Health-related quality of life and cancer clinical trials

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Abstract: The measurement of patient-reported outcomes, including health-related quality of life, is a new initiative which has emerged and grown over the past four decades. Following the development of reliable and valid self-report questionnaires, health-related quality of life has been assessed in tens of thousands of patients and a wide variety of cancers. This review is based on a selection of data published in the last decade and is intended primarily for healthcare professionals. The assessments in clinical trials have been particularly useful for elucidating the effects of various cancers and their treatments on patients' lives and have provided additional information that enhances the usual clinical endpoints used for determining the benefits and toxicity of treatment. With growing experience the quality of the health-related quality of studies has improved and, in general, recent studies are more likely to be methodologically robust than those that were performed in earlier decades. Health-related quality of life has become a more accurate predictor of survival than some other clinical parameters, such as performance status. The overall outlook for the routine assessment of patient-reported outcomes in clinical trials is assured and, eventually, it is likely to become a standard part of clinical practice. However, there is still a need for a clear method for determining the clinical meaningfulness of changes in scores. The answer will probably come from the greater use of patient-reported outcomes and the consequent growth of experience that is necessary to make such judgements.

Keywords: breast cancer, clinical meaningfulness, clinical trials, colorectal cancer, health-related quality of life, lung cancer, palliative care, patient-reported outcomes, prediction of survival, prostate cancer, supportive care, symptom control

Introduction

The past four decades have seen the development of a new technology in medicine that is based entirely on data obtained from patients' self-reports of their symptoms and functional status. The initial workers in this area termed the results of self-evaluation as 'health status' or 'outcomes' assessment. Assessment could be performed either in patients or the general population. Eventually, the work that was directed primarily towards patient evaluation came to be known as 'health-related quality of life' (HRQOL) to distinguish it from the quality of life of the general population since the latter depends, in part, on factors that are unrelated to health. HRQOL refers to multidimensional assessments that include at least the physical, emotional (or psychological) and social domains, and may also include other domains such as cognitive

functioning, sexuality and spirituality. While single domains, such as performance status or symptoms, may be components of HRQOL they are, by themselves, insufficient to constitute a complete HRQOL assessment. In addition, the assessment of HRQOL does not usually include some other patient reported assessments, such as needs assessment and satisfaction with care. Thus, patient-reported outcomes (PROs), a more inclusive term, was suggested to include any data that are reported directly by the patient without an intermediary such as a family member or a healthcare professional [Willke *et al.* 2004]. The process of obtaining PRO data is sometimes referred to as PRO measurement (PROM).

Oncology is a fertile ground for research on HRQOL and PROM. Patients with cancer exhibit many symptoms and losses of functional

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ability. Many of the symptoms and functions are not measureable with laboratory tests or imaging procedures and it is necessary to rely on the patients' self-reports. Some examples are role functioning, social functioning, sense of wellbeing, pain, fatigue and overall or global HRQOL. In oncology there is a broad scope of clinical settings in which PRO may be measured. These range from primary and secondary prevention, through to adjuvant treatment, primary treatment with intent to cure, palliative treatment of metastatic disease, end-of-life palliative treatment and prediction and prognosis.

One of most comprehensive reviews of outcomes research in cancer was published in 2005 [Lipscomb *et al.* 2005]. However, because of the length of time it takes to publish a book, the four chapters dealing with most commonly-occurring cancers, i.e. breast, prostate, lung and colorectal cancer (CRC), only reviewed publications that were available up to about 2001. Thus, they did not include work from most of the current decade. In addition, some of the above reviews compared PRO with the usual clinical outcomes of disease progression and survival, while others did not.

This review has two main objectives. The first is to provide an update of the results of PROM in clinical trials and in palliative and supportive care settings in patients with cancer reported in the last decade. The past decade was chosen with the intent of adding to the previous extensive review [Lipscomb *et al.* 2005] and of highlighting results that are of 'added value' for healthcare professionals and patients in clinical settings. The second objective is to summarize some of the recent developments and interesting directions of PROM. This is not an exhaustive review of all of the literature in this field of the past decade, but rather a selection of that which the author considers to be the most informative.

