

Quality-of-Life Assessment in Oncology

Achievements and Challenges

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Acta Oncologica Vol. 41, No. 3, pp. 229–237, 2002

In this article important areas of health-related quality of life (HRQL) research and major achievements are described, illustrated by studies conducted with cancer patients. Some of the challenges facing this line of research are elucidated. The areas of HRQL research described are distinguished according to their intended objective, including research aimed to assess treatment outcome and/or to qualify rates of survival, to assess late problems, to predict mortality, and to support information-giving. It was found that HRQL assessments are useful in clinical trials and cost-effectiveness studies and that they point to areas where former cancer patients may experience serious problems. It was also found that HRQL data are strong predictors of survival. Finally, HRQL assessments were found to stimulate doctor–patient communication. Three challenges are discussed, including the use of proxy respondents, the need to take response shift into account, and the interpretation of HRQL results as clinically meaningful. New research areas, such as HRQL related to genetic testing and as experienced by ethnic minorities urgently need to be taken on.

Received 27 August 2001

Accepted 3 January 2002

The field of health-related quality-of-life (HRQL) research has burgeoned in the past two decades. The prevalence of peer-reviewed journal articles on the topic has expanded exponentially, and the inclusion of HRQL measures in medical research has become common (1). For example, the traditional endpoints in comparative cancer clinical trials are tumor response, survival and/or time to disease progression, and treatment-related toxicity. While these outcome parameters remain essential, there is general recognition of the need to assess the impact of cancer and its treatment on patients' HRQL (2–5).

The aim of this study is to describe important areas of HRQL research and to highlight major achievements, illustrated by studies conducted with cancer patients. Furthermore, some of the challenges facing this line of research are elucidated. For those for whom HRQL is a relatively new phenomenon, a brief introduction to the concept of HRQL and its measurement may prove helpful.

HEALTH-RELATED QUALITY OF LIFE

It is generally accepted that HRQL is a multidimensional construct incorporating at least three broad domains—physical, psychological, and social functioning—that are affected by one's disease and/or treatment (6, 7). Physical

functioning is usually defined as the performance or the ability to perform a range of activities of daily living, as well as physical symptoms resulting either from the disease itself or from treatment. Psychological functioning ranges from severe psychological distress to a positive sense of well-being and may also encompass cognitive functioning. Social functioning refers to quantitative and qualitative aspects of social relationships and interactions, and societal integration. Beyond this core set of HRQL domains, additional issues may be more relevant for specific groups of cancer patients, depending on the functional domains affected by the disease or treatment (e.g. sexual functioning in patients undergoing mutilating surgery). In addition, there is consensus that HRQL assessments also entail an overall judgement of health and/or quality of life. Finally, the subjective nature of HRQL frequently causes confusion and discomfort in clinicians. However, by subjectivity, we do not mean to oppose it to 'objective', where it would imply unreliability and a poorly defined concept. On the contrary, HRQL can be measured reliably and validly. Rather, by subjectivity, we mean that HRQL is important to the subject and that the patient should be the primary source of information regarding his/her HRQL (6, 7). The subjectivity of HRQL will thus help clinicians to gain

insight into the patients' perspectives of their disease and treatment.

ASSESSMENT OF HEALTH-RELATED QUALITY OF LIFE

Multidimensional HRQL instruments are available that, while relatively brief, provide adequate coverage of the basic HRQL domains. The most common instruments in HRQL research are generic, cancer-specific, and domain-specific questionnaires.

Generic instruments

Generic instruments are intended for use across a wide range of chronic disease populations. Such health profiles are single instruments composed of a number of subscales, each assessing a different HRQL dimension. The major advantage of these health profiles is that they allow for comparison of results across different patient populations. However, they may not adequately address those issues of relevance to cancer patients, such as disease symptoms and treatment side effects (8). Examples of generic health profiles that have well-established levels of reliability and validity include the Sickness Impact Profile (SIP) (9), the Nottingham Health Profile (NHP) (10), the Medical Outcome Study Short Form Health Survey (SF-36) (11), and the EQ-5D (formerly known as the EuroQol) (12).

