International Perspective on Health-Related Quality-of-Life Research in Cancer Clinical Trials: The European Organisation for Research and Treatment of Cancer Experience

Andrew Bottomley and Neil K. Aaronson

ABSTRACT

Over recent decades, health-related quality of life (HRQOL) research has been increasingly integrated into cancer clinical trials. The purpose of this review is to examine the overall approach taken towards clinical trial–based HRQOL investigations within the European Organisation for Research and Treatment of Cancer (EORTC). This article reports a literature review of clinical trial–based HRQOL investigations and provides selective examples of HRQOL studies in phase III clinical trials in various disease sites. The findings of this review highlight that, historically, assessing HRQOL was a challenge. However, as EORTC has become more experienced in the assessment of HRQOL and has developed a portfolio of appropriate tools, HRQOL has become a more accepted end point in large-scale trials. The trials reviewed in this article show that, in general, HRQOL data do provide information that can both inform clinicians about the effectiveness of the treatments and also serve as an invaluable source of information for patients to make informed decisions regarding the treatment choice.

INTRODUCTION

Historically, the evaluation of new cancer therapies has focused on such biomedical outcomes as tumor response, disease-free and overall survival, and treatment-related toxicity. Although these broad outcome parameters remain central in the evaluation process, there is increasing recognition of the need to assess more systematically the impact of cancer and its treatment on the functional, psychological, and social health of the individual.

Increasingly, oncology clinical research is characterized by close international cooperation and collaboration. The establishment of strong international links among clinical investigators carries with it a number of important advantages. Such networks facilitate the rapid exchange of information, minimize redundancy of effort, encourage the standardization of research methods, and accelerate the rate of patient accrual onto clinical trials.

Although multinational research can add complexity to the randomized controlled trial (RCT) process, particularly in terms of organization and quality control, the geographic and cultural backgrounds of patients and investigators do not influence the definition or measurement of the biologic end points of primary interest (eg, tumor response, survival). However, such a culture-free research environment cannot be assumed when one is interested in assessing more subjective outcomes such as symptoms, psychological well-being, or social functioning. To the contrary, the ways in which individuals define, recognize, and report their illness experience, whether expressed in terms of symptoms or levels of functioning, can be highly influenced by such factors as gender, culture, and socioeconomic status.

This review outlines the ongoing efforts of a multinational clinical trials group, the European Organisation for Research and Treatment of Cancer (EORTC), to develop an integrated system for assessing the health-related quality of life (HRQOL) of cancer patients, provides examples of both the challenges and the successes encountered in conducting HRQOL investigations within the context of EORTC clinical trials, summarizes the lessons learned from these trials, and indicates directions for future work.

EORTC

EORTC, one of the oldest and largest RCT research groups in Europe, with its base at its Data Center and Coordinating Office in Brussels, Belgium, is organized into a series of tumor-oriented (eg, breast cancer, lung cancer) groups, each responsible for developing and implementing its clinical trials.
program. All Western European and an increasing number of Eastern European countries are represented within the EORTC, with close cooperation with other clinical trials groups within Europe, the United States, and Canada.

In 1980, in response to an expressed need within the EORTC for a coherent approach to conducting HRQOL research, a Quality of Life Group (QLG) was created to advise the Data Center and the various clinical groups on the design, implementation, and analysis of HRQOL studies within selective clinical trials. Currently, 16 European countries as well as Australia and Canada are represented within the QLG. From its inception, the QLG included a broad range of professionals, all working on a voluntary basis, including oncostologists, radiologists, surgeons, psychiatrists, psychologists, social workers, biostatisticians, and other research methodologists. This mix, defined as much in terms of professional background as language and geography, has proven invaluable in shaping the group’s approach to HRQOL assessment.

In 1993, the EORTC Data Center created an in-house Quality of Life Unit to further facilitate the integration of HRQOL studies in its clinical trials. Composed of a small core staff, this unit works closely with the clinical groups in conducting EORTC and intergroup trial-based HRQOL studies. It also coordinates HRQOL questionnaire translations, disseminates HRQOL questionnaires and support materials to the larger research community, provides training on HRQOL assessment, and has its own research program focused on evaluating the quality of clinical trial–based HRQOL investigations and the prognostic value of HRQOL data.