It may not be correct to expect PRO to supersede, i.e. 'trump', clinical outcomes, and it may be more likely that PRO provide 'added value' to the usual clinical outcomes. Indeed, most studies in which there was longer survival in one group of patients as compared with another show either improved or, at least, stable PRO in the group with the longer survival. 'Added value' means that the PRO data either support the biomedical outcomes or provide improved descriptions of the treatment experiences of patients with cancer.

Methods

For this review a search was made in PubMed using 'Neoplasms'[Mesh] AND 'Quality of Life'[Mesh]) AND 'Clinical Trials as Topic'[Mesh] as the main headings but limited the search to only items with abstracts, humans, clinical trials, journal articles, English, core clinical journals, nursing journals, cancer, all adult and published in the last 10 years. A total of 238 articles were found of which 226 had a full text. These were reviewed and 118 articles were chosen for citation because they provided PRO data that would be useful for health care professionals in their clinical work.

PRO in cancer

Breast cancer

Goodwin and colleagues *et al.* concluded that that the contribution of HRQOL measurement to clinical decision making depended on the clinical setting [Goodwin *et al.* 2003]. Additive value could be found in the primary treatment setting when various therapeutic options were equivalent, but did not provide treatment-altering value in the adjuvant treatment or palliative treatment settings. However, HRQOL information often guided treatment decisions in the symptom control/palliative care and psychosocial support settings. Another review concluded that although valuable insights into the care and treatment of women with breast cancer were found, many of the studies suffered from methodological limitations [Bottomley and Therasse, 2002].

Large studies of adjuvant treatment have elicited the varying toxicity profiles of different adjuvant therapies. One of the earlier studies reported that sexual functioning scores indicated more problems in patients receiving chemotherapy (either alone or with tamoxifen) than did patients receiving no adjuvant therapy ($p = 0.0078$) [Ganz *et al.* 1998]. Hot flashes, night sweats and vaginal discharge were reported more often when breast cancer survivors were taking tamoxifen ($p = 0.0001$). Vaginal dryness and pain with intercourse also differed significantly by adjuvant treatment, occurring more often in survivors treated with chemotherapy. While the physical functioning composite scores in those women who did not have adjuvant therapy were similar to the physical functioning scores of healthy controls, they were significantly lower in the women who were treated ($p = 0.012$). When tamoxifen was compared with anastrozole, either singly or

in combination, only small differences were reported between the treatment groups at 2 years of follow up [Fallowfield *et al.* 2004]. In a 5-year follow-up report it was concluded that anastrozole and tamoxifen had similar impacts on HRQOL, which was maintained or slightly improved during the treatment period for both groups [Cella *et al.* 2006a]. Differences were reported in the side effects experienced between the women who received tamoxifen (more dizziness and vaginal discharge) and those receiving anastrozole (more diarrhoea, vaginal dryness, diminished libido and dyspareunia). Another study reported little difference between taking tamoxifen or exemestane apart from vaginal discharge, which was more pronounced with tamoxifen ($p < 0.001$) [Fallowfield *et al.* 2006]. The above-mentioned differences may be important to some women who should, therefore, be informed about them when being counselled about therapy. Stage II/III breast cancer patients who received taxanes as part of their adjuvant chemotherapy had significantly worse emotional distress and probable clinical depression as well as worse mental HRQOL throughout adjuvant treatment as compared with patients receiving regimens without taxanes [Thornton *et al.* 2008]. They took more than twice as long to recover (2 years) than women who did not receive taxanes (6–12 months).

At the end of primary treatment for breast cancer, women who had a mastectomy or received chemotherapy reported decreased physical functioning as compared with women who had a lumpectomy or no chemotherapy [Ganz *et al.* 2004]. Symptoms, including muscle stiffness, breast sensitivity, aches and pains, tendency to take naps, and difficulty concentrating, were common among patients in all groups and were statistically significantly associated with poor physical functioning and emotional wellbeing. Sexual functioning was worse for women who received chemotherapy than for those who did not, regardless of type of surgery ($p < 0.001$). The finding of decreased physical functioning in women treated with chemotherapy had been reported previously [Mosconi *et al.* 2002]. A more recent study of 2208 women whose age ranged from 26 to 87 (mean 56.9) years showed that older and younger subgroups reported poorer HRQOL for different domains [Hopwood *et al.* 2007]. Younger women and those who had previous chemotherapy reported decreased HRQOL in most domains as well as

worse body image, sexual functioning and breast and arm symptoms ($p < 0.001$). Mastectomy was associated with greater body image concerns ($p < 0.001$) and wide local excision with more arm symptoms ($p = 0.01$). Endocrine therapy had no effect on HRQOL.

