Health-related quality of life research in EORTC cancer clinical trials: an emphasis on quality

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A short review on health-related quality of life, including patient reported outcomes measurements in oncology to help increase awareness in the Belgian oncological community. This review is also meant for educational purposes and to highlight the benchmarks that the work of EORTC has contributed to the field.
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Introduction

Health-Related Quality of Life (HRQOL) has been defined by Gotay et al. as a state of well-being that is a composite of two components: the ability to perform everyday activities that reflect physical, psychological, and social well-being and the patient's satisfaction with the levels of functioning and the control of disease and/or treatment-related symptoms.[1]

For over half a century, the European Organisation for Research and Treatment of Cancer (EORTC) has developed, conducted, coordinated, and stimulated translational and clinical research in Europe to improve the management of cancer and related problems by increasing overall survival (OS) and patient quality of life.[2]

Dedicated to these aims, EORTC created the Quality of Life Group (QLG) in 1980 to develop measures of HRQOL, and to promote and coordinate clinical studies concerning the HRQOL of cancer patients. The EORTC Quality of Life Department (QLD) was established in 1993 to provide administrative, practical and scientific support to co-operative groups conducting randomised clinical trials with HRQOL outcomes. In the same year, the need for a robust and validated psychometric tool to make self-reported quality of life assessment possible led to the development of the core questionnaire, EORTC QLQ-C30.[3] EORTC QLQ-C30 is referenced in 1,858 PubMed publications (February 2015) and is among the most widely used cancer-specific HRQOL questionnaires in the world.[4-6] Other widely used general measures in cancer clinical trials include the Functional Assessment of Cancer Therapy – General (FACT-G), Short Form (36) Health Survey (SF-36), EQ-5D, etc.[7-9]

EORTC HRQOL measures

HRQOL in cancer clinical trials is a field that the EORTC has championed for over three decades in recognition of the need for robust measures to evaluate, in a systemic and vigorous manner, patients' perspectives of their own quality of health. The QLG took on the task of creating and ensuring that HRQOL measures are accessible to researchers worldwide. The core questionnaire, which is applicable to the general cancer population, has been supplemented with several modules. The QLQ-C30 is comprised of 30 questions measuring fifteen HRQOL parameters: five functioning scales (physical, role,

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cognitive, emotional and social), three symptom scales (pain, fatigue, nausea/vomiting), six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial problems) and global health status/quality of life (*Appendix 1*). The differences between QLQ-C30 and other available tools (FACT-G) in measuring HRQOL in cancer clinical research have been described earlier by Luckett et al.[10] Each module covers a disease site (e.g. QLQ-BN20 for brain cancer) or a particular issue in more specific detail (e.g. QLQ-FA13 for fatigue, QLQ-OH17 for oral health, QLQ-SWB36 for spiritual wellbeing). Apart from the cancer-specific modules, EORTC has developed a 15-item questionnaire to assess the quality of life of palliative cancer care patients (QLQ-C15-PAL) and a 32-item satisfaction with care questionnaire to measure patients' appraisal of hospital doctors and nurses, as well as aspects of care organisation and services (IN-PATSAT32). The QLD coordinates the translation and distribution of QLQ-C30 and disease modules to researchers. To date, EORTC has developed 38 modules and has an additional twelve modules under development which are available free of charge for academic research. Translation of questionnaires plays an important role in the field of patient-reported outcomes (PROs) and allows researchers to collate data from different countries. At the moment there are more than 1,000 translations of the various EORTC modules, and there are more than 92 different languages and language variations available for use. All language versions of the validated modules are available in an Item Bank. The Item Bank consists of more than 6,000 items in different languages. Researchers working on new questionnaires may retrieve existing items and translations of different modules to be reused – saving time and resources, and, importantly, making the questionnaires more consistent. Via QLG's website (www.eortc.be/qol) researchers can follow the latest developments in HRQOL research and also download the Scoring Manuals, the QLQ-C30 and the disease-specific modules. In addition, the QLD oversees the implementation of HRQOL into the clinical trials run by EORTC Headquarters. This involves collaborating with the EORTC disease-oriented groups to design, run, analyse and report on HRQOL in trials where the patient perspective is deemed to be of added value.

HRQOL in cancer clinical trials

Clinical trials have long been dominated by clinically based endpoints such as OS and progression-free survival in order to measure the effectiveness of a treatment. Adverse event assessment by the treating clinician provides information concerning safety and tolerability. Neither of these endpoints, however, measures a patient's perception of their quality of life, and research has shown that HRQOL can only be captured accurately by the patients themselves using PROs.[11]

EORTC has implemented HRQOL assessment in over 150, mainly phase III, clinical trials and has a vigorous research program with more than 40 ongoing methodological and clinical research studies. Most of the trials have typically included a HRQOL outcome as a secondary endpoint. The result of combining robust tools within the framework of rigorous EORTC clinical trials, with motivated investigators from all groups, has enabled HRQOL measures to be used by clinicians to help them make decisions regarding treatment for patients as well as assess the impact of the disease on these patients. Most regulatory bodies, such as the European Medicines Agency and the Food and Drug Administration, now fully accept HRQOL as a valid endpoint.

