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Methodological issues in designing and reporting health-related quality of life in cancer clinical trials: the challenge of brain cancer studies

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Abstract Health-related quality of life (HRQOL) and other types of patient-reported outcomes (PROs) are now important outcome measures in cancer clinical trials. A number of potentially less toxic drugs are available, and newer treatments can potentially offer cancer patients the possibility to be treated with less aggressive approaches, making PROs more critical in evaluating treatment effectiveness. However, assessing PROs in clinical trials requires careful consideration of a number of methodological issues. Robust methodology and accurate reporting of results are crucial to provide the scientific community and health care providers with a transparent message about the impact of a given drug or a new medical approach on patients' health status. This paper provides basic guidance on methodological issues to be addressed when designing and reporting HRQOL in clinical trials and presents examples of relevant brain cancer studies.

Keywords Quality of life · Clinical trial · Brain cancer

Clinical trials

Clinical trials, particularly randomized controlled trials (RCTs), play a crucial role in cancer research. They provide the major scientific evidence needed to adopt the best treatment for all cancer patients [1]. The provision of high quality care depends on the ability to make choices from robust scientific data. The main purpose of RCTs has historically been to help establish improved survival rates, but they also serve as vehicles to provide other important information which might be indicative of improved clinical response, such as disease-free survival, progression-free survival, or tumor response. While these still remain important endpoints to evaluate when examining the effectiveness of a potentially valuable new treatment, the research community has also recognized the need to go beyond this "biomedical model" which does not take into account the patient's perspective on the burden of the disease and that of the related treatment [2].

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Health-related quality of life and patient reported outcomes a matter of terminology

Defining the construct of health-related quality of life (HRQOL) is challenging, but there is now general agreement that it refers to key areas including minimally physical, psychological, and social functioning as well as symptoms induced by the disease and its treatment [3, 4]. More recently, the term "patient-reported outcome" (PRO) has been introduced in the literature to describe a broader set of parameters, which are self-reported by the patient [5]. The US Food and Drug Administration (FDA) defines a PRO as: "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" [6]. PROs include a wide spectrum of measures ranging from single item instruments, assessing a specific health domain (e.g., pain or fatigue), to broader

multidimensional constructs such as HRQOL. It is important to make such a distinction, as both terms are now frequently reported in the medical literature. To be consistent with the bulk of previous literature on the subject, we will refer in this article to the term HRQOL.

Why should we measure HRQOL in clinical trials?

Using HRQOL as an outcome measure in a clinical trial is, in essence, the only way of obtaining evidence-based data on the effect of a treatment from the patient's view. As stated by the FDA, "use of a PRO instrument is advised when measuring a concept best known by the patient or best measured from the patient perspective" [6]. To this end, HRQOL outcomes have the potential to provide invaluable data to fully evaluate treatment effectiveness.

HRQOL methodology is crucial

Measuring HRQOL in clinical trials requires making critical decisions concerning the methodology of measurement. The assessment of HRQOL in a clinical trial should thus be as rigorous as possible. Indeed, if HRQOL data are to fulfill their potential of allowing health-care providers to make informed decisions about the overall value and impact of a given treatment, investigators should pay careful attention to a number of methodological issues. Previous work investigating the quality of HRQOL assessment in oncology over the last 20 years has found a number of methodological drawbacks that have hampered a critical appraisal of result in several occasions [7–10].

Some administrative and methodological decisions should be taken already at the time of protocol writing while others are mainly relevant when reporting and disseminating results.

Some key issues to be addressed at the stage of protocol writing

It is important that a separate chapter in the study protocol be dedicated to the HRQOL assessment. This will inform on a number of aspects related to the design, analysis, and logistic of this outcome assessment. At this stage, one of the basic steps is that of providing a rationale for HRQOL assessment in the particular study, and of specifying what adds to the primary endpoint of the study (in case PRO is planned as a secondary endpoint).

The selection of the most appropriate instrument (e.g., questionnaire) for the particular trial also deserves attention and should be justified in the protocol. Selecting the 'right' questionnaire is a fundamental step in designing and conducting a thoughtful assessment and needs careful evaluation of various aspects. Questions need to be asked, such as: is the content of the questionnaire appropriate to the research question? Does the questionnaire has robust psychometric properties (in terms of validity, reliability and responsiveness)? How interpretable are the scores? Detailed guidelines on how to make this choice have been published and will likely assist investigators when designing future studies [11].