**EARLY EXPERIENCES WITH HRQOL ASSESSMENT IN EORTC CLINICAL TRIALS**

In the early years, the EORTC experienced a number of false starts and aborted efforts in introducing HRQOL assessments as an integral part of its clinical trials program. Many of the participating local hospitals did not have an adequate research infrastructure to collect patient-reported data, resulting in substantial missing data. The initial enthusiasm for collecting HRQOL data outpaced the logistical capabilities at both the central and the local institution level.

Despite initial problems, there was some success in the early days of EORTC HRQOL assessment. A good example is a phase III RCT (EORTC protocol 10801) comparing breast-conserving therapy (BCT) with radical mastectomy (RM) in a sample of more than 900 stage I and II breast cancer patients. No statistically significant differences were observed between treatment groups in survival or local recurrence. The central HRQOL-related research hypothesis was that BCT would better preserve body image than RM but that this would come at the expense of heightened fear of disease recurrence. In total, 2-year post-treatment HRQOL questionnaire data were available for 278 patients (127 RM and 151 BCT patients). As hypothesized, the BCT group reported significantly better body image than the RM group, but there were no statistically significant differences observed in fear of recurrence. This latter finding was particularly important in informing the discussions that take place regarding the potential psychological disadvantages associated with the less invasive type of surgery.

A number of important lessons were learned from this initial period of HRQOL research within the EORTC. First, not all of the clinical groups were capable of carrying out the additional work involved in collecting patient-reported outcomes; thus, the decision was taken to focus on those groups with a clear HRQOL-related research agenda and committed investigators. Second, EORTC HRQOL activities could not be coordinated by a QLG composed entirely of volunteers; a dedicated, centralized, full-time staff was required. Thus, the Quality of Life Unit was established at the Data Center in Brussels. Third, having HRQOL assessment as an optional element of RCTs only invited noncompliance, and thus, where relevant, HRQOL data collection was included as mandatory. To emphasize this point, the availability of a baseline HRQOL questionnaire was added as a standard eligibility criterion for patient inclusion, and although no formal procedures were put in place to systematically question why any given trial did not include HRQOL data, efforts were made to ensure that an expert in HRQOL was involved in the protocol development process. Finally, standardized procedures were introduced for monitoring compliance with HRQOL data collection, including regular and semi-public (during clinical group meetings) feedback to individual investigators about their performance in this regard.

**EORTC MODULAR APPROACH TO HRQOL ASSESSMENT**

The EORTC has developed a modular approach to HRQOL assessment, comprising a core questionnaire intended for use among a wide range of cancer patients, irrespective of specific diagnosis, and supplementary questionnaire modules designed to assess disease symptoms related to a specific tumor site (eg, urinary symptoms in prostate cancer), adverse effects associated with a given treatment (eg, chemotherapy-induced neuropathy), and additional HRQOL domains affected by the disease or treatment (eg, sexuality, body image, fear of disease recurrence). This modular approach is intended to reconcile the following two principal requirements of HRQOL assessment in EORTC clinical trials: a sufficient degree of generalizability to allow for cross-study comparisons, and a level of specificity adequate for addressing those research questions of particular relevance in a given RCT.

The Quality of Life Questionnaire C30 (QLQ-C30) core questionnaire, which was originally published in 1993, is now in its fourth revision. The current version contains 30 items organized into five functional scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, and pain), and an overall HRQOL scale. Additional single items assess other common symptoms of cancer and its treatment (eg, dyspnea, loss of appetite, constipation, and diarrhea). The questionnaire uses a 1-week time frame and 4-point categoric response choices. It is the standard instrument used in nearly all EORTC clinical trials and is also used widely by other clinical trial groups in Europe and North America (eg, the United Kingdom Medical Research Council and the National Cancer Institute of Canada [NCIC]). Translated into more than 65 languages, its psychometric properties have been evaluated extensively in multinational research settings. Recently, an abbreviated version of the core questionnaire was developed for use in palliative care settings (QLQ-C15-PAL).