HRQOL plays a role in practice-changing trials

There are many examples of practice-changing EORTC trials that have included HRQOL measurements using the EORTC QLQ-C30 and the disease-specific module. The results of EORTC trial 22952-26001 demonstrated that whole-brain radiotherapy (WBRT) did not improve OS and also adversely affected HRQOL. This trial compared WBRT with observation following either surgery or radiosurgery of a limited number of brain metastases in patients with stable solid tumours. Patients who received WBRT reported lower scores for global health status/quality of life, physical/cognitive functioning, and fatigue, and showed that WBRT following surgery or radiosurgery of a limited number of brain metastases may negatively impact HRQOL; observation with close monitoring by magnetic resonance imaging instead of WBRT did not harm HRQOL.[12] Another EORTC study in glioblastoma investigated the addition of concomitant and adjuvant temozolomide to the standard treatment with radiotherapy, and demonstrated that temozolomide significantly improved survival without a negative effect on HRQOL. This treatment is now the standard of care in newly diagnosed patients with glioblastoma.

Recently findings have demonstrated that since survival rates are increasing, it is critical to evaluate the HRQOL of cancer patients.[13] Increasing survival and the impact of past cancer treatment on HRQOL are

factors that must go hand in hand. However, many fundamental questions remain that still need to be answered about the HRQOL of cancer patients. Research needs to be undertaken to establish a common and gold standard HRQOL measure that can be used across all oncology clinical trials and ensuring that it captures emerging data on the side effects and HRQOL impact of novel therapies.

EORTC QLD statistical research activities focus on evaluating and implementing various methods of collecting, analysing, interpreting and reporting HRQOL data in cancer clinical trials. Optimal design and analysis often requires a balance between broad generalisable concepts and study-specific requirements. Moreover, as HRQOL is rarely the primary endpoint, its design space is often limited by the overall trial requirements. Analysing HRQOL data can be complicated for several reasons: repeated measures are obtained, data may be collected on ordered categorical response scales, the instrument may have multi-dimensional scales and complete data may not be available for all patients. In addition, it could be necessary to integrate HRQOL with clinical outcomes. The QLD has an ongoing interest in all of these areas to establish a standard methodology for HRQOL analysis that allows sufficient flexibility. Both longitudinal modelling and summary measures are evaluated for their properties, relevance and sensitivity to missing data.

PROBE

At the EORTC, the Patient-Reported Outcomes and Behavioural Evidence (PROBE) team, established in 2009, is dedicated to meta-analysis and pooled analysis of HRQOL data from EORTC randomised clinical trials. The PROBE database has over 22,000 entries of patient data from 58 closed clinical trials and is a point of HRQOL research reference in the field for more efficient data use. The PROBE team has established an interactive consortium of advisors comprising established professionals from the fields of psychology, biostatistics, psychometrics, medicine, ethics, oncology, radiotherapy, psychiatry and neurology from nine different countries.

One of the major challenges is to pool data and test meaningful HRQOL hypotheses of psychosocial and HRQOL functioning to improve cancer care and treatment delivery. Another important assignment for the PROBE team is to expand the database by including commercial clinical trials and biomarker data. Prognostic indicators of survival and meaningful interpretation of change of HRQOL scores are only some of the research topics for PROBE as we move towards a more accurate mapping of symptoms and functioning related to each cancer. However, a large part of the work is standardising the actual data to be able to combine results across different trials. But these efforts are worth their while and have revealed important results that have informed clinical practice. PROBE analyses have shown the association between baseline HRQOL scores of the EORTC QLQ-C30 and survival, where variables such as global health status/quality of life, physical function, dyspnoea and appetite loss provided significant prognostic information in addition to the sociodemographic and clinical variables.[14,15] The impact of one of these studies in clinical practice was recognised in ASCO's annual report on progress against cancer, "Clinical cancer advances 2012", as having successfully informed and changed clinical practice.[16]

In addition, investigations into the effect of completion-time windows in the analysis of HRQOL outcomes, minimal important differences for interpreting HRQOL scores of QLQ-C30, joint modelling of longitudinal HRQOL data and survival, patient-proxy agreement in HRQOL data, and sources of missing data are ongoing research areas.

