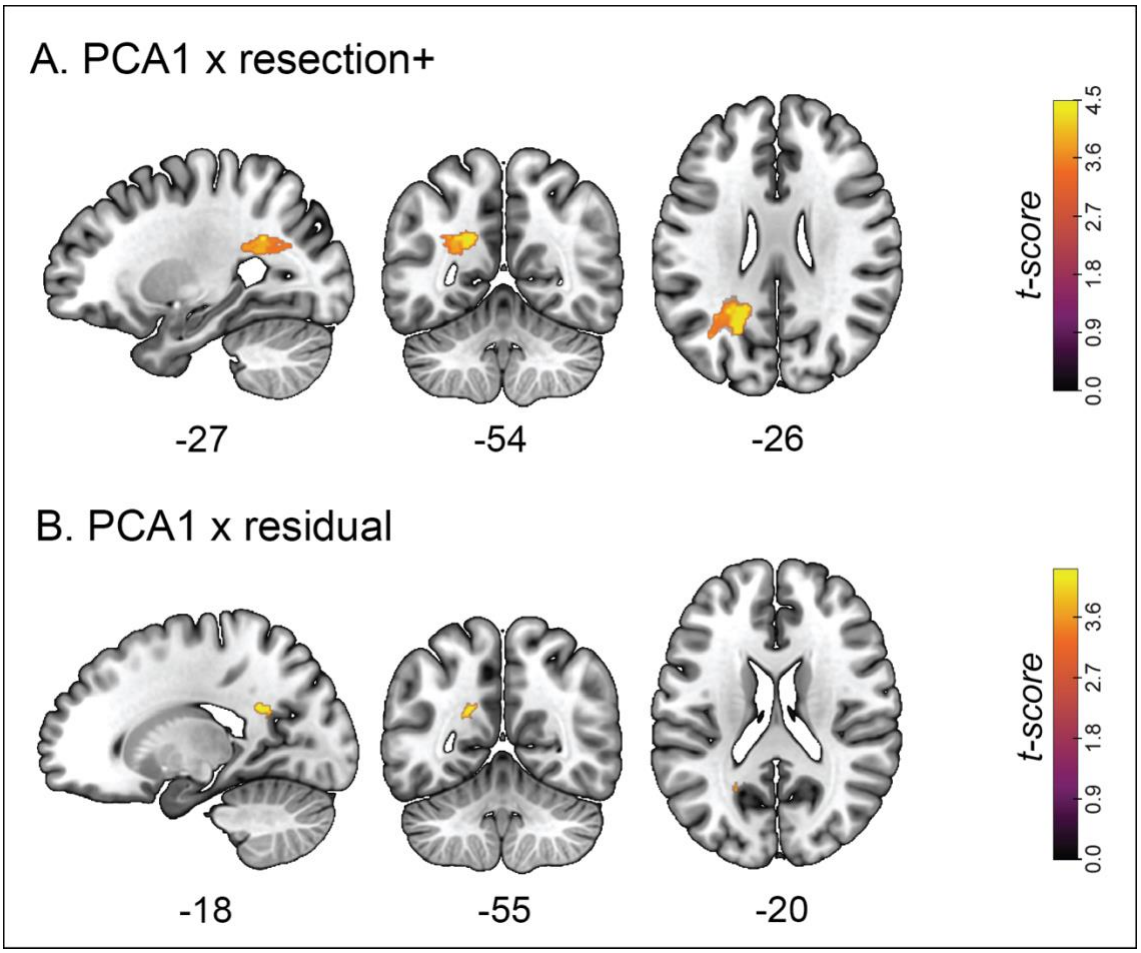

Figure 2. Results of the VLSM analyses, overlaid on the three canonical slices of the MNI152 template provided with MRIcroGL software. (A) HRQoL PCA1 associated with resection+ lesions; (B) HRQoL PCA1 associated with residual lesions. Only voxels surviving permutation-based FWE cluster-size thresholding with a vowel-wise threshold of $p < .001$ are shown.

Tract-wise disconnection analyses

None of the tract-wise analyses examining the relationship between disconnection severities in the six major language tracts and the HRQoL components were significant.