In an ECOG study of 464 women receiving chemotherapy, 164 participated in an HRQOL substudy [Richardson *et al.* 2007]. Declines in HRQOL during therapy predicted early treatment discontinuation even after accounting for age and chemotherapy-related side effects. The authors caution that in an age of increasing aggressiveness of chemotherapy, women should be aware of the adverse impacts on HRQOL. Indeed, when women underwent high-dose chemotherapy followed by autologous bone marrow transplantation they experienced difficulty sleeping, headaches and decreased sexual interest in the longer term despite having recovered or improved function in other domains [Conner-Spady *et al.* 2005].

Still, women treated for breast cancer adjust remarkably well. With a median of 20 years of follow up, only a minority appeared to be having ongoing problems, usually with sexual problems, lymphedema and numbness [Kornblith *et al.* 2003]. These patients also had a higher incidence of posttraumatic stress disorder as did those with a lower level of education ($p = 0.026$), less adequate social support ($p = 0.0033$), more severe negative life events ($p = 0.0098$) and greater dissatisfaction with their medical care ($p = 0.037$) than did other survivors. Another study concluded that at 9.4–16.5 years after their original diagnosis, differences in physical role functioning among breast cancer survivors who had received three different dose levels of chemotherapy were explained by clinical and demographic variables, such as age, fatigue, menopausal symptoms and various comorbidities [Paskett *et al.* 2009].

Patients experiencing recurrence of disease suffered greater decrements in HRQOL, particularly in symptoms and physical functioning, than did patients with metastatic disease or primary, nonmetastatic disease [Siddiqi *et al.* 2009].

With the exception of axillary dissection, the processes of care, such as choosing therapy, good patient–physician communication, receiving treatment concordant with preferences

about body image and low perceptions of bias, and not the therapy itself, seem to be the most important determinants of long-term quality of life in older women [Mandelblatt *et al.* 2003].

Lung cancer

A previous review concluded that HRQOL assessment is of added value in lung cancer trials since it does not correlate perfectly with biomedical outcomes, but suggested that it would be necessary to evaluate more fully whether it is worth the increased time and expense [Earle and Weeks, 2005]. There have been further extensive reviews since then [Tanvetyanon *et al.* 2007; Bottomley *et al.* 2003] and studies of neoadjuvant [Gralla *et al.* 2009] and adjuvant [Bezjak *et al.* 2008] chemotherapy in non-small-cell lung cancer (NSCLC). The negative effects on HRQOL are temporary and improvement with a return to baseline function is likely in most patients. A quality-adjusted time without symptoms or toxicity (Q-TWiST) analysis of adjuvant vinorelbine and cisplatin given after resection of stage IB-II NSCLC showed that the adjuvant chemotherapy group had a statistically significant better Q-TWiST in the range of 5 to 6 additional months as compared with an observation-only group of patients [Jang *et al.* 2009].

There is dispute about whether there are HRQOL benefits from combination chemotherapy over single-agent therapy in advanced NSCLC. For example, gemcitabine plus vinorelbine showed no benefit in response rate, time to progression, survival or quality of life as compared with each agent alone in elderly patients [Gridelli, 2002]. At other times, chemotherapy actually may be deleterious. For example, when marimastat was given after induction therapy for small-cell lung cancer, there was no improvement in survival and a negative impact on HRQOL [Shepherd *et al.* 2002].

Gefitinib may be of value particularly in patients with epidermal growth factor receptor mutations [Frampton and Easthope, 2004]. Improvements in HRQOL were reported in a subgroup of chemotherapy-naïve Asian patients who were treated with gefitinib as compared with carboplatin plus paclitaxel [Sanford and Scott, 2009].