Supplementary questionnaire modules are developed according to standardized procedures, including generation of relevant HRQOL issues, development of questionnaire items and scales, modular pretesting, and large-scale, international field testing. Modules are developed on the basis of input from health care professional and patients from a range of geographic, cultural, and language groups. Currently, more than 20 modules are available (www.eortc.be/home/qol).
ized approaches to HRQOL assessment in brain cancer were needed. Higher compliance with HRQOL data collection and that standardization of HRQOL data collection schedule was 78% at baseline and between 55% and 71% at subsequent assessment points up to 2.5 years after radiotherapy. When compared with radiotherapy alone, radiotherapy plus adjuvant chemotherapy increased progression-free survival but also resulted in a short-term negative impact on some aspects of HRQOL during the first year after radiotherapy (eg, increased fatigue). However, longer term follow-up indicated that there were no significant differences between the treatment groups in HRQOL outcomes. Thus, if the combined-modality therapy is to be adopted in the future, greater attention and perhaps focused interventions should be directed towards alleviating or at least minimizing short-term adverse effects such as fatigue.

Breast Cancer

Bottomley et al9 investigated the HRQOL of patients with locally advanced breast cancer treated with a standard anthracycline-based chemotherapy regimen versus a dose-intensive anthracycline regimen (EORTC trial 10921). HRQOL assessments were carried out before random assignment and then once a month for the first 3 months and then every 6 months thereafter to month 54. Four hundred forty-eight patients were entered onto this trial, of whom 384 (86%) completed the baseline HRQOL questionnaire. The clinical results demonstrated that there were no differences in survival between the two groups.10 The intensified treatment resulted in significantly poorer HRQOL outcomes during the first 3 months of follow-up. However, thereafter, the HRQOL scores returned to baseline levels, and at 12 months, no significant differences were observed between the treatment arms. During the remainder of the follow-up, the HRQOL levels were comparable between the study arms. The combined clinical and HRQOL results from this trial suggest that dose-intensive therapy achieves similar survival outcomes without sacrificing the patients’ HRQOL.

Genitourinary Cancer

In EORTC trial 30941/United Kingdom Medical Research Council trial TE20, HRQOL was investigated in patients with metastatic testicular cancer treated with four different schedules of bleomycin, etoposide, and cisplatin chemotherapy (four × three cycles administered over 5 × 3 days).11 HRQOL data were prospectively collected in 666 patients using the EORTC QLQ-C30 and a testicular cancer-specific module. Questionnaires were completed before random assignment; at months 3, 6, 9, and 12; and 2 years after random assignment. Compliance at baseline was 88%. The pattern of changes over time in global HRQOL was similar in the four groups. Two years after chemotherapy, 36% of patients reported improved global HRQOL compared with baseline, and 13% reported poorer HRQOL. At 3 months, patients receiving the 3-day regimen experienced significantly increased GI adverse effects compared with patients receiving the 5-day regimen, with the difference reaching the level of clinical relevance (≥ 10-point change) if four cycles were administered. The 3-day schedule increased the 2-year risk of tinnitus, with clinical relevance demonstrated after four cycles. Long-term peripheral neuropathy and Raynaud-like phenomena were not associated with the
number of cycles or days per cycle. At 2 years, Raynaud-like phenomena, tinnitus, or reduced hearing were reported by 21% to 26% of the patients. The excess of acute GI toxicity and the increased risk of tinnitus after the 3-day regimen led to a recommendation that the 5-day regimen be used if four cycles of bleomycin, etoposide, and cisplatin are planned. If only three cycles are to be administered, then the 3-day regimen is acceptable, even given the increased risk of nausea and vomiting at 3 months.