Voxel-wise disconnection analyses

None of the voxel-wise disconnection analyses involving the resection and resection+ lesion maps revealed significant associations with the HRQoL components. For the residual lesion map, communication-related QoL component scores were negatively correlated with disconnection severity of projections between the caudate and thalamus in the internal capsule (peak maxima = [0, -11, -1], $Z = 3.86$, $k = 1679$, $p_{FWE} = .049$; see Figure 3). Better communication-related QoL scores were related to more severe disconnection. The analysis between disconnection severities involving the residual lesion map and mood-related QoL measure did not reveal any significant relationship.

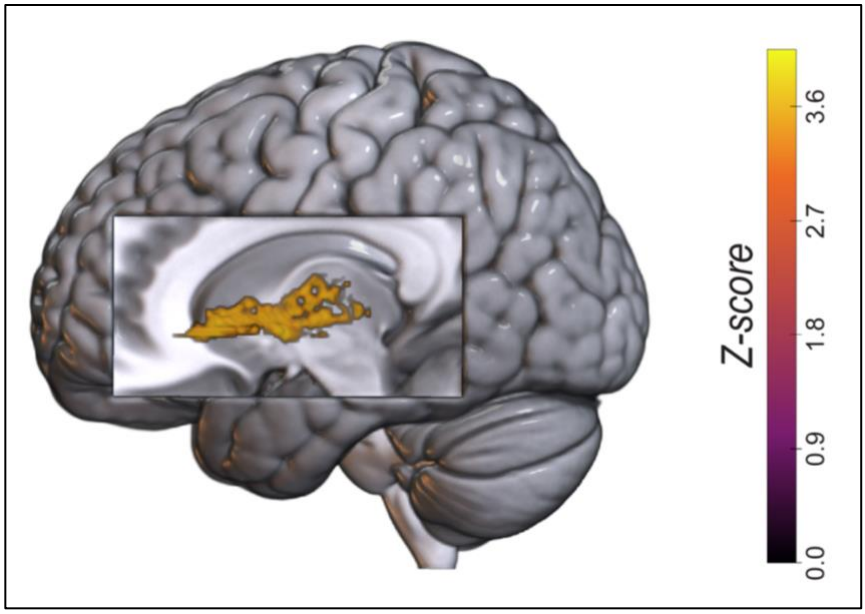

Figure 3. Significant voxel-wise disconnection severities associated with the HRQoL PC1 measure, shown on a 3D rendered view of the MNI152 template provided with MRIcroGL software. Significant disconnections of projections between the caudate and thalamus in the internal capsule were found for the residual lesions. Only voxels surviving a threshold of $p < .001$ with a cluster thresholding of $p_{FWE} < .05$ are shown.

Discussion

To further refine treatment planning, recovery, and rehabilitation services for individuals with brain tumours, it is essential to consider the impact on long-term HRQoL. The current study investigated the relationship between lesion location and HRQoL in a sample of participants 6-24 months post-surgical resection of left-hemisphere primary tumours. On average, we found that participants rated HRQoL within normal limits, although a range of scores was observed. The variation in HRQoL was explained by two principal components that were loaded with communication- and mood-related measures, respectively. When examined relative to lesion location, communication-related QoL, but not mood-related QoL, was significantly associated with lesions comprising both the resection+ and residual maps in the left medial inferior parietal lobe. Tract-wise analyses of white-matter disconnection severities, focused on the major language tracts, did not show significant associations with either QoL component. Whole-brain voxel-wise analyses of white-matter disconnection severities, however, revealed significant associations between communication-related QoL and thalamostriatal fibres for the residual lesions. Paradoxically, better communication-related QoL was related to more severe disconnection.

HRQoL within normal limits 6-24 months after surgery

Despite evidence of chronic language impairments for the majority of participants on multiple CAT (Swinburn et al., 2004) subtests, self-rated HRQoL was largely within normal limits according to available normative data. This accords with prior reports of lower-than-expected correlations between self-reported symptoms and cognitive impairments in cancer populations (Gehring et al., 2015). This may suggest minimal impact of language impairment on HRQoL due to, for example, subtle deficits, or the language impairment being less impactful on

HRQoL relative to the main priority of survival. While HRQoL typically decreases in the initial months post-diagnosis, previous studies have indicated improved HRQoL over time, with some studies showing a return to normal levels more than a year after diagnosis (Bosma et al., 2009; Piil et al., 2015) (cf. (Teng et al., 2021)). This improvement may be related to several factors beyond the language impairment, such as adapting to and learning to cope with the diagnosis, increased social support, and improved function in response to treatment (Piil et al., 2015).