Docetaxel has also been shown to be of value in older patients who are candidates for chemotherapy [Horn *et al.* 2007]. There appeared to be no

age-related HRQOL differences in patients younger than 70 years as compared with those who were 70 or older when treated with a combination of carboplatin and paclitaxel in two different dosage regimens [Hensing *et al.* 2003]. The survival rates were not different between the two age groups, and there was no difference in progression of HRQOL outcomes.

Prostate cancer

A review of several trials assessing the methodology for measuring HRQOL in prostate cancer showed that trials performed in recent years before the review were more robust than the earlier ones [Efficace *et al.* 2003].

HRQOL assessments of the side effects of radical surgery and radiation therapy for localized prostate cancer have shown that major functioning domains such as physical, emotional and social functioning seem not to be affected or to recover within a short time after treatment [Litwin and Talcott, 2005]. However, an earlier study showed that social functioning does suffer in patients randomized to receive radiation therapy *versus* deferred treatment, as a result of hematuria, incontinence, mucus and intestinal problems [Fransson *et al.* 2001]. The proportions of patients reporting late bowel symptoms were unchanged 15 years after external beam radiation therapy in comparison with the 4-year follow-up but were increased as compared with age-matched controls [Fransson and Widmark, 2007]. Incontinence increased between the 8-year and the 15-year follow up ($p=0.038$) [Fransson, 2008]. Side effects associated with treatment, such as urinary function and bother, and sexual function and bother, were independently associated with worse general HRQOL in all domains [Downs *et al.* 2003; Penson *et al.* 2003].

Hormone therapy combined with either prostatectomy or radiotherapy for localized and locally advanced prostate cancer was associated with significant clinical benefits [Kumar *et al.* 2006]. Although improved local control and survival could be achieved, probably with improved HRQOL, there were significant side effects, such as hot flushes and gynecomastia, as well as cost implications.

In patients with advanced prostate cancer and a history of bone metastases, skeletal-related events had important and significant effects on HRQOL

with clinically meaningful and statistically significant declines in physical wellbeing and emotional wellbeing after radiation and pathologic fractures and in functional wellbeing after radiation [Weinfurt *et al.* 2005].

In metastatic hormone-refractory prostate cancer (HRPC) mitoxantrone and prednisone produced significant improvement in pain [Tannock *et al.* 1996] and in several HRQOL domains [Osoba *et al.* 1999]. Docetaxel plus mitoxantrone provided longer survival and improvement in pain and HRQOL compared with mitoxantrone and prednisone [Tannock *et al.* 2004a]. Atrasentan, a novel, selective endothelin-A receptor antagonist, appeared to benefit patients with an increase in the quality-adjusted time to progression of disease [Cella *et al.* 2006b]. However, it did not confer a survival advantage over placebo and resulted in conflicting evidence as to time to progression of radiological disease despite apparent benefits in prostate-specific antigen levels and bone alkaline phosphatase doubling times [Nelson *et al.* 2008; Carducci *et al.* 2007].

Colorectal cancer

Two studies in which an enhanced postoperative recovery program was compared with conventional care in patients being operated on for CRC showed a 49% shorter hospital stay for those on the enhanced program with no difference in the number or type of complications, readmissions or reoperations as compared with historic controls who had open surgical resection [King *et al.* 2006b]. The enhanced recovery program consisted of preoperative counselling, epidural analgesia, early feeding and mobilization. In the second study, patients were randomized to laparoscopic resection or conventional open resection [King *et al.* 2006a]. Again, hospital stays were significantly shorter for the laparoscopic group and the relative risk of complications, and the quality of life results and cost data were similar in the two groups. Thus, the shortened hospital stay did not adversely affect HRQOL.

Asymptomatic patients with metastatic CRC who received immediate chemotherapy did not experience a survival benefit or improved HRQOL as compared with withholding treatment until symptoms occurred [Ackland *et al.* 2005].

In patients with advanced, chemotherapy-refractory CRC, cetuximab improved overall

and progression-free survival, particularly in patients with wild-type KRAS tumours [Jonker *et al.* 2007]. In patients who had tumours with wild-type KRAS status, cetuximab therapy resulted in less deterioration in physical functioning and improved global health status, whereas patients who received best supportive care alone deteriorated. No significant differences were noted between study arms for patients with mutated KRAS tumours [Au *et al.* 2009].

