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Sizoo, E.M.

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## Chapter 3.2

### Measuring health-related quality of life at the end of life in high-grade glioma patients using a proxy-reported retrospective questionnaire

Eefje Sizoo\*

Linda Dirven\*

Jaap Reijneveld

Tjeerd Postma

Jan Heimans

Luc Deliens

Roeline Pasman

Martin Taphoorn

In preparation

\* Equal contribution

## **Abstract**

### ***Objective***

To develop, validate, and report on use of a retrospective proxy-reported questionnaire measuring health-related quality of life (HRQoL) in the end-of-life (EOL) phase of high-grade glioma (HGG) patients.

### ***Methods***

Items relevant for the defined construct were selected using existing questionnaires, topics identified as important in literature, and expert opinion. Psychometric properties, content validity and internal consistency, were determined and the questionnaire was subsequently adapted. Proxy-reported HRQoL data of HGG patients in the EOL, including changes over time, were analysed.

### ***Results***

Twenty-nine items were selected covering seven domains; physical comfort, physical and cognitive functioning, psychological, social and spiritual well-being, and overall quality of life. Relatives of 83 deceased HGG patients completed the questionnaire. Content validity was assessed to be adequate. Internal consistency in the domains varied from reasonable to good. Two items were excluded due to poor psychometric properties.

Symptom burden increased ( $p < 0.01$ ), except for nausea ( $p = 0.058$ ), as death approached. Cognitive, physical and psychological functioning deteriorated over time (all  $p < 0.01$ ). Acceptance of disease seemed to increase slightly towards death, but this was not significant ( $p = 0.058$ ). Scores for social activities and family life were low ( $\leq 50$ ), whereas scores for support and dignity were high ( $> 50$ ). Moreover, overall quality of life was rated as poor, mean(SD) of 29(26).

### ***Conclusion***

Measuring HRQoL at the EOL of HGG patients with a retrospective, proxy-reported questionnaire was feasible, yielding a validated instrument. HRQoL was poor and deteriorated as death approached.

## **Introduction**

Despite aggressive anti-tumour treatment, patients with high-grade glioma (HGG) have a poor prognosis and cannot be cured from their disease.<sup>4,9</sup> Inevitably, the end-of-life (EOL) phase will commence when tumour directed treatment is no longer possible and the condition of the patient deteriorates. Palliative care in this stage becomes of paramount importance, aiming to preserve or improve health-related quality of life (HRQoL) of patients and their families.<sup>127</sup>

The EOL phase of HGG patients is distinctive from the EOL phase of the general cancer population.<sup>49</sup> Patients with HGG not only have cancer, but also a progressive brain disease. Several studies have reported on the EOL phase of HGG patients demonstrating that the symptom burden of HGG patients is high and that disease-specific symptoms such as cognitive dysfunction, seizures and progressive neurological deficits are common.<sup>25, 46-49, 92</sup> It is suggested that especially these disease-specific factors contribute to a lower HRQoL in the EOL phase<sup>25, 26, 45</sup>, but data are lacking so far.

HRQoL is considered as a multidimensional construct covering physical, psychological, social and spiritual aspects.<sup>99, 128</sup> Numerous HRQoL instruments are available, differing considerably. There is no consensus on the number of relevant domains to measure HRQoL nor on the content of these domains.<sup>128</sup> Generic HRQoL instruments generally do not capture experiences unique to the dying process, such as comfort, dignity and spiritual well-being.<sup>128-131</sup>

Several instruments have been developed to measure HRQoL in the EOL phase or in the palliative care setting specifically<sup>132-135</sup>, but there is no measure that includes all domains that are thought to be relevant for HGG patients. In addition, these instruments are patient-reported outcome measures and therefore only suitable for prospective research. However, prospective studies on EOL in HGG patients applying patient-reported measures are difficult if not impossible, since these patients not only have a poor health status but are often cognitively impaired or incompetent, therefore not being able to complete questionnaires. In EOL research, retrospective studies relying on reports by formal and informal caregivers (proxies) are therefore widely accepted.<sup>91</sup>

To date, no questionnaire exists to retrospectively measure HRQoL in the EOL phase of HGG patients. Therefore, we developed a new proxy-reported questionnaire, to retrospectively measure HRQoL in HGG patients in the EOL, and here report on the construction, validation and first results of this questionnaire.