Proxy Assessment

Assessing HRQOL in patients with brain tumours is challenging. A commonly reported symptom of patients with gliomas is cognitive deficit, and this also hampers adequate reporting of HRQOL by the patient. Not only are there practical issues with obtaining the actual data (the patient will have difficulties reading and responding to the questionnaires), the resulting values may no longer be an adequate reflection of the patients' HRQOL due to problems with memory, perception or interpretation. Exclusion of patients with cognitive deficits from analysis obviously leads to underreporting of these problems in the evaluation of HRQOL for new treatments. In EORTC trial 26091, a trial assessing the significance of bevacizumab in recurrent grade II and III gliomas, two EORTC HRQOL instruments were used to assess patient HRQOL through their caregivers or relatives (proxies). The assessments reported by the patients are then compared to those reported by their proxies to find out if the proxies can represent patient views and to what extent the two are in agreement. If proxies have a different perspective, the next question would be which reports the more relevant information.

Electronic patient-reported outcomes

A further development that EORTC is pursuing is the use of HRQOL data collection via computer systems instead of the classical paper questionnaires. Such an electronic system would have several advantages, both for the patient (automatic language selection, adaptive display format, etc.) as well as the researchers (automatic data transfer, real-time updates on compliance, etc.). However, many technological as well as administrative and legal barriers need to be tackled. In order to have a machine- independent system, EORTC is developing an online version that will run in all common web-browsers and does not require any local software installation. Once validated, this can be extended to handheld devices and to introduce the questionnaires that can be adapted according to the clinical status of the patient or tailored to his/her previous answers. Ultimately electronic PROs hold the promise that the patient can enter his/her data directly into the clinical trial database, even from home, which is expected to improve compliance significantly. This would reduce the burden on institutions and allow patients to assess their HRQOL outside of the hospital setting. An electronic version of QLQ-C30, CHES.EORTC, has been jointly developed by the QLG and the company Evaluation Software Development to facilitate the integration of the EORTC HRQOL measures into research projects and daily clinical practice. In this version patients are able to complete the QLQ-C30 before the visit to the clinic so the clinician has the graphical representation of the patient's HRQOL during the visit (http://ches.at/ches).[17]

Future opportunities

The patient's perspective has consistently been considered important in palliative and curative EORTC trials, and recent findings have altered clinical practice and provided data needed to support major recommendations and future improvements. Clinicians, regulatory bodies and industry representatives acknowledge the value of the patient perspective, and the EORTC will continue to include HRQOL endpoints where appropriate. Meta-analysis of HRQOL data has proven clinically informative, despite the challenges of funding HRQOL research and the complexities of pooling data. EORTC supports the development of new methods of electronic assessment of PROs and storage in a central EORTC database. Such efforts increase the volume of the HRQOL dataset for research purpose. Therefore HRQOL data collected in clinical trials would not only be used to assess the treatment evaluation at hand but become immediately available for larger research projects on broader issues which can inform clinicians, policy makers, health care payers, etc.

The QLD has been fostering the involvement of patients in informed decision-making and in the past has organised two conferences at the European Parliament to disseminate the latest information on HRQOL to health and social care professionals, and citizens affected, directly or indirectly, by cancer, a disease that is recognised as the second largest cause of death. The European Union is well aware of HRQOL, and under the fifth Framework program (1998–2002) made the entire call related to quality of life. Research and clinical trials have advanced since this framework program, and now research is fundamentally aimed at HRQOL, where patients play an active role in the management of their disease. PROs have evolved to include any endpoint derived from patient reports, health status, adherence, and satisfaction with treatment.

Conclusion

Nurtured by the EORTC's continuous support for HRQOL research, the QLD will expand further, as more research fields are integrated into cancer clinical trials, and technological advances in cancer care

About the EORTC

The EORTC brings together European cancer clinical research experts from all disciplines for trans-national collaboration. Both multinational and multidisciplinary, the EORTC Network comprises more than 2,000 collaborators from all disciplines involved in cancer treatment and research in more than 300 hospitals in over 30 countries. Through translational and clinical research, the EORTC offers an integrated approach to drug development, drug evaluation programs and medical practices. EORTC Headquarters, a unique pan European independent clinical research infrastructure, is based in Brussels, Belgium, from where its various activities are coordinated and run. www.eortc.org.

Key messages for clinical practice

1. There is an increased research focus on the impact of HRQOL assessment on clinical decision making.
2. HRQOL scores provide significant prognostic information in addition to the sociodemographic and clinical variables.
3. Collecting, analysis and reporting of PRO data should follow the same rigorous guidelines as other clinical trial data.
4. Electronic PROs will facilitate HRQOL data collection in general and the long-term follow-up of cancer survivors specifically.

require more innovative methods of HRQOL assessment. EORTC undertakes the challenge to provide EORTC HRQOL tools in electronic format, with the intent of reducing the burden on the patient but also enabling higher quality data for treatment evaluations and methodological research. The electronic PRO development will help EORTC to successfully capture the various issues associated with the long-term follow-up of cancer survivors.

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