Other cancers

A comparison of platin-5-fluorouracil alone *versus* combination with cetuximab as first-line treatment in recurrent or metastatic squamous cell cancer of the head and neck region showed no significant differences in most HRQOL scores between the two treatment arms, but patients in the cetuximab arm displayed significant improvements in pain, swallowing problems, speech and social eating problems [Rivera *et al.* 2009].

A Q-TWiST comparison of CHOP (cyclophosphamide, doxorubicin, oncovin, prednisone), CAP (cyclophosphamide, doxorubicin, prednisone) and fludarabine in advanced chronic lymphocytic leukemia favoured fludarabine over CHOP and both of these over CAP [Levy *et al.* 2001].

A phase III randomized placebo-controlled trial examined the impact of everolimus in patients with clear cell renal cancers and progressive disease on, or within 6 months, of sunitinib and/or sorafenib [Coppin, 2010]. Progression-free survival increased from a median of 1.9–4.9 months (hazard ratio 0.33, $p < 0.001$) and 25% were still progression free after 10 months of everolimus therapy. There was a delay in time to decline of performance status and trends to improvement in quality of life, disease-related symptoms, and overall survival despite crossover of the majority of patients assigned to placebo.

In patients with glioblastoma multiforme randomized to radiation therapy with or without concomitant temozolamide, the combined therapy group experienced a clinically meaningful and statistically significant survival benefit [Stupp *et al.* 2005]. The addition of temozolamide did not adversely affect HRQOL [Taphoorn *et al.* 2005].

Palliative care, symptom control and supportive care

Patients with newly diagnosed metastatic NSCLC who were assigned to early palliative care had higher HRQOL scores at 12 weeks than did patients assigned to standard care ($p=0.03$) [Temel *et al.* 2010]. Fewer patients had depressive symptoms (16% *versus* 38%, $p=0.01$) and median survival was longer among patients receiving early palliative care (11.6 months *versus* 8.9 months, $p=0.02$).

Impaired cognition, fatigue, and diminished HRQOL are commonly associated with breast cancer chemotherapy [de Ruiter *et al.* 2010; Vardy and Tannock, 2007; Tannock *et al.* 2004b; van Dam *et al.* 1998]. In an attempt to prevent this side effect, patients were randomized to receive either epoetin alpha, 40,000 U subcutaneously once weekly, or placebo at the beginning of four cycles of chemotherapy administered over 12 weeks [O'Shaughnessy *et al.* 2005]. Mean hemoglobin levels were higher in the epoetin alfa group compared with the placebo group after four cycles of chemotherapy, and score changes from baseline to cycle 4 in the epoetin alpha group trended in favour of improved executive function. In another study, patients received epoetin-alpha or standard care [Fan *et al.* 2009]. Groups were well matched for age and type of chemotherapy and at 12–30 months after chemotherapy there were no significant differences in the Revised Hopkins Verbal Learning Test and in fatigue, but patients who had received epoetin alpha reported better HRQOL. The main differences between these two studies were the different times of evaluation and the different assessment tests. Larger studies will be required to settle this question.

Fatigue is a common symptom in cancer patients receiving radiation therapy, but a double-blind randomized crossover trial of multivitamins *versus* placebo in patients with breast cancer receiving radiation therapy did not improve radiation-related fatigue [de Souza Fêde *et al.* 2007].

A wide variety of other supportive care measures are used to assist patients with cancer. Such measures range from mindfulness-based stress-reduction programs [Foley *et al.* 2010; Ando *et al.* 2009; Lengacher *et al.* 2009; Witek-Janusek *et al.* 2008; Carlson *et al.* 2003], to yoga [Vadiraja *et al.* 2009], to diet and exercise

[Wolin *et al.* 2010; Morey *et al.* 2009], while other measures focus on the treatment of symptoms.

Another area of supportive care is doctor–patient communication during cancer treatment. Here, the results of HRQOL assessment have been found to be very useful [Velikova *et al.* 2010, 2004; Hilarius *et al.* 2008; Detmar *et al.* 2002; Detmar and Aaronson, 1998]. Patients who have answered HRQOL questionnaires report that there is better exchange of information between them and their physicians and nurses and that they are more satisfied with their overall interaction with the healthcare providers than are patients who have not answered questionnaires. In addition, they may have an improvement in their HRQOL scores [Velikova *et al.* 2004].