Cancer-specific instruments

In contrast to the generic instruments, the major advantage of the cancer-specific instruments is that they are more likely to be responsive to disease-related changes in HRQL. Conversely, the specificity of these measures precludes their being used for comparing results across different disease populations. Examples of cancer-specific measures that have well-established levels of reliability and validity include the Rotterdam Symptom Checklist (RSCl) (13), the Functional Living Index-Cancer (FLIC) (14), the Cancer Rehabilitation Evaluation System Short Form (CARES-SF) (15), the Functional Assessment of Cancer Therapy-General (FACT-G) (16), and the EORTC Core Quality of Life Questionnaire (EORTC QLQ-C30) (17). The last two of these questionnaires have been developed according to the so-called modular approach to HRQL assessment. In this approach a generic or 'core' instrument, applicable to a broad range of cancer patients, is combined with a specific questionnaire ('module') that assesses topics of relevance to specific cancer patient subgroups in more detail. The combination of a core instrument and a module allows for a sufficient degree of generalizability (via the core instrument) and specificity (via the module). The FACT-C and EORTC QLQ-C30 are such core instruments that are intended to be supplemented by site- and or treatment-specific modules. A comprehensive overview of cancer-specific instruments is provided by Gunnars et al. (18).

Domain-specific instruments

Domain-specific questionnaires are designed to address one specific aspect of HRQL in greater detail and are, in general, not specific to cancer. Examples of such questionnaires with documented levels of reliability and validity include the Multidimensional Fatigue Inventory (MFI) (19), the McGill Pain Questionnaire (20), and the Hospital Anxiety and Depression Scale (HADS) (21).

AREAS OF QUALITY-OF-LIFE RESEARCH

HRQL assessment is used as an outcome measure, as a predictor, or as an intervention. The research areas where HRQL functions as an outcome measure can be distinguished according to their intended objective and include research aimed to assess treatment outcome (e.g., randomized clinical trials), to qualify quantity of survival (e.g., cost-effectiveness studies), and to assess late physical and/or psychosocial problems. When HRQL is used as predictor, the research objective is to predict mortality, or its reverse, survival duration. In clinical care, HRQL can be used as an intervention. The objective is then to support the information-giving process during the clinical consultation. While these five objectives are not exhaustive, they concern important HRQL research areas. These fields will be briefly described and illustrated. In effect, the cited studies have adopted the described HRQL concept and made use of generic, cancer-specific, or domain-specific questionnaires, or a combination of these measures. A systematic review was not conducted, as this was prohibited by the diversity and extension of the research domains. Rather, the description and choice of studies reflect to some extent the particular perspective of the author. Whereas the description is not intended to be comprehensive, it will highlight major achievements in HRQL research.

To assess treatment outcome and to qualify quantity of survival

Support for incorporating HRQL in cancer clinical trials is voiced by prominent clinical trial groups (2, 3) and national and international cancer institutes and societies (4, 5). Consequently, the question of whether HRQL needs to be measured in the context of a clinical trial is shifted to the question of when one should opt for inclusion of such a measure. In general, assessment of HRQL in the context of phase I and II clinical trials is less opportune given the limited number of patients, although inclusion of HRQL in these contexts has also been advocated (22). In phase III trials, HRQL may assume primary importance when significant differences in survival gain or tumor response are not to be expected. HRQL may thus be most informative in trials of advanced-stage cancer where different palliative treatments are compared with limited effects on survival gain and tumor response (23, 24). Furthermore, HRQL is

relevant when survival is gained, however, at the expense of major toxicity. In special cases of clinical trials and cost-effectiveness studies, health outcomes are most commonly expressed in terms of quality-adjusted life years (QALYs). Such QALYs adjust quantity of life by incorporating estimates of preferences or utilities (valued between 0.0 and 1.0) (25) for each health state constituting survival (e.g. a period with post-treatment symptoms, recurrence-free period, a period with presence of local recurrence and distant metastases). An alternative measure that combines survival with HRQL is the quality-adjusted time without symptoms or toxicity. This Q-TWiST partials survival into areas without disease symptoms or toxicity, areas with toxicity and/or symptoms, and the time spent in relapse (26). To date, hundreds of clinical trials and cost-effectiveness studies have been conducted that included HRQL as the endpoint. These trials examined a wide range of patients differing in type and localization of tumor, disease stage, and treatment modality. In a number of these trials, HRQL results legitimized the institution of the cancer treatment. For example, the US Food and Drug Administration approved gemcitabine for cancer of the pancreas and epoetin alpha for chemotherapy-induced anemia and fatigue on the grounds of clinical trial-based HRQL data (27).