## **Methods**

### ***1. Development of the HRQoL questionnaire***

#### *Construct*

The demarcated subject of measurement (so-called construct) for this study is HRQoL of HGG patients in the EOL phase, measured retrospectively by proxies. Individuals confronting death define HRQoL differently from those not facing imminent death.<sup>136</sup> In the literature, seven domains are identified as important aspects of HRQoL in the EOL phase and include (1) physical comfort, (2) physical functioning, (3) cognitive functioning, (4) psychological well-being, (5) social well-being, (6) spiritual well-being and (7) overall quality of life.<sup>128, 130</sup>

#### *Development of the questionnaire (item selection)*

In order to reduce the response burden for proxies, it was decided not to include complete questionnaires covering a specific domain, but only relevant items. Items relevant for the defined construct were selected using existing questionnaires in HRQoL and EOL research.<sup>100-102, 137, 138</sup> In addition, aspects relevant for the seven predefined domains which were previously identified as important for HGG patients in the EOL phase<sup>21, 25, 46, 47</sup>, and clinical observation and expert opinion of experienced neuro-oncologists (JCR, TJP, JJH and MJB) and EOL experts (LDe and HRWP) were used to construct items. Items were related to the last three months before death and/or the last week before death.

Similar to the generic EORTC QLQ-C30 questionnaire, an adjectival scale was chosen for most HRQoL items; responses ranged from 'not at all', 'a little', 'quite a bit' to 'very much' or from 'no', 'more or less' to 'yes'. Items formulated using an adjectival scale are easily understood and quantified, and force respondents to give a meaningful reply. Overall quality of life was evaluated on a 7-point Likert scale, ranging from 'very poor' to 'excellent'. To reduce the amount of missing data and to prevent proxies from randomly filling in items, most items included the response option 'unknown'.

#### *Psychometric properties of the questionnaire*

First, the content validity was determined. Content validity is 'the degree to which the content of a measurement instrument is an adequate reflection of the construct to be measured'.<sup>139</sup> One aspect of content validity is face validity, defined as 'the degree to which a measurement instrument, indeed, looks as though it is an adequate reflection of the construct to be measured'.<sup>139</sup> The purpose of the content validation is to assess whether the questionnaire represents the construct under study; the HRQoL in the EOL phase of HGG patients. Content validation is a qualitative assessment, by definition subjective in nature and assessed based on expert opinion.

Next, the internal consistency of multi-item scales was assessed. Internal consistency is defined as 'the degree of relatedness among the items'<sup>139</sup> and is a measure of the extent to which items assess the same construct. To do so, Cronbach's alphas( $\alpha$ ) were determined as well as inter-item correlations (Spearman's rho ( $r_s$ )). The optimal value for Cronbach's alpha is between 0.7 and 0.9. Inter-item correlations should range between 0.2 and 0.9: items that are not correlated with any of the other items (<0.2) could be omitted immediately, whereas items that are correlated highly are likely to measure the same.

Based on this psychometric evaluation and the results of an analysis of missing data (to determine how often the proxy opted 'unknown' for a specific item), the questionnaire was adapted. See the appendix for the final questionnaire.