Prediction and prognosis

A somewhat unexpected benefit of PROM has been the apparent ability of pretreatment PRO scores to predict overall survival and, to some extent, the response of a patient's cancer to treatment [Montazeri, 2009; Gotay *et al.* 2008]. The most common PRO associated with survival is the global QOL scale of the EORTC QLQ-30, likely because this instrument was most often included in these studies [Gotay *et al.* 2008].

The predictive value of PROs is a complex area of study with many factors to consider [Osoba, 2007a]. One factor is the large number of associations between various HRQOL variables and outcomes that have been described. Several examples may be given. In 275 women with metastatic breast cancer, substantial loss of appetite was the only independent PRO predicting poor survival and was strongly correlated with fatigue, role and physical functioning [Efficace *et al.* 2004]. Baseline global QOL was a strong independent predictor of survival in patients with advanced CRC in one study [Maisey *et al.* 2002], while in another study, the patient's score on the social functioning scale translated into a 9% decrease in the patient's hazard of death for any 10-point increase in the score (0 to 100 scale) [Efficace *et al.* 2008, 2006a]. A correlation between various pretreatment PRO domain scores, including overall quality of life [Qi *et al.* 2009], global quality of life [Movsas *et al.* 2009; Langendijk *et al.* 2000], pain and dysphagia [Efficace *et al.* 2006b] and survival have been seen in advanced NSCLC. In addition, fatigue in high-grade glioma [Brown *et al.* 2006], overall

quality of life in advanced hepatocellular carcinoma [Bonnetain *et al.* 2008], social functioning in advanced gastric cancer [Park *et al.* 2008], global quality of life in advanced ovarian cancer [Carey *et al.* 2008], physical functioning in advanced bladder cancer [Roychowdhury *et al.* 2003] and total quality of life score in metastatic HRPC [Sullivan *et al.* 2006] and in localized prostate cancer [Sadetsky *et al.* 2009] have been associated with survival.

Some authors caution that the intercorrelations between PRO variables and correlations between PROs and clinical variables make it difficult to identify prime predictors [Grande *et al.* 2009]. Recent studies have relied on multivariate models to determine which domains or symptoms are predictive of survival because of the known strong correlations between these factors. In a meta-analysis of 30 randomized controlled trials from the EORTC started between 1986 and 2004 including survival data for 10,108 patients with 11 different cancer sites, HRQOL scales provided prognostic information in addition to that provided by sociodemographic and clinical measures [Quinten *et al.* 2009].

However, others have not found a correlation between PRO variables and survival. Whereas low baseline quality of life and depression did predict a poorer survival in low-grade glioma this was not the case in high-grade glioma [Mainio *et al.* 2006] or in glioblastoma [Mauer *et al.* 2007a] or anaplastic oligodendroglioma [Mauer *et al.* 2007b]. HRQOL variables were not helpful in predicting survival in one study of HRPC [Collette *et al.* 2004]. Whether this lack of a correlation is site-specific to brain cancers is unknown.

Changes in PROs during treatment may presage disease recurrence or failure to respond to treatment. For example, in patients receiving adjuvant chemotherapy for breast cancer, changes in physical wellbeing and nausea/vomiting significantly predicted recurrence [Kenne Sarenmalm *et al.* 2009], and in patients with head and neck cancer functional wellbeing predicted most significantly for locoregional control after radiation therapy but not for overall survival [Siddiqui *et al.* 2008].

Perhaps it should not be surprising that a large number of associations between HRQOL variables and survival have been described.

The diseases that are grouped under the term 'cancer' vary in their biology and a great variety of treatments and outcomes are possible. Another important consideration is the interval between PRO assessment and death [Osoba, 2007a]. PROs are more likely to be predictive if the interval is relatively short than if it is long. This may explain why PROs are more predictive in patients with advanced or metastatic disease than when the disease is still localized. In the latter situation, because of the long interval between measurement and death, other variables may intervene and confound the data.