To illustrate, Tannock and colleagues (28) randomly allocated 161 hormone-resistant prostate cancer patients with pain to receive prednisone alone or a combination of mitoxantrone and prednisone. The primary outcome was pain relief, defined as a 2-point decrease on the 6-point pain intensity scale of the McGill Pain Questionnaire (20), without an increase in analgesic medication. The secondary outcome was, among others, a decrease of at least 50% in use of pain-relieving medication without an increase in pain. Both outcomes had to be maintained for a predefined period of time. HRQL was assessed with the EORTC QLQ-C30 and two prostate cancer-specific quality of life instruments. HRQL was considered as supportive evidence. Patients treated with the combination treatment had a significantly better total response rate as assessed by the primary and secondary endpoints combined (i.e., a decrease in pain or pain medication without an increase in the other). These patients also reported, in general, better HRQL. This is an additional trial whose self-reported pain and HRQL outcomes led the US Food and Drug Administration to license the combination treatment (29).

To assess late problems

While the survival rates of cancer patients largely depend on specific type, location, and stage of the tumour at diagnosis, the long-term quality of life may be affected by cancer therapies whether they are surgical, systemic or radiotherapeutic. A legitimate question is how patients fare after their initial treatment. To date, hundreds of

studies have assessed the short- to long-term HRQL of cancer patients within more or less homogeneous groups formed according to tumour site and/or treatment modality. A specific question is related to the long-term HRQL of those who survived pediatric cancer.

During the past decades, survival rates of childhood cancer have increased considerably, thanks to improvements in treatment and care. Approximately 65% of children are expected to survive at least 5 years following their cancer diagnosis (30). As a consequence, the objective of pediatric oncology is changing from mere survival gain to survival gain accompanied by an HRQL comparable to that of the survivor's peers. However, there is growing evidence that different therapies affect physical outcome adversely in the long term (30). Furthermore, survivors may also experience problems with cognitive and academic achievement (31), occupational or vocational accomplishments (32), and psychosocial adjustment (33, 34). Studies examining long-term psychosocial sequelae basically conclude that survivors, in general, do not fare poorly, but that subgroups of patients can be identified that experience serious psychosocial problems (33, 34).

The psychological consequences of childhood cancer were the focus of a systematic review of 20 studies conducted by Eiser and colleagues (35). The results pointed clearly in one direction: in comparison to population norms or matched controls, cancer survivors did not report a higher level of anxiety or depression or a lower level of self-esteem. While these results support earlier findings of descriptive studies, the authors cautioned for a number of methodological flaws. These included, among others, poorly reported medical information, heterogeneous and self-selected samples and unsuitable measures. For example, while few differences between cancer survivors and population norms can be detected with standardized domain-specific measures, larger discrepancies are found when other data collection methods are used, such as interviews. The underlying message of this review is that we need better studies before we are able to say anything definite about cancer survivors' psychological adaptation and HRQL.

To predict mortality

An important clinical question is related to the identification of parameters capable of predicting survival duration. While, traditionally, tumor size is an important predictor, there is ample evidence that HRQL indices independently predict survival. This finding is documented for patients with breast cancer (36–38), melanoma (39), lung cancer (40–42), colorectal cancer (43), prostate cancer (28), and for patient samples heterogeneous to cancer site (44). In some of these studies, HRQL was found to be even more predictive of survival than known biologic prognostic factors (36, 40–43). It should be noted, however, that in a few other studies no significant relationship was found between