## ***II. HRQoL in the EOL phase of HGG patients***

### *Subjects*

Proxies of deceased patients from a cohort of adult patients diagnosed with HGG in 2005 and 2006 in three tertiary referral centres for brain tumour patients (VU University Medical Centre Amsterdam, Academic Medical Centre Amsterdam, and Medical Centre Haaglanden The Hague, the Netherlands) were approached for participation. Proxies were identified through information retrieved from the medical charts or by the physician who was involved in the EOL care of the deceased patient.<sup>56</sup>

Proxies were approached by mail with information on the study and a reply form and envelope. Proxies were requested to indicate if the researchers could contact them for further information on the study or if they declined any interest in participation. If proxies indicated they wanted to participate in the study, questionnaires on HRQoL in the EOL phase were sent to them.

The Medical Ethics Committees of each participating centre approved the study protocol and all proxies provided written informed consent.

### *HRQoL measurements*

Data on HRQoL of the patients were collected retrospectively. Proxies completed the questionnaire after death of the patient and the scales referred to the last three months and/or the last week before death.

All ordinal items and/or scales in the HRQoL questionnaire were converted to 0-100 scales using the EORTC QLQ-C30 algorithm.<sup>140</sup> On symptom scales (physical comfort domain), a higher score represents *worse* HRQoL, whereas on functional and well-being scales (physical, cognitive, psychological, social and spiritual domains) and the quality of life scale, a higher

score represents *better* HRQoL. Items with a nominal character are reported separately. Moreover, scores >50 were classified as 'high' and scores ≤50 as 'low'.

### *Statistical analysis HRQoL*

Demographic and clinical baseline characteristics for patients and proxies were described using descriptive statistics. For HGG patients, HRQoL in the last three months and/or the last week before death were described.

To determine if the HRQoL scores of the patients on the different domains significantly changed over time, HRQoL scores three months before death and one week before death were compared using a Wilcoxon Signed Rank Test. To reduce the amount of missing items, last observation carried forward was used for items for which no sudden improvement/deterioration was expected in the last week of life.

To analyse the data, SPSS version 20.0 software (SPSS, Chicago, IL, USA) was used. All tests were two-tailed and  $p < 0.05$  was considered to be statistically significant.

## **Results**

### ***Subjects***

A total of 223 patients diagnosed with HGG in 2005 and 2006 were identified in the participating centres. Of these, 39 patients were still alive, 4 were emigrated and 25 were not traceable. Proxies of the remaining 155 deceased patients were considered eligible for inclusion. Proxies of 131 patients could be identified and approached for participation. Forty-eight of these proxies either did not respond or declined participation. Thus, a total of 83 proxies participated in this study. The proxies completed the questionnaire about 27 (18-34) months (median, interquartile range) after the patient died.

Proxies were mostly female (64%) with a median (range) age of 60 (30-86) years. Proxies were the partner of the deceased patient in 80% of patient-proxy dyads, and the parent, child and sibling, in 11%, 7% and 2% respectively. Patients were on average 62 years at the time of diagnosis and mostly male (64%). Further patient and proxy characteristics are outlined in table 1. Of notice, respondent burden for completing the questionnaire was found to be limited.

### ***1. Development of the HRQoL questionnaire***

Twenty-nine items were selected to be relevant for the construct to be measured, covering seven domains including physical comfort, physical functioning, cognitive functioning,

psychological well-being, social well-being, spiritual well-being and overall quality of life (table 2). The selected items were qualitatively assessed on content validity by experts and found to be an adequate reflection of the construct to be measured. Next, in domains with multi-item scales (cognitive and physical functioning, and psychological well-being), the internal consistency was assessed using Cronbach's alpha and inter-item correlations (table 3).



Table 1. Baseline characteristics of the HGG patients and their proxies.