A brief commentary on recent developments and directions

Integration of PRO with biomedical endpoints

Over the past few years several advances have been made in the study of PRO in cancer that are reasons for optimism even though much still remains to be done. Many clinical trials groups are now using PRO assessment and this is providing much needed data that help us to gain a better understanding of the value of PRO assessment as well as the effects of cancer and its treatment on patients' lives [Bruner *et al.* 2007; Osoba, 1999]. However, there needs to be a greater integration of PRO results with the standard biomedical endpoints (e.g. tumour regression, time to progression, survival) to provide more comprehensive analyses and results in a single publication. The separate reporting of PRO results from the main study results should be discouraged although it is understandable given the restrictions regarding manuscript length placed on authors.

Objective versus subjective measures

Oncologists chose outcomes such as survival time, time to disease progression and tumour response as providing objective data. However, most of these data are derived from physicians' subjective assessments of clinical and imaging or laboratory data – e.g. time to progression, tumour response, performance status (PS), and toxicity (using the Common Toxicity Criteria [CTC]). These opinions are thought to be objective because of the training that physicians receive to make these observations, but the demonstration of low interrater reliability in the measurement of simulated tumour masses dispelled the belief that physician's measurements of palpable tumour masses are reliable [Warr *et al.* 1984]. The use of computerized tomography and

magnetic resonance imaging has improved the ability of physicians to measure tumour size more accurately than was possible with conventional X-rays. Nevertheless, time to progression is difficult to judge accurately since it also depends on the frequency of measurement. Only survival time, as measured from the first treatment until death, is free of error.

The assessment of PS and symptoms can be problematic. A study of patients with advanced NSCLC demonstrated that self-reported PS of patients was incongruent with physician's assessments of Eastern Cooperative Oncology Group (ECOG) PS in 54% of patients [Dajczman *et al.* 2008]. Patients' self-ratings showed a worse PS than did their physicians ratings. If the patients' ratings had been used for determining eligibility in a hypothetical clinical trial almost half of patients would have excluded themselves. There are other studies showing that the correlations between physicians' and their patients' ratings of common toxicities and HRQOL are weak [Greimel *et al.* 2010]. In a total of 2110 patients with ovarian cancer (stage IIB–IV) toxicities were graded according to the CTC and HRQOL was assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). Correlations between CTC grading and the QLQ-C30 functioning scales were weak (<0.30); correlation coefficients between CTC ratings and the QLQ-C30 symptom scales including nausea, vomiting, constipation, pain and dyspnea ranged from 0.32 to 0.49 except for constipation (0.55). Exact agreement about symptom severity between clinician and patient reporting ranged from 54.2% (pain) to 80.8% (emesis/vomiting). Patients reported greater severity for pain, constipation and dyspnea whereas clinicians graded vomiting and nausea as being more severe than did the patients. The above findings are in keeping with previous reports [Savage *et al.* 2002; Brundage *et al.* 2000, 1993; Paul *et al.* 1991].

In addition, some other clinical endpoints and laboratory endpoints are not necessarily as 'hard' as once thought [Sprangers, 2010; Hahn *et al.* 2007]. When PROs are compared with other clinical measurements, including some laboratory data, the PROs compare favourably in their reliability and validity. Thus, the guidelines of the Food and Drug Administration (FDA) in the USA [Food and Drug Administration, 2009]

and European Medicines Agency (EMA) [European Medicines Agency, 2005] accept PROs as one of the methods by which new drug labelling approvals may be obtained. It is not intended that PROs be a substitute for other clinical and laboratory endpoints, but rather that they be considered in addition to the more traditional endpoints used in cancer clinical trials. PROs are meant to provide added value to biomedical outcomes.