HRQL and time to death (45, 46). There is some dispute about the explanation of these contradictory findings. Butow and colleagues (47) argue that the non-significant findings may be due partly to methodological flaws, such as small and/or heterogeneous samples, failure to control for cancer stage and severity of disease symptoms, and inappropriate use of statistical analyses. Conversely, Hurdon et al. (48) reason that HRQL is a significant predictor of survival only if the available clinical measures provide an incomplete or imprecise prognostic profile, which they believe to be the case in most of the studies reporting positive findings. In their own investigation, poorer HRQL predicted significantly poorer survival. However, after adjustment for a range of clinical factors, the only HRQL domain that remained independently predictive of survival was self-reported pain. Their reasoning and findings do not discredit this line of research, however. Their results also confirm that the detailed and refined HRQL information adequately reflects the patient's physical condition. Since administering an HRQL questionnaire to patients is often easier and less costly than obtaining most of the biological and clinical values, HRQL is, at the very least, a good proxy measure for clinical status.

To elucidate: in a recent study, Butow and colleagues (47) administered a series of questionnaires to 125 patients with metastatic melanoma, immediately after their diagnosis. Survival was measured from the date of study entry to the date of death or to the date of last follow-up for surviving patients. HRQL was measured with the GLQ-8 (49), which consists of eight visual analog scales addressing physical and emotional functioning, combined to form one overall score. In addition, patients were asked to complete a measure on coping, psychological adjustment, social support, and perceived aim of the treatment. After controlling for demographic and disease variables, these five psychosocial variables were independently prognostic of time to death. The significant impact of HRQL on survival duration emphasizes the need to include HRQL in cancer clinical trials and also suggests that initial HRQL should be controlled when compared with the survival benefit between treatment arms. Interestingly, the largest effect on survival was perceived aim of the treatment. Those patients who believed that treatment would lead to cure or long-term survival, lived longer. These patients were not different with respect to demographic or disease variables from those who believed that the treatment was aimed at short-term survival or reduction of symptoms. Possible explanations of these findings include an early perception by the patient and/or the doctor of subtle signs of disease progression not recorded as prognostic features. Additionally, the authors hypothesized that the optimistic coping style adopted by some patients, may have affected the disease process positively. A third explanation is that HRQL is indicative of patients' adherence to treatment and follow-up schedules and is thus indirectly related to

the disease process. While future research is needed to further test the viability of these explanations, the results underscore the prognostic power of psychosocial variables.

To support information giving

Although both oncologists and patients are willing to discuss a wide range of HRQL issues (50), time pressure, clinical constraints (51) and suboptimal communication skills may prohibit such exchange. To identify HRQL issues of concern to individual patients and to facilitate the communication between the doctor and his/her patient, standardized HRQL questionnaires are increasingly being used in daily clinical practice (52). Most typically, a patient is asked to complete a HRQL questionnaire while waiting to see his/her treating physician. A computer immediately processes the patient's responses, producing a clearly interpretable summary highlighting the most prevalent problems. In some instances, responses provided at previous visits are also included in the overview, allowing detection of changes over time. This synopsis can then be used by the physician and/or patient during the subsequent clinic appointment. The effectiveness of such interventions conducted in a wide range of non-cancer healthcare settings has recently been reviewed (53, 54). Based on 24 randomized trials (Of the 21 clinical trials reviewed by Espallargues et al (54) and the 13 reviewed by Greenhalgh et al. (53), 10 were overlapping.), feedback to clinicians was found to enhance the identification of psychological, and to a lesser extent, functional problems. Additionally, there is some evidence to suggest that such feedback leads to an increase in diagnoses and utilization of health services. However, this feedback was not found to affect other aspects of care, such as the number of prescriptions or changes in treatment. Patient outcomes, such as health status and satisfaction with care, remained unaffected by these interventions. The authors pointed to the heterogeneity of the studies to partly explain these findings. For example, HRQL feedback was provided either before, during, or after a medical consultation. They call for more stringent evaluations of these types of intervention.