**Gynecologic Cancers**

Pfisterer et al22 reported the results of a joint Arbeitsgemeinschaft Gynäkologische Onkologie Studiengruppe Ovarialkarzinom (AGO OVAR), NCIC, and EORTC clinical trial investigating gemcitabine plus carboplatin versus carboplatin alone in platinum-sensitive, recurrent ovarian cancer. Three hundred fifty-six patients took part in this phase III RCT. The clinical results demonstrated that gemcitabine plus carboplatin significantly improved progression-free survival. The HRQOL was assessed with the EORTC QLQ-C30 and the EORTC ovarian module. More than 80% of the patients completed both a baseline and follow-up HRQOL assessment. The results indicated that, at baseline, both groups scored similar in terms of HRQOL scores. During treatment and at subsequent points, the combined treatment arm was comparable in terms of HRQOL compared with the carboplatin alone arm. These results indicated that gemcitabine plus carboplatin represented a new treatment option for patients with platinum-sensitive recurrent ovarian cancer.

**Lung Cancer**

Shepherd et al13 examined HRQOL outcomes in a joint NCIC-EORTC (08962) phase III placebo-controlled trial (N = 532) of marimastat versus placebo in the adjuvant treatment of small-cell-lung cancer (SCLC). The primary end point of this trial, survival, showed no significant difference between arms. Toxicity was similar in both groups except for musculoskeletal symptoms and lethargy, which occurred more frequently in the marimastat arm. Approximately one third of the patients in the marimastat arm permanently stopped treatment as a result of toxicity. HRQOL was assessed at baseline; at 3, 6, 12, 18, and 24 months; and yearly thereafter. Patients on marimastat reported significantly poorer HRQOL at 3 and 6 months when reported on the EORTC QLQ-C30 and lung cancer module. In this trial, the clinical and HRQOL results converged. Treatment with marimastat after induction therapy for SCLC did not result in improved survival and had a negative impact on QOL.

In EORTC trial 08983, van Meerbeeck et al14 investigated whether first-line treatment with raltitrexed and cisplatin resulted in superior outcomes compared with cisplatin alone in 250 patients with malignant pleural mesothelioma. In this RCT, the clinical findings were borderline statistically significant in support of raltitrexed and cisplatin (overall survival, P = .048). The HRQOL data compliance was high (> 85% throughout the course of the trial). Importantly, HRQOL data showed no significant difference between the treatment arms, with some indication of improvement in dyspnea in the combined treatment arm. This study provided confirmatory evidence that led to the recommendation that, in selected patients, both raltitrexed and cisplatin should be offered as a treatment approach.

In the EORTC phase III RCT 08971-08971B, Giaccone et al15 investigated survival and HRQOL effects of adjuvant vaccination with Bec2/bacille Calmette-Guerin in patients with limited-disease SCLC who had responded to initial standard treatment. Patients were randomly assigned to receive five vaccinations of Bec2 (2.5 mg)/bacille Calmette-Guerin or to an observation arm. Vaccination was administered over a 10-week period. Survival was the primary end point, with HRQOL as a secondary end point using the EORTC QLQ-C30 and the Lung Cancer 13 module. In total, 515 patients were randomly assigned (258 to the observation arm and 257 to the vaccination arm). There were no statistically significant differences observed in overall or progression-free survival. At baseline, patients in both arms reported significantly impaired HRQOL. No significant group differences or benefits to patients over time in symptoms or HRQOL were observed. The converging survival and HRQOL data indicated no benefit from this adjuvant vaccination program, and thus, its use was discontinued.