Our principal components analysis revealed two underlying components of HRQoL: communication-related and mood-related QoL. Interestingly, patients with aphasia (defined as impairment on 2 or more CAT subtests) reported worse communication-related but not mood-related QoL, but it is important to emphasise that overall HRQoL was still within normal limits. In addition, neither QoL component was significantly associated with time post-surgery or WHO grade. An alternative, but at this point speculative, interpretation of HRQoL measures falling within normal limits may be limited patient insight (anosognosia) into their communicative ability. Anosognosia is more commonly associated with right-hemisphere lesions in the parietal, temporal and insular cortex and subcortically in the thalamus and basal ganglia (Starkstein et al., 2010). Interestingly, our results implicated the parietal cortex as well as white matter fibres between the thalamus and basal ganglia; however, all lesions in the current study were in the left hemisphere. Individuals with left-hemisphere lesions are often excluded from studies of anosognosia due to their language impairment; the frequency of anosognosia associated with left-hemisphere lesions may therefore be underestimated (Cocchini et al., 2009; Della Sala et al., 2009). Two recent studies reported a mismatch between subjective self-ratings and objective assessments of language impairment in 8/22 patients following left-hemisphere tumour resection (Brownsett et al., 2019) and in 24/53 of patients with post-stroke aphasia (van der Stelt et al.,

2021), which may also indicate anosognosia in some patients. Future studies may benefit from obtaining measures of awareness of impairment and, importantly, corroborating evidence of HRQoL from family members. to supplement the self-reported measures of HRQoL.

Communication-related QoL associated with resection+ and residual tumour lesions

Communication-related QoL was associated with the resection+ and residual lesion maps, highlighting the importance of residual lesion characteristics in this population. The relationship between communication-related QoL and lesions in the left precuneus and angular gyrus is consistent with the involvement of those regions in sentence comprehension and semantic processing (Binder et al., 2009; Price, 2010). These domains correspond to subtests on the CAT on which participants had aphasic impairments (Table 2; e.g., naming actions, comprehension of spoken/written sentences).

The relationship between communication-related QoL and lesions in the white matter in the left parietal lobe is also consistent with the involvement of left parietal white matter in lexical decision-making (Gold et al., 2007) and reading accuracy (Klingberg et al., 2000). Both lexical decision-making and reading accuracy were impaired in our study sample (Table 2; e.g., naming actions, reading words/complex words). The SLF-III, in particular, forms connections between parietal regions and prefrontal regions (Makris et al., 2005) and has been implicated in language processing (Dick et al., 2014). However, neither our tract- nor voxel-wise disconnection analyses implicated the SLF-III.

The current findings are in contrast to the two previous LSM studies examining the relationship between HRQoL and lesion location in brain tumour patients (Fortin et al., 2021; Sagberg et al., 2019), where they did not report any significant findings for the left hemisphere. There are two key differences between the previous studies and current work. First, the previous

studies employed HRQoL scales that did not include questions related to language/communication. Second, the lesions in the prior studies were defined based on the primary tumour and did not differentiate the resection cavity and residual tumour.

Neither communication nor mood-related QoL were associated with the resection lesion maps. This finding may be due to less involvement of the left medial inferior parietal lobe in the surgical resection, compared to the resection+ and residual lesion maps. The difference between these maps, however, is not limited to location in the brain, and may further be impacted by the different involvement of surgical resection, infiltration by residual tumour, radionecrosis following radiotherapy, among others, on brain tissue. In addition, it should be noted that the sample size of 37 may be a limitation of the current LSM analysis (Lorca-Puls et al., 2018), and further research with larger samples is needed to verify the results.

Thalamostriatal disconnection severity associated with communication-related QoL

We did not detect any significant relationships between disconnection severity in the six major language tracts and communication or mood-related QoL. Recall that the included tracts were the arcuate fasciculus, frontal aslant tract, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, uncinate fasciculus, and the SLF-III. This result builds on a prior study that examined lesion overlap (but not disconnection severity) in three of the white matter tracts included in the current study, namely the arcuate fasciculus, inferior longitudinal fasciculus, and uncinate fasciculus, relative to HRQoL (Sagberg et al., 2019). In that study, HRQoL scores before and in the first year after surgery were also not related to lesions involving these tracts.