The only published study in cancer patients at the time of manuscript preparation is the investigation of Taenzer and colleagues (55). They sequentially assigned 53 lung cancer patients to a usual care control group and subsequently to an intervention group. The latter group of patients completed a computerized version of the EORTC QLQ-C30 to provide the treating physicians with HRQL information prior to the consultation. In the experimental group, significantly more HRQL issues were discussed during the clinic appointment, marginally more of the HRQL concerns of patients were charted, and a trend towards further medical action being taken was found. Patients reported a high but similar level of satisfaction to that in the control group. This study has a number of caveats, the quasi-experimental design and small sample

size being among them. Currently, a number of large-scale, randomized clinical trials employing prospective designs are being conducted in Germany, the UK, and The Netherlands. These studies will allow more definite conclusions about the impact of this relatively simple means to enhance the identification of HRQL concerns and to stimulate physician–patient communication of these concerns.

CHALLENGES OF ASSESSING HRQL

The field of HRQL research, like any other respected science, faces major challenges. Three of these methodological issues will be discussed in more detail. These include the viability of proxy ratings where patients are unable to respond to HRQL questionnaires, the need to take response shift into account when patients have changed their perspective over time, and the interpretation of findings as clinically relevant or meaningful.

Patients are unable to complete HRQL questionnaires

Acknowledging that the patient is the most appropriate source of information on HRQL does not imply a wholesale rejection of alternative sources of such information. If patients are severely ill, frail or old, emotionally distressed, cognitively or mentally challenged, we need to draw upon significant others (e.g. spouses, relatives, friends) and/or healthcare providers (e.g. physician, nurse) as either complementary or alternative sources of information on patients' HRQL. The immediate question that arises is how accurately can such 'proxy' informants assess the patients' HRQL.

Sneeuw and colleagues conducted a review of 23 studies, published between 1991 and 2000, which assessed the patient-proxy agreement for a range of established HRQL questionnaires (unpublished study). The level of agreement was found to be dependent on sample size, with larger samples showing better agreement. In large studies (i.e. more than 50 patient-proxy pairs) comparing patients and significant others, median correlations for physical HRQL domains were between 0.60 and 0.70 and for psychosocial domains around 0.50. The results were mixed for studies employing healthcare providers as proxy raters, primarily because of small sample size. The median standardized differences were generally around 0.20. Substantial discrepancies between patient and proxy ratings were rare. Based on these findings, the authors concluded that both healthcare providers and significant others are reasonably accurate observers of patients' HRQL.

The differences between patients' responses and proxy judgements, albeit small, are not random, however. Proxies tend to underestimate patients' HRQL. They report more problems and lower levels of functioning than patients do (Sneeuw et al., unpublished study, 56). This systematic difference is not equally distributed across HRQL domains. As might be expected, proxies are more

accurate when the information is concrete and observable (56, 57). In other words, both healthcare providers and significant others are better able to judge the patient's physical performance than his/her mood.

A serious problem in longitudinal research, such as clinical trials, is patient loss to follow-up. Patient attrition does not appear to be a random event, but is often related directly to declining health status. Yet, it is precisely at the point of disease progression or acute symptom experience that we may be most interested in assessing changes in HRQL. In designing longitudinal studies, the bias as a result of proxy observations needs to be balanced against the bias caused by patient attrition. If patient loss to follow-up is anticipated, it is recommended that proxies be included from the beginning of the study. When the patient is still being studied, the concordance level between patient and proxy responses can be calculated. The trial results can then be based on the complete proxy responses adjusted for this concordance level, thus reducing systematic bias. Such calibrated proxy scores have been successfully used in a study among stroke survivors (58).

Patients have changed their perspective over time

Sometimes articles documenting HRQL data report paradoxical or counter-intuitive findings. For example, although patients may report a stable HRQL over time, their clinical health status may be deteriorating considerably (59, 60). Furthermore, as noted previously, cancer survivors, in general, report a level of HRQL comparable to that of healthy people (35). In other studies, cancer patients under active treatment were also found to report levels of HRQL not inferior to those of healthy individuals (59, 61). The recurrent finding that cancer patients report higher levels of HRQL compared with those observed by their healthcare providers and significant others, as noted in the previous paragraph, is another source of puzzlement. Such findings might be interpreted as resulting from changes in patients' internal standards, values, and/or the conceptualization of HRQL over the course of the disease trajectory. These changes, which are inherent to the process of accommodating to the illness, are referred to as 'response shift' (62, 63).