Another relevant issue to be addressed at this stage is the challenge of HRQOL missing data. Difficulties with data collection and compliance have historically been considered a major problem to the successful implementation of HRQOL assessment in clinical trials [12]. HRQOL data are collected at different time points during the course of the study, and missing data at different scheduled assessments are unavoidable, mainly due to patients' health conditions and/or administrative failures. As missing data might not be missing at random, they cannot be ignored without introducing bias in outcome interpretation. Thus, investigators are recommended to take actions to minimize as much as possible the number of missing data during the study [12–14].

Other issues to be addressed during protocol development are the a priori definition of what constitutes a "minimally important difference" (MID) in the HRQOL measure, and the clinical significance of outcomes. Using HRQOL poses unique problems inherent in their subjective nature. For example, what is the meaning of a given statistically significant difference in terms of HRQOL from a patient's perspective? Does a statistically significant difference in a HRQOL domain, between treatment arms necessarily reflect a subjectively meaningful difference perceived by patients? Basically, the challenging question is how to evaluate "a tangible benefit" (that is an improvement in the patient's health condition) with an "intangible construct" (i.e. quality of life) [15]. Since statistical significance is dependent on sample size, it is possible that a 2–3 units change on a 0–100 HRQOL scale results in a significant p value if the results are based on a large sample. Clearly, this finding would most likely not be clinically meaningful. As an illustration, previous work has shown that the MID for one of the most widely used cancer-specific questionnaires, that is the European Organisation for Treatment and Research of Cancer (EORTC) QLQ-C30, equals a 10-point shift on its 0–100 response scale [16].

For further details on the main steps that should be taken into consideration at an early stage of protocol writing, to ensure a successful HRQOL implementation, we refer the readers to other relevant documents in this area [17, 18].

At the stage of reporting and disseminating HRQOL findings

Accurate reporting of data is of vital importance when evaluating HRQOL in clinical trials, in order to provide the

scientific community and health care providers with a clear and transparent message about the impact of a therapeutic approach on the patients' health status. HRQOL publications stemming from a poor study design or simply reporting inadequate information can potentially mislead readers when interpreting study outcomes. In Table 1, we report a number of practical basic issues that investigators should definitely consider when reporting HRQOL or other type of PRO data in clinical trials. We do not intend to provide a comprehensive list of all the detailed issues that ideally should be reported, rather we provide a brief pragmatic guide on the main topics deserving attention when reporting outcomes. These basic issues are taken from the "Minimum standard checklist for evaluating HRQOL outcomes in cancer clinical trials" that has been previously developed based on good practice in reporting HRQOL studies and was published in the *Journal of Clinical Oncology* in 2003 [19]. This tool is of pragmatic use, has been adopted in several studies to evaluate consistency and level of reporting, and has been shown to be sensitive in picking up difference of quality reporting over time [20–23]. The international community has recently recognized the need to standardize HRQOL outcomes reporting in clinical trials. In this regard, it is worth noting that the Consolidated Standards of Reporting Trials (CONSORT) Group is working on a development of a checklist for reporting HRQOL/PRO data from clinical trials. This effort will eventually lead to improved reporting of quality of life data in clinical trials and will enable robust evidence to inform patient choice and aid clinical decision making (http://www.consort-statement.org/).

HRQOL assessment in brain cancer patients

Malignant brain tumors are among the most feared diseases. Not only is the patient inflicted by an incurable malignancy but the disease also directly involves the brain, thereby threatening the "being" of the patient. In brain tumor patients, HRQOL has long been a neglected area, given the relative scarcity of this disease compared to other cancers and its dismal prognosis [24]. Compared to traditional outcome measures such as (progression-free) survival and neurological functioning, the evaluation of

Table 1 Minimum standard checklist for evaluating HRQOL outcomes in cancer clinical trials