Surprisingly, better communication-related QoL was associated with more severe thalamostriatal disconnection. This was surprising because patients who performed worse on two or more subtests of the CAT (our operational definition of aphasia) showed poorer

communication-related QoL, even though their overall HRQoL was within normal limits. This finding may also implicate a mechanism for anosognosia and warrants further study. The thalamus has been implicated as one of the key brain regions involved in anosognosia following stroke along with the parietal lobe, although it is predominantly observed after lesions to the right hemisphere and in relation to hemiplegia (see the systematic review by Orfei et al., 2007; Starkstein et al., 2010). Disconnection with frontal and parietal regions has been proposed as one potential mechanism by which thalamic lesions contribute to anosognosia. The function of the thalamostriatal pathway is not currently well understood but is thought to be involved in regulating alertness and attention (Smith et al., 2014). To explore the relationship between language deficits and thalamostriatal disconnection, we conducted a post-hoc analysis. We performed an ANCOVA with the mean tract disconnection severity values from the voxelwise analysis of communication-related QoL (extracted using the MarsBaR region of interest toolbox for SPM; Brett et al., 2002) and aphasia status (again operationally defined as impairment on two or more subtests on the CAT), with WHO grade, age, education, time post-surgery and residual lesion volume as covariates. Patients with vs. without aphasia did not differ according to thalamostriatal disconnection severity, $F(1,31) = 2.462$, $p = .127$, $\eta^2 = 0.05$. This corroborates the notion that thalamostriatal disconnection might be associated with a lack of awareness of deficit.

A potential limitation of the current disconnection severity analyses is the reliance on the population-averaged tractography atlas in predicting disconnection (Griffis et al., 2021), rather than reconstructing the tracts from the patients' own imaging data as in Zigiotto et al. (2022). The population-averaged tractography atlas method was originally developed and validated for use with focal brain lesions post-stroke and may not account for the distortions in tracts

associated with brain tumour masses. Future studies are needed to compare these probabilistic atlas-derived disconnection measures to tractography-derived results in this population.

Communication, not mood-related, QoL associated with lesions and white matter disconnection

Communication-related QoL significantly predicted lesion location and white matter disconnection, but mood-related QoL did not. This finding highlights the importance of routinely including measures of communication-related QoL when evaluating brain tumour patients. Communication-related questions can be limited in more general scales of HRQoL. We therefore recommend the Aphasia Impact Questionnaire-21, an updated version of the CAT Disability Questionnaire employed in the current study, available separately from the CAT (Swinburn et al., 2018). Importantly, the Aphasia Impact Questionnaire was developed with input from people with aphasia and takes less time to administer than the CAT Disability Questionnaire. Minimising the response burden for patients is vital, given the amount of testing they experience and their concomitant cognitive issues.

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Disclosure of Interest

The authors report there are no competing interests to declare.

Author Contributions

Katie McMahon and Greig de Zubicaray contributed to the study conception and design. Data collection was performed by Katharine Drummond, Rosalind Jeffree, Sarah Olson, Emma Murton, and Benjamin Ong. Data processing and analysis was performed by Elaine Kearney, Sonia Brownsett, Valeriya Tolkacheva, Katie McMahon, and Greig de Zubicaray. The first draft of the manuscript was written by Elaine Kearney and all authors amended and/or commented on subsequent versions of the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are openly available on OSF at https://osf.io/h5s9z/.

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Table 1

Demographic and clinical assessment data

	Variables		N	Mean ± SD	Range
Demographics	Age (years)		37	47.24 ± 13.49	19–74
	Education (years)		37	12.97 ± 2.40	10–18
	Time post-surgery (days)		37	295.41 ± 123.20	168–710
	WHO grade		37	2.76 ± 0.98	2–4
		Grade II	23		
		Grade IV	14		

SD: standard deviation; WHO = World Health Organization.