Variable	Proxies (n=83)	Patients (n=83)
<i>Age at diagnosis, median (range) years</i>	60 (30-86)	62 (20-86)
<i>Gender, no. (%)</i>		
Male	30 (36)	53 (64)
Female	53 (64)	30 (36)
<i>Religious, no. (%)</i>		
No	45 (55)	45 (55)
Yes, not important	8 (10)	13 (15)
Yes, important	29 (35)	25 (30)
<i>Educational level, no. (%)</i>		
Low	31 (37)	37 (45)
Intermediate	26 (31)	21 (25)
High	26 (31)	25 (30)
<i>Relation to patient, no. (%)</i>		
Partner	66 (80)	
Parent	9 (11)	
Child	6 (7)	
Sibling	2 (2)	
<i>Intensity contact patient, no. (%)</i>		
Lived together	59 (71)	
Daily	22 (27)	
Weekly	2 (2)	
<i>Tumour grade, no. (%)</i>		
Grade III		11 (13)
Grade IV		72 (87)
<i>Survival in months, median (range)</i>		
Grade III		13 (0.5-38)
Grade IV		12 (0-43)
<i>Place of death, no. (%)</i>		
At home		48 (58)
Hospital		8 (10)
Hospice		14 (17)
Nursing home		10 (12)
Other		3 (3)

Table 2. All domains that are covered in the HRQoL questionnaire for HGG patients in the EOL phase as well as the content of these domains and the corresponding scales.

Domain	Content	Scales
<i>Physical comfort</i>	- Pain - Specific symptoms	Single item: headache, pain Single item: nausea, <i>visual deficits*</i> , motor dysfunction, fatigue, drowsiness, bladder control, seizures, dyspnoea, dysphagia, communication deficits
<i>Psychological well-being</i>	- Emotional well-being	Domain emotional functioning: anxiety, sadness, irritability, <i>loss of interest*</i>
<i>Social well-being</i>	- Social connection	Single items: family life, social activities, support
<i>Spiritual well-being</i>	- Acceptance of death - Dignity	Single item: acceptance Single item: dying with dignity
<i>Physical functioning</i>	- Mobility - Ability to care for self	Domain physical functioning: mobility, self-care
<i>Cognitive functioning</i>	- Ability to think, comprehension, attention - Avoiding confusion	Domain cognitive functioning: memory, concentration, understanding, confusion, behavioural change
<i>Overall quality of life</i>	- Overall rating quality of life	Single item: general quality of life

\* Items excluded after validation

Table 3. Internal consistency (Cronbach's alpha and inter-item correlation ( $r_s$ )) of the three multi-item scales for patients, and the items that are retained in the questionnaire.

Domain	Cronbach's alpha	Correlation ( $r_s$ ) (range)	Items retained
<i>Cognitive functioning</i> 3 months before death 1 week before death	0.88 0.86	0.47 – 0.70 0.40 – 0.67	Memory, concentration, understanding, confusion, behaviour change
<i>Physical functioning</i> 3 months before death 1 week before death	0.79 0.43	0.69 0.29	Mobility, self-care
<i>Psychological well-being</i> 3 months before death 1 week before death	0.64 0.67	0.26 – 0.46 0.29 – 0.52	Anxiety, sadness, irritability

For the domain cognitive functioning in the last three months before death, a Cronbach's alpha ( $\alpha$ ) of 0.88 was found, inter-item correlations ( $r_s$ ) ranged from 0.47 to 0.70. Similar results were found for cognitive functioning in the last week before death:  $\alpha=0.86$  and  $r_s=0.39-0.68$ . It was concluded that this domain has a good internal consistency and therefore all items were retained.

Likewise, a good internal consistency was found in the domain physical functioning in the last three months before death:  $\alpha=0.79$  and  $r_s=0.69$ . However, for physical functioning in the last week before death,  $\alpha=0.43$  and  $r_s=0.29$ . Although the internal consistency for the items in the last week before death cannot be considered as optimal, we decided to have these items included because of good internal consistency measuring physical functioning in the last three months before death.