Conceptual			
A priori hypothesis stated Assessed whether authors had a pre-defined HRQOL endpoint and/or stated expected changes due to the specific treatment	Yes ❑	No ❑	N/A ❑*
Rationale for instrument reported Assessed whether authors gave a rationale for using a specific HRQOL measure.	Yes ❑	No ❑	
Measurement			
Psychometric properties reported Assessed whether a previously validated measure was used or psychometric properties were reported or referenced in the article.	Yes ❑	No ❑	
Cultural validity verified Assessed whether the measure was validated for the specific study population.	Yes ❑	No ❑	N/A ❑†
Adequacy of domains covered Assessed whether the measure covered, at least, the main HRQOL dimensions relevant for a generic cancer population and/or according to the specific research question.	Yes ❑	No ❑	
Methodology			
Instrument administration reported Assessed whether authors specified who and/or in which clinical setting the HRQOL instrument was administered.	Yes ❑	No ❑	
Baseline compliance reported Assessed whether authors reported the number of patients providing an HRQOL assessment before the start of treatment.	Yes ❑	No ❑	
Timing of assessments documented Assessed whether authors specified the HRQOL timing of assessment during the trial.	Yes ❑	No ❑	
Missing data documented Assessed whether authors gave some details on HRQOL missing data during the trial.	Yes ❑	No ❑	
Interpretation			
Clinical significance addressed This refers to the discussion of HRQOL data being clinically significant from a patient's perspective and not simply statistically significant.	Yes ❑	No ❑	
Presentation of results in general Assessed whether authors discussed the HRQOL outcomes, giving any comments regardless of the results (either expected or not).	Yes ❑	No ❑	

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* If a study explicitly states an exploratory HRQOL evaluation

† If the HRQOL measure is validated in the same population as the one of the trial

HRQOL and cognitive functioning may be regarded as time-consuming and burdensome for both the brain tumor patient and the doctor. Moreover, the perception that the disease will affect the patient's ability to judge his or her own functioning could hinder the use of PRO assessments. Previous work has pointed out that neurocognitive function is a key determinant of HRQOL [25].

For gliomas, the most common primary brain tumors, treatment options have increased over the past decade (i.e., temozolomide chemotherapy, combined chemo-radiotherapy, bevacizumab) and more targeted therapies are under investigation [26, 27]. As more effective treatment options could have severe side-effects and increased risk of neurotoxicity, HRQOL has become an important secondary endpoint for treatments comparison in randomized controlled trials in glioma patients [28]. Also, in patients with metastatic brain tumors from systemic cancers, clinical studies increasingly incorporate HRQOL as an endpoint.

At present, no single gold standard tool exists to measure HRQOL. Generic and disease specific tools need development and validation to assess HRQOL for cancer and non-cancer patients.

For cancer patients, one of the most frequently used tools was developed by the EORTC quality of life group: the EORTC QLQ-C30 [29]. The EORTC QLQ-BN20, specifically developed and validated for patients with brain cancer, includes 20 items assessing visual disorder, motor dysfunction, various disease symptoms, treatment toxicity, and future uncertainty [30]. This tool, in combination with the EORTC QLQ-C30, is often used in clinical trials in glioma patients undergoing chemotherapy and radiation therapy.

Another widely used (brain) cancer-specific HRQOL tool is the functional assessment of cancer therapy (FACT). Next to a general FACT module (FACT-G), a brain cancer-specific module was developed (FACT-Br) [31]. Compared to the EORTC questionnaires, the FACT modules are more focused on psychosocial aspects rather than symptom issues.

An alternative recently developed PRO for brain tumor patients is the MD Anderson Symptom Inventory Brain Tumor Module (MDASI-BT), which has been validated for both primary brain tumor patients and patients with brain metastases [32, 33]. Given that this questionnaire addresses symptoms, it has some similarities with the EORTC QLQ-BN20. The MDASI-BT might be useful to describe symptom occurrence throughout the disease trajectory and to evaluate interventions designed for symptom management.

When patients are unable to self-report, for example due to cognitive disturbances, one might consider using proxies or health care professionals to rate patient quality of life. In the past, this method was regarded as far from optimal. However, a review found moderate to good agreement in various studies evaluating the concordance between patient and proxy measures [34]. Mixed results have been reported for patients and health care providers. Proxies and health care providers tend to report more HRQOL problems than do patients themselves, and proxy ratings tend to be more in agreement with patient physical HRQOL domains compared to the psychological domains. The EORTC QLQ-C30, EORTC QLQ-BN20, and the FACT-Br showed moderate agreement between patient and proxy HRQOL assessment, provided cognitive functioning was not severely affected [34, 35]. The use of a nonpatient-based report should, therefore, only be used when patients are incapable of self-report.