Table 2

Language assessment and percent classified as impaired

Comprehensive Aphasia Test subtest	N	T-Score Mean ± SD	Range	Percent Impaired (%)
Line bisection	35	54.51 ± 7.47	36-66	3
Semantic memory	37	57.59 ± 5.11	43-60	19
Word fluency	37	70.30 ± 5.43	49-75	3
Recognition memory	37	53.46 ± 6.71	39-59	14
Gesture object use	37	67.22 ± 2.76	55-68	0
Arithmetic	37	59.73 ± 6.95	34-65	3
Comprehension of spoken words	37	62.70 ± 4.61	47-65	5
Comprehension of spoken sentences	37	66.16 ± 6.65	46-72	16
Comprehension of spoken paragraphs	37	56.59 ± 6.56	34-60	8
Comprehension of written words	37	58.86 ± 5.79	50-65	22
Comprehension of written sentences	37	68.05 ± 5.64	48-72	5
Repetition of words	36	64.78 ± 1.33	57-65	0
Repetition of complex words	36	62.00 ± 0.00	62-62	0
Repetition of nonwords	36	66.17 ± 3.56	49-67	3
Repetition of digit lists	36	62.03 ± 5.19	50-66	6
Repetition of sentences	36	63.00 ± 0.00	63-63	0
Naming objects	37	69.51 ± 4.98	60-74	5

Naming actions	37	63.19 ± 5.91	52-69	46
Spoken picture description	36	66.11 ± 5.34	58-75	22
Written picture description	37	71.89 ± 4.15	61-75	8
Reading words	37	66.11 ± 5.55	48-69	14
Reading complex words	37	65.19 ± 4.79	49-67	14
Reading function words	37	61.27 ± 4.44	35-62	3
Reading nonwords	37	64.59 ± 8.12	40-68	11
Writing: copying	37	60.51 ± 2.96	43-61	3
Writing picture names	37	64.22 ± 4.16	53-67	3
Writing to dictation	37	64.43 ± 5.69	45-68	16

SD: standard deviation.

Table 3.

Scanning parameters for acquiring images across different scanners.

Scanner	3D FLAIR				MPRAGE 3D T1			
	TR (ms)	TE (ms)	TI (ms)	FOV	TR (ms)	TE (ms)	TI (ms)	FOV
Prisma	5000	332	1800	256x256x176mm, 1mm^3 voxels	2100	3.03	1100	256x240x192mm, 1mm^3 voxels
Skyra	7000	381	2050	250x250x160mm, 0.98mm^3 voxels	2020	2.35	1020	256x256x176mm, 1mm^3 voxels
Trio	6000	390	2100	250x250x160mm, 0.98mm^3 voxels	2150	3.03	1100	256x240x160mm, 1mm^3 voxels

TR = repetition time; TE = echo time; TI = inversion time; FOV = field of view.

Table 4

Descriptive statistics for HRQoL measures

Assessment	Measures (scale)	Mean ± SD	Range
Comprehensive Aphasia Test Disability Questionnaire	Disability total (0–64)	11.76 ± 9.98	0–41
	Impact total (0–60)	13.22 ± 11.86	0–44
Depression Anxiety Stress Scale-21	Depression (0–21)	3.89 ± 4.38	0–17
	Anxiety (0–21)	3.35 ± 3.88	0–15
	Stress (0–21)	6.54 ± 4.49	0–18
Functional Assessment of Cancer Therapy-Brain	Physical well-being (0–28)	22.09 ± 5.39	10–28
	Social/family well-being (0–28)	23.37 ± 4.90	8–28
	Emotional well-being (0–24)	16.63 ± 4.62	7–24
	Functional-well-being (0–28)	18.89 ± 6.08	3–28
	Disease-specific concerns (0–92)	64.83 ± 14.82	36–86

SD: standard deviation.

Table 5

Factor loadings based on a principal component analysis with varimax rotation for ten HRQoL measures

	Component		
	1	2	3
Disability total[1]	0.922		
Impact total[1]	0.873		
Disease-specific concerns[2]	-0.765		
Physical well-being[2]	-0.690		
Depression[3]		0.862	
Emotional well-being[2]		-0.857	
Stress[3]		0.830	
Anxiety[3]	0.615	0.628	
Social/family well-being[2]			0.864
Functional-well-being[2]			0.709

Note. Loadings above .6 are reported.[1]Comprehensive Aphasia Test Disability Questionnaire (Swinburn et al., 2004); [2]Functional Assessment of Cancer Therapy-Brain (Thavarajah et al., 2014; Weitzner et al., 1995); [3]Depression Anxiety Stress Scale-21 (Osman et al., 2012).