Clinical significance

The current reporting of PROs in clinical trials often fails to assist the potential user in answering an extremely important question: what are the proportions of patients who benefit from treatment A as compared with treatment B, and is the difference in these proportions statistically and, most importantly, clinically significant? The FDA guidance [Food and Drug Administration, 2009] has moved away from recommending the use of the 'minimally important difference' [Guyatt *et al.* 2002], but this move still begs the question of how much change is clinically important. Other guidelines for analyzing and interpreting PRO data propose that a change of 10 points on a 0–100 scale is a sufficient change to have clinical meaning [Osoba *et al.* 2005, 1998]. This magnitude is about the same as the 0.5 standard deviation that has been suggested as being universally acceptable [Norman *et al.* 2003] although 0.3 may also be more accurate with some instruments [Farivar *et al.* 2004]. The magnitude of change considered to be clinically significant may need to be determined on a trial-by-trial basis since it may vary because of the patient population and the modality of treatment being studied. As more studies are completed, clinicians will gain greater insight into the magnitude of change that is clinically important. Eventually, a universal standard will emerge as being acceptable.

Response shift

Response shift is the name given to an adaptation response resulting from changes in an individual's internal standards, values and/or conceptualization [Sprangers, 2010; Schwartz *et al.* 2006; Sprangers and Schwartz, 1999a, 1999b; Sprangers *et al.* 1999]. The stimulus for this adaptation appears to arise from a change in the individual's health over time and leads to a change in how that individual views her/his HRQOL. The result is a change in the rating of HRQOL domains in which observers would not

have discerned reasons for change. There have been varying attempts to quantify the magnitude of this shift and its importance in interpreting the clinical significance of changes in HRQOL scores. While it is still uncertain how this information can be used in clinical trials or day-to-day practice it is, without doubt, a real phenomenon and deserves continuing study.

Routine assessment in clinical practice

Although PROM is becoming standard practice in clinical investigation and also has been shown to be of value in clinical practice [Velikova *et al.* 2010, 2004; Detmar *et al.* 2002], it still has not become a routine procedure. Partly this is because there is concern that the instruments that can be used in investigative studies are not as free from measurement error as would be desired for use in individuals [Osoba, 2002], and partly because of the perception that implementation of PROM would be too expensive and time consuming in clinical practice. However, physicians are cognizant of the value of applying PROM in their patients [Bezjak *et al.* 2001; Morris *et al.* 1998; Tanaka and Gotay, 1998] and it has been demonstrated that it is feasible to carry out HRQOL measurement as part of the standard care in a community hospital [Hilarius *et al.* 2008]. It should be possible to move forward with the information we have now to find ways to include HRQOL assessment in daily clinical practice [Osoba, 2007b].

Individualization of assessments

There is a move towards greater individualization of PROM with computer adaptive testing (CAT) based on item response theory (IRT), as exemplified by the Patient-Reported Outcomes Measurement Information System (PROMIS) initiative [Cella *et al.* 2010; Reeve *et al.* 2007]. The PROMIS offers the potential for efficiency (minimum item number without compromised reliability), flexibility (optional use of interchangeable items) and precision (minimal error in estimates) in the measurement of commonly studied PROs. Also, a better understanding of the topics that are relevant for oncology patients can contribute to identifying problems, serving as a reminder of topics to discuss and tracking changes over time [Snyder *et al.* 2010].

Recent attempts to understand the genetic basis of patients' responses [Rausch *et al.* 2010; Sprangers *et al.* 2010; Sloan and Zhao, 2006] will allow the tailoring of instruments to an

individual patient's needs based on genetic markers and would advance the reliability of measurement.

Missing data

Statistical approaches to dealing with missing data have been improved so that the results can be more representative of the data in groups of patients where attrition due to recurrence of disease and death are frequent events and inevitable. This topic is beyond the scope of this review (see Fayers and Machin [2000] and Fairclough [2002] for texts that deal with it in detail).

Guidelines for labelling claims

Regulatory agencies have developed guidelines for the reporting of PRO in support of labelling claims and have issued approvals based on PROs alone [Rock *et al.* 2007]. This has enabled pharmaceutical companies to plan studies with PRO components in their protocols.

Quality assurance

PROM is now being used to evaluate the quality of services offered by the National Health Service in England [Black and Jenkinson, 2009] because 'only patients can report on their symptoms and quality of life'. Since April, 2009, all patients in England having hip and knee replacement, hernia repair or varicose vein surgery will provide information on their health status before surgery and 3–6 months afterwards. This approach is intended to improve services to patients based not on previous biomedical benchmarks but on PROs and is, therefore, an entirely new approach to quality assurance. More health service providers should adopt this approach.

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