HRQOL in clinical trials of brain cancer patients

The benefit of radiotherapy is well established in the treatment of high grade glioma (HGG) patients, because tumor progression is postponed and overall survival extended. By stabilizing disease and delay progression, HRQOL can be maintained. Two randomized studies evaluating the combination of chemotherapy and radiation versus radiation therapy alone included HRQOL as an outcome measure [28, 36]. No negative effects of radiotherapy on HRQOL were observed in anaplastic oligodendroglioma patients and patients with glioblastoma multiforme with a good performance status. On longer follow-up, >1.5 years after completion of radiotherapy, HRQOL scores of HGG patients without progression even improved compared to scores at the start of the treatment. In long-term (i.e., >2 years from initial treatment) HGG survivors without disease progression, who had initial radiotherapy, HRQOL scores were observed meeting the level of healthy controls. Specifically in the elderly population (age >70 years), a moderate survival benefit from radiotherapy was established for patients who had a good performance status at the start of the treatment. More importantly, HRQOL, performance status and cognitive functions did not further deteriorate compared to the observation arm of this study, in which patients only received supportive care [37].

Successful chemotherapy regimens in glioma patients are PCV chemotherapy (combination of procarbazine, CCNU, or lomustine, and vincristine) and temozolomide. The combination of temozolomide chemotherapy and radiotherapy significantly prolonged survival in patients with glioblastoma compared to patients treated with radiotherapy alone [26]. The effect of this new dual-treatment modality on HRQOL was evaluated separately [28]. During treatment and follow-up, both treatment group changes over time, in seven preselected HRQOL domains, were not substantial during the first year of follow-up,

provided there was no progression of disease. For several scales, scores even improved over time. However, during treatment, the patients in the combination treatment group reported more side effects (nausea, vomiting, appetite loss, and constipation) compared to the radiotherapy only group, which can be attributed to the use of temozolomide and antiemetics. Overall, it can be concluded that the addition of temozolomide during and after radiotherapy significantly improved survival without a long-lasting negative effect on HRQOL. As for treatment, patients with anaplastic oligodendroglioma, adjuvant treatment with PCV chemotherapy after radiotherapy significantly prolongs progression-free survival, but not overall survival [38]. With respect to HRQOL, patients receiving PCV chemotherapy show a significant increase in nausea/vomiting and appetite loss during and shortly following treatment compared to patients receiving only radiotherapy. Furthermore, patients on PCV report more drowsiness. These differences, however, resolve over time: after 1 year follow-up, differences were no longer observed in HRQOL between treatment groups [36]. Overall, there is a short-lasting negative impact of PCV chemotherapy on HRQOL during and shortly after treatment, but no long-term effects or HRQOL have been established. More importantly, because PCV chemotherapy postpones tumor progression, the impact of progression on well-being and HRQOL should be evaluated in future studies.

HRQOL as a prognostic factor in brain cancer patients

In addition to HRQOL use in clinical trials to evaluate treatments, HRQOL may also serve as an early indicator of disease progression and have prognostic significance. HRQOL could thereby help the physician in daily practice to closely monitor and tailor treatment to the individual patient [39].

In two studies by Mauer et al., the use of refined statistical analysis showed that indexes measuring the predictive accuracy of the models did not exhibit major improvement when adding HRQOL scores to clinical factors [40, 41]. The usefulness of baseline HRQOL scores to predict survival in brain tumor patients therefore remains a highly debated topic and promises to continue to produce new research in the near future.

Conclusions

HRQOL assessment in brain cancer is of great importance, as it provides the unique patient's view on the burden of the disease and treatment. However, HRQOL assessment has been a neglected issue for many years in brain cancer patients for a number of reasons. HRQOL information cannot be drawn by looking at toxicity data or other types of physician-reported data. The inclusion of HRQOL as an endpoint in a clinical trial setting can provide invaluable information on the overall treatment effectiveness, and it is basically the only way to have information regarding HRQOL. However, HRQOL assessment in a clinical trial has to be rigorous and a number of methodological issues need to be fully considered. There are few examples from the literature which illustrate the value of such assessment and the way such information can indeed facilitate more informed treatment decisions.

Conflict of interest The authors declare that they have no conflict of interest.

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