While response shift is not new from a clinical (64) or intuitive perspective, it is a relatively new phenomenon from a methodological viewpoint. Shifting internal criteria, values, and conceptualization of life may render assessments completed over time incomparable. Since the units of comparison have changed, the comparison itself loses its meaning. For example, in the context of treatment evaluations, response shifts may attenuate or inflate estimates of treatment effects if patients adapt to treatment toxicities or disease progression over time. To quote Longo (65): '...toxicity to which the patient has accommodated still is toxicity'. More importantly, differences in HRQL across treatment arms may be jeopardized when response shift

affects the treatment groups differentially (66, 67). Random allocation to treatment arms does not solve this problem since treatments may still result in different levels and types of toxicities. Assessing response shift may therefore be needed to obtain a valid and sensitive assessment of change over time.

By integrating measures of changes in internal standards, values, and conceptualization into research designs, the effects of response shift can be explicitly measured and taken into account. Since this is a relatively new field, methods to assess the different components of response shift are now emerging. Schwartz & Sprangers (62) have described a range of detection procedures, including individualized approaches (68), qualitative methods (69), preference-based techniques (70), and design approaches. Perhaps the best-established approach in this last-cited family of methods is the retrospective pretest--post-test design to assess changes in internal standards (71). A retrospective pretest or 'then-test' is administered at follow-up, and invites patients to provide a renewed judgement of their baseline level of HRQL. The comparison of the baseline and retrospective measure would provide an indication of the amount and direction of response shift effects. Since the post-test and then-test are completed at the same follow-up assessment, it is hypothesized that these measures are completed with respect to the same internal standard of measurement. Consequently, their comparison would provide an estimate of change that is not confounded by response shift (71). While not without criticism, this approach has proven to provide valuable information in a number of clinical studies on oncology (66, 72–75). These and other investigations are the first of an emerging line of research addressing explicitly the dynamic nature of HRQL.

When are statistically significant results also clinically meaningful?

If a clinical trial results in statistically significant changes in HRQL outcomes, the key question is the extent to which these results are clinically meaningful. Since statistical significance is dependent on sample size, a one-unit change on a HRQL scale ranging from 0 to 100 may result in a p -value < 0.001 if the result was based on a large sample (e.g. > 1000 patients). Clearly, this finding would most likely be trivial. Lydick & Epstein (76) distinguished two approaches to establishing clinical meaningfulness. The first cluster of approaches is so-called distribution-based and relates the results to some measure of variability. For example, originating from the social sciences, Cohen (77) proposed to use standardized mean scores or effect sizes, defined as the mean change score divided by the standard deviation of stable subjects, e.g., as obtained at baseline. His guidelines to interpret effect sizes in the range of 0.2 standard deviation units as small, 0.5 as moderate, and 0.8 as large, have been widely adopted. The

criticism to this approach, however, is that the magnitude of effect sizes is sensitive to the variability (standard deviation) of the population under study. More importantly, the interpretation of the magnitude of change is not intuitively meaningful. The second series of measures, the so-called anchor-based approaches, incorporate a meaningful, external measure that is more clearly understood than HRQL scores themselves. For example, frequently used approaches such as the minimal clinically important difference (78, 79) and the subjective significance questionnaire approach (80) correlate change over time with patients' overall evaluations regarding the extent to which they improved, remained stable, or deteriorated. The method is critically dependent, however, on the patients' ability to validly indicate change. There is evidence to suggest that such transition scores reflect patients' current HRQL rather than the change in HRQL over time (81).

Recent research has attempted to empirically test the relationship between the distribution- and anchor-based approaches. For example, Osoba and colleagues (80) compared their subjective significance questionnaire (SSQ) approach with effect sizes. Cohen's guidelines were confirmed in this study in that small, moderate, and large effect sizes coincided with the same magnitude of change as indicated by the SSQ ratings. Norman and colleagues (82) recently demonstrated that effect size and a minimal clinically important difference (MCID) provide equivalent information. Based on simulation data and four empirical studies, an MCID of 0.5 on a seven-point scale, a frequently reported finding (79), almost equalled an effect size of 0.5 (as the standard deviation of the change scores was consistently near one). Interestingly, they also found that larger effect sizes coincided with a larger proportion of patients benefiting from treatment (i.e., the difference between the proportion improving and the proportion deteriorating in the treatment and control groups). Since this relationship was found to be approximately linear, the practical implication is that an effect size can be translated into the proportion benefiting from treatment. These findings led Norman and colleagues to the intriguing conclusion that the differences between distribution- and anchor-based approaches are perhaps more illusory than real.