**Head and Neck Cancer**

Bernier et al16 examined the HRQOL effect of adding docetaxel to neoadjuvant treatment with cisplatin plus fluorouracil in patients with locally advanced, unresectable squamous cell carcinoma of the head and neck (EORTC trial 24971). Eligible patients with primary tumor sites in the oral cavity, oropharynx, hypopharynx, and larynx and WHO performance status ≤ 1 were randomly assigned to two to four cycles of cisplatin followed by a continuous infusion of fluorouracil (PF) or docetaxel 75 mg/m² plus cisplatin followed by fluorouracil (TPF) from days 1 through 5, followed by locoregional radiation therapy. HRQOL was a secondary end point. Three hundred fifty-eight patients were randomly assigned to PF (181 patients) or TPF (177 patients). TPF was superior to PF in terms of response rate, progression-free survival (primary end point), overall survival, and tolerability. HRQOL was assessed with the EORTC QLQ-C30 and the head and neck module. Compliance with the QLQ-C30 questionnaire was good at baseline (96%) and was similar between the treatment arms. HRQOL scores were comparable at baseline between the two arms (P = .54) and improved in both arms on starting treatment. Over time, HRQOL scores remained stable with TPF but decreased after radiotherapy with PF. Positive changes in head and neck–specific HRQOL aspects over time were observed in the TPF arm (ie, normality of diet, eating in public, understandability of speech). Moreover, TPF was associated with a 30% reduction in the risk of WHO performance status deterioration. These results suggest that the use of doxetaxel in neoadjuvant treatment of squamous cell carcinoma of the head and neck improves clinical efficacy without deleterious effects on HRQOL and functional outcomes.

As clinical trials become more complex and resource intensive and with the recent implementation of the new European Clinical Trial Directive, it is clear that undertaking HRQOL investigations as part of clinical trials will also become more complicated. Nevertheless, this review demonstrates that, although early EORTC trials in which attempts to assess HRQOL were found wanting, the more recent RCTs conducted within the EORTC have been far more successful. They have aided in documenting the benefits and costs of treatment and in identifying the most appropriate approaches to treating patients from a broader perspective.

At the same time, there remains much to be done within the EORTC to improve the quality and, thus, the usefulness of clinical trial–based HRQOL investigations. This includes the following:
providing continuing education opportunities for clinicians and nurses to better familiarize them with the purpose and nature of HRQOL studies, the procedures involved, and the potential value added of these types of data in the clinical decision-making process; continuing to develop the library of condition-specific HRQOL questionnaire modules that provide more detailed information on the impact of specific forms of cancer and their treatment on patients’ physical and psychosocial health; developing guidelines and templates for key HRQOL-related paragraphs in clinical trial protocols; setting further standards for minimal levels of compliance with HRQOL components of clinical trials and for decision rules for early closure of the HRQOL as a result of unacceptably low compliance; developing standard statistical analysis strategies for examining and dealing with missing data and for making group comparisons over time in the presence of censored data; and developing methods and guidelines for interpreting HRQOL results in clinically meaningful terms and for reporting HRQOL outcomes as part of larger clinical trial reports and as free-standing publications.

CONCLUSION

The EORTC has been involved in cancer clinical trials for more than 40 years, and for 25 of those years, these trials have involved studies with HRQOL end points. Although the majority of these studies were begun in the last decade, early studies still provided useful information that guided the development of methods and also yielded clinically relevant results. There are continuing challenges for the HRQOL research committee, including adapting to the changing RCT arena, refining existing and developing new HRQOL instruments, and improving on the design, implementation, and statistical analysis to ensure that the additional effort involved in collecting HRQOL data has a continued pay off in terms of improved patient care and management.

REFERENCES


Acknowledgment

All European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group investigators who have helped in designing EORTC trials and measurement systems over the last two decades are acknowledged for their valued contribution to health-related quality-of-life research. This work was also supported, in part, by the EORTC Charitable Trust.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Andrew Bottomley, Neil K. Aaronson
Administrative support: Andrew Bottomley, Neil K. Aaronson
Provision of study materials or patients: Andrew Bottomley, Neil K. Aaronson
Collection and assembly of data: Andrew Bottomley, Neil K. Aaronson
Data analysis and interpretation: Andrew Bottomley, Neil K. Aaronson
Manuscript writing: Andrew Bottomley, Neil K. Aaronson
Final approval of manuscript: Andrew Bottomley, Neil K. Aaronson

Andrew Bottomley, Neil K. Aaronson

Copyright © 2007 American Society of Clinical Oncology. All rights reserved.