For the domain psychological well-being in the last three months before death,  $\alpha=0.63$  and  $r_s=0.14-0.46$ . Similar results were found for psychological well-being in the last week before death:  $\alpha=0.67$  and  $r_s=0.21-0.52$ . The item 'loss of interest' had low correlations with the other items in the scale and was therefore omitted. After removal of this item,  $\alpha=0.64$  and  $\alpha=0.67$  and  $r_s=0.26-0.46$  and  $r_s=0.29-0.52$  in the last three months and last week before death, respectively. Internal consistency in this domain is reasonable, with Cronbach's alpha's slightly below  $<0.7$ , and it was therefore decided to keep the items anxiety, sadness and irritability in the questionnaire.

Furthermore, the analysis of missingness (data not shown) revealed that proxies often ( $>10\%$ ) opted 'unknown' for the item 'visual deficit'. Therefore, this item was removed from the questionnaire. After exclusion of the items 'loss of interest' and 'visual deficit', twenty-seven items were retained in the final questionnaire (table 2).

## **II. HRQoL in the EOL phase of HGG patients**

Mean scores on the different scales of the HRQoL questionnaire are shown in table 4.

Symptom burden of HGG patients, according to their proxies, increased significantly on all scales (all  $p$ -values  $< 0.01$ ) except for nausea ( $p = 0.058$ ), as death approached. Furthermore, proxies reported seizures in the last three months of life as well as in the last week of life in 32% of the patients. In addition, 4% of patients developed de novo seizures in the last week before death, 21% of patients had seizures in the last three months before death but not in the last week, and 43% of patients did not have any seizures in the EOL phase.

Cognitive, physical and psychological functioning deteriorated significantly as death approached (all  $p$ -values  $<0.01$ ). Although not significant ( $p=0.058$ ), acceptance of disease increased slightly towards death. Within the domain social well-being, mean (standard deviation (SD)) scores for social activities and family life were low (17 (26) and 45 (39), respectively), whereas the mean (SD) scores for support and dignity were high (81 (27) and 71 (28)). Moreover, overall quality of life of the patients was rated as poor, with a mean (SD)

of 29 (26). Place of death (at home versus not at home) did not affect perceived overall quality of life or dying with dignity ( $p=0.761$  and  $p=0.182$ , respectively).

*Table 4. Mean (SD) scores of the different single and multi-item scales of the HRQoL questionnaire for HGG patients, measured in the last three months and/or the last week before death or in the total EOL phase.*

<b>Domain</b>	<b>Last three months</b>	<b>Last week</b>	<b>p-value</b>
Single item scales	<b>Mean (SD)</b>	<b>Mean (SD)</b>	
<i>Physical comfort (symptoms)</i>			
Headache	31 (35)	42 (41)	<0.01
Pain	29 (33)	48 (41)	<0.001
Nausea	20 (27)	24 (32)	0.058
Motor dysfunction	62 (37)	77 (36)	<0.001
Fatigue	72 (27)	88 (21)	<0.001
Drowsiness	51 (32)	84 (27)	<0.001
Bladder control	36 (41)	69 (41)	<0.001
Dyspnoea	17 (25)	43 (41)	<0.001
Dysphagia	23 (32)	54 (42)	<0.001
Communication deficit	40 (34)	71 (38)	<0.001
<i>Psychological well-being</i>	70 (24)	63 (27)	<0.01
<i>Physical functioning</i>	50 (33)	7 (15)	<0.001
<i>Cognitive functioning</i>	54 (28)	34 (29)	<0.001
<i>Spiritual well-being</i>			
Acceptance	57 (33)	64 (33)	0.058
	<b>Total EOL phase</b>		
	<b>Mean (SD)</b>		
Dying with dignity	71 (28)		
<i>Social well-being</i>			
Family life	45 (39)		
Social activities	17 (26)		
Support	81 (27)		
<i>Overall quality of life</i>	29 (26)		

## **Discussion**

Up to now, no questionnaire exists to adequately measure HRQoL in the EOL phase of HGG patients in retrospect by their proxies. Therefore, a new HRQoL questionnaire to measure this construct was developed and validated. The content validity of this questionnaire was

found to be adequate and the internal consistency of the multi-item scales varied from reasonable to good. Furthermore, HRQoL of HGG patients as reported by their proxies was poor and deteriorated as death approached.