There are many ways to demonstrate meaningful or minimally important changes in HRQL outcomes, and no one approach is perfect. While the findings of Norman and colleagues are reassuring, individual methods and the convergence of the different methods require further validation. This fact led Revicki and colleagues (83) to advocate the use of multiple sources of evidence of clinical meaningfulness in the same study. It is hoped that such studies as well as clinicians' day-to-day use of HRQL measures will ultimately lead to the sort of clear interpretability of HRQL results that has become common for most clinical parameters.

DISCUSSION

In the past decades we have witnessed major improvements in HRQL research and a growing acceptance by the medical community and society at large. HRQL research 'has helped describe and draw attention to the human side of cancer treatment' (27: p. 885) and has influenced the treatment itself. Clinical trial based HRQL data are increasingly being used for FDA-approved marketing. Quality of life assessments have not only been useful in clinical trials and cost-effectiveness studies, but have also pointed to physical, cognitive, and psychosocial areas where former pediatric cancer patients may experience serious problems, even years after diagnosis. Furthermore, HRQL data have been found to be strong predictors of survival. Finally, HRQL data have proven to be useful in clinical care studies, particularly in stimulating doctor-patient communication of psychosocial issues. HRQL studies thus yield relevant results that inform both physicians and patients, and help them explicitly to weigh the costs and benefits of different treatment options, thus contributing to treatment decisions and cancer care. While this line of research has many achievements, it also faces a number of challenges. Three of these have been discussed in some detail, including the use of proxy respondents when patients are unable to respond to HRQL questionnaires, the need to take response shift into account when patients have changed their perspective over time, and the interpretation of HRQL results. This list is far from exhaustive, as other, much needed, methodological tasks are also undertaken, such as the development of individualized measures, the calibration of different questionnaires (e.g. how does an increase of 10 points on the emotional well-being scale of the FACT-C translate to an increase on the emotional functioning scale of the EORTC QLQ-C30), and the development of computer adaptive testing (27, 84).

Clearly, not all challenges are methodological in nature. New areas of research call for additional effort. For example, the human genome project will have a major impact on clinical and health services research in general and HRQL research in particular. To date, HRQL investigations are focused on medically confirmed, diagnosed cancer patients. With the increasing availability of genetic tests, the focus needs to be expanded to include asymptomatic individuals potentially having a genetic predisposition to cancer, asymptomatic and symptomatic mutation carriers, individuals who receive inconclusive test results, and family members. There is evidence to suggest that genetic testing can have a profound, adverse impact on the psychosocial well-being and daily life of clinic attendees (85). Another research area of increasing interest is that of ethnic minorities. In the USA ethnic minority groups, such as African American and Hispanics, are known to have a higher cancer incidence and a lower survival rate than non-Hispanic Whites (86). In parts of northern and west-

ern Europe, the ethnic minorities that are now in the cancer risk age group, originate essentially from two groups: those who come from former colonies, and former residents of primarily Mediterranean countries. The latter group came to northern and western Europe in the 1950s and 60s to strengthen the labor force. While the composition and history of the ethnic minorities in the USA and Europe differ, they are equally excluded from HRQL studies, the reason being that such studies require that respondents have a sufficient command of the host language to complete a questionnaire. A prerequisite of including cancer patients of different origin is the availability of a valid language version of the questionnaire. Recent and current research endeavors are directed towards the translation and validation of such translated HRQL questionnaires. To date, published data on HRQL after cancer among persons of different ethnicity hardly exist (87) and urgently need to be collected.

ACKNOWLEDGEMENTS

The author is indebted to Symone Detmar and Martha Grooten-huis for helpful suggestions on the literature, and to Hanneke de Haes for useful comments on an earlier draft.

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