Recently, the COSMIN taxonomy was presented, showing all measurement properties that should be considered in the validation of a questionnaire<sup>139</sup>. Measurement properties can be divided into three categories, each including different parameters; validity (content, construct and criterion validity), reliability (test-retest, internal consistency and measurement error) and responsiveness. In this study, the content validity and internal consistency were assessed. However, since validation is an ongoing process, validation can be improved over time if this questionnaire (including 27 items) will be used in future studies.

Although patients are the best source to rate their HRQoL<sup>141</sup>, patient-by-proxy ratings should be considered as an appropriate alternative in situations where patients are cognitively impaired, incompetent, have a poor health status or have died. Applying patient-reported measures to HGG patients in the EOL phase is difficult if not impossible, and patient-by-proxy ratings may be considered an appropriate alternative to substitute patient ratings. Although retrospective studies relying on reports by proxies are widely accepted in EOL research<sup>91</sup>, the reliability of these patient-by-proxy ratings remains debatable. Some studies have shown moderate to good agreement between patient and patient-by-proxy ratings<sup>107, 142-144</sup>, whereas others revealed that patient-by-proxy and patient ratings are not always consistent. Patients and proxies often agree on symptom scales, but less on the psychosocial scales<sup>145, 146</sup>. Moreover, proxies tend to underestimate the patients' HRQoL<sup>147</sup>. However, differences between patient and patient-by-proxy ratings do not necessarily reflect inaccuracy<sup>105</sup>. Appreciation of aspects of the patients' HRQoL by proxies however, may be influenced by feelings such as depression and anxiety, which are frequently reported in proxies,<sup>42</sup> although the relatively long interval in our study between the patient's death and the report by the proxy will decrease the chance for this.

Despite the methodological limitations, data generated from this questionnaire provide valuable information on relevant HRQoL aspects in the EOL phase of HGG patients. HRQoL of HGG patients as reported by their proxies was poor and deteriorated over time. With the symptom burden increasing towards death, a concomitant decrease was reported for cognitive, physical, social and psychological functioning. In several other studies, that applied different questionnaires on various aspects of HRQoL, symptom burden was also found to be high in the EOL phase with disease-specific symptoms prevailing<sup>25, 46-49, 92</sup>. A decline in mental, physical, social and existential well-being has also been reported previously<sup>45</sup>, with a higher rate of poor functional status and a higher need for social support in HGG patients compared to a general palliative care population<sup>49</sup>. This emphasizes that HGG patients are a unique population with specific supportive care needs<sup>42</sup>.

Overall quality of life was classified as poor in 86% of the patients, which comes as no surprise. Previously, poor or unacceptable quality of life was reported in 61% of the HGG patients<sup>26</sup>, and was explained by severe disability restricting activities of daily living, personality changes and physical deterioration. At the same time, acceptance of disease increased as death approached and most proxies reported that the patient died with dignity. We have previously demonstrated that being able to communicate, the absence of transitions between health care settings and satisfaction with the EOL care provided by the physician are predictive for a dignified death<sup>148</sup>.

In conclusion, this study yields a questionnaire to retrospectively measure all HRQoL aspects that are relevant in the EOL phase of HGG patients. This study demonstrates that the questionnaire is a feasible and potentially useful instrument for future retrospective clinical studies, and not yet for use in daily clinical practice, in this unique population. However, further validation in a separate cohort is warranted. Ideally, the questionnaire should be helpful to determine if enhanced (organization of) palliative care for HGG patients goes along with preservation or improvement of HRQoL in the EOL phase. Vice versa, identification of specific problems in HRQoL may possibly direct future treatment and subsequently the organization of care for HGG patients.