Patient-reported outcomes in daily clinical oncology practice: a tool for patient monitoring and quality of care assessment

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Introduction
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In developing new cancer treatment options, the major focus is on controlling tumor growth and reducing cancer-related morbidity and mortality. Since the 1960’s, survival rates for some forms of cancer, such as acute lymphoblastic leukemia, breast cancer, and prostate cancer, have improved substantially. As the clinical outcome for cancer patients has improved, attention has broadened to include an evaluation of the impact of treatment on the patients’ health-related quality of life (HRQL). Patients arguably are in the best position to report on the impact of cancer and its treatment in terms of physical and psychosocial functioning and symptom burden.

It has been argued that information derived from the patients’ perspective – patient-reported outcomes (PRO’s) – represent clinically meaningful endpoints that should be incorporated into clinical decision-making. Thus, while achieving cure or increasing survival rates still are the two primary goals of anti-neoplastic treatment, HRQL considerations, defined most typically in terms of the patient’s physical, psychological and social functioning and well being, have come to play an increasingly important role in selecting treatment options and in monitoring the effects of such treatments over time.

Where cure is the aim, HRQL information can aid in identifying those treatments that carry with them the fewest side-effects, both physical and psychosocial. In the palliative treatment setting, HRQL information can be useful in weighing the costs of (often aggressive) anti-tumor therapies against the potential benefits in terms of extended survival. Where the goal of treatment is palliation of symptoms, evidence of improvement in the patients’ HRQL is, by definition, of primary interest.

HRQL outcomes in clinical oncology research

One of the earliest clinical investigations to explicitly include HRQL considerations was a study of Karnofsky and colleagues that evaluated the efficacy of nitrogen mustard in the treatment of lung cancer. In this study, clinicians assessed the patients’ functioning, using a relatively crude, and at the time untested and not validated measure; a measure that subsequently became known as the Karnofsky performance status index.

Since that time, enormous efforts have been devoted to developing more psychometrically sophisticated approaches to investigating HRQL outcomes based on information obtained directly from patients via either written questionnaires or oral interviews. The availability of valid and reliable measures for assessing patients’ HRQL has led to a dramatic increase of such measures in clinical oncology research. HRQL data can be used in observational studies to better understand the burden of cancer and the adverse effects of
cancer therapy, and in clinical trials as either a primary or secondary outcome.

Most recently, the US Food and Drug Administration (FDA) has published a guidance document for the use of PRO’s in product labelling. According to the FDA guidance, findings measured by a well-defined, reliable and valid PRO instrument in appropriately designed investigations can be used to support a claim in medical product labelling. The amount and type of evidence that should be provided to the FDA for PRO’s is the same as for any other labelling claim based on other data. Use of a PRO instrument is advised when measuring a concept best known by the patient or best measured from the patient perspective.

PRO’s in daily clinical practice

In recent years there has been increasing interest in using PRO’s not only in clinical research, but also in daily clinical practice. PRO assessment may have several potential benefits in daily clinical practice. First, patient information collected using standardized questionnaires may facilitate detection of physical or psychological problems that might otherwise be overlooked. PRO instruments can also be applied as standardized measures to monitor disease progression and to provide information about the impact of prescribed treatment. Another benefit of using PRO measures in routine clinical care may be in facilitating patient-clinician communication and thus promoting the model of shared decision making. Patients and clinicians often need to establish common priorities and expectations regarding the outcomes of treatment and illness. PRO measurement in clinical care may also be used to monitor outcomes as a strategy for quality improvement or to reward presumed superior care.

Applications of PRO’s in daily clinical practice can be organized roughly by the level at which the data are aggregated, i.e. at the individual level versus the population level.

Individual PRO data used in daily clinical practice

Much of the literature on the use of individual PRO’s in clinical practice has focused on their use as a screening tool. This application has most frequently been used in screening for depression or anxiety. The assumption underlying this application is that it may provide information on health problems of which the physician or nurse is not aware. Information on patients’ HRQL may help the physician and other health care providers in providing the most appropriate treatment, counseling, and supportive care, and ultimately in achieving the best possible health status and HRQL.

In daily clinical practice, HRQL assessment typically involves asking patients to complete a questionnaire at the time of an outpatient visit,
either in paper-and-pencil format or via a (touchscreen) computer, and generating a summary of the results in the form of a graph or profile that is then made available to the health care provider immediately prior to the consultation. It has been hypothesized that the availability of such standardized HRQL data can have a cascade of effects: (1) enhanced provider-patient communication regarding HRQL-related issues; (2) improved provider awareness/detection of patients’ physical and psychosocial problems; (3) improved patient management; (4) enhanced patient and provider satisfaction with their interactions; and ultimately (5) improvement in patients HRQL (e.g., fewer symptoms, better functioning) over time.

The results of the feasibility studies in this area are consistent and encouraging. Administration of self-report HRQL questionnaires in outpatient clinic and family practice settings requires only a modest investment in material and personnel, and is acceptable to patients and staff alike. The practicality, reliability and validity of computer-assisted HRQL assessments have been demonstrated in a number of recent studies of patients with cancer and other chronic illnesses.

In addition to computer-assisted HRQL assessments, web/internet-based technologies have also been introduced as a means of collecting HRQL data. Use of internet-based technologies is particularly promising in monitoring patients’ symptoms following chemotherapy administration, because many of these symptoms occur while patients are at home. The Memorial Sloan-Kettering Cancer Centre in New York has developed and tested an online patient self-reporting system for chemotherapy toxicities, based on the National Cancer Institute’s Common Criteria for Adverse Events. Basch and colleagues have reported that more than 85% of patients were compliant with self-reporting of toxicities during scheduled clinic visits, and approximately 66% voluntarily logged on to the system while at home, demonstrating the feasibility of using the internet to self-report chemotherapy toxicities.

Another relevant methodological initiative is the Patient-Reported Outcomes Measurement Information System (PROMIS). PROMIS is a large scale program supported by the U.S. National Institutes of Health to develop patient-reported outcomes based on modern (i.e., item-response) test theory, with as end product a portfolio of computer-adaptive tests (CAT) to be used in clinical research and practice. A number of PROMIS instruments are currently available in short forms or as item banks for use in computer-adaptive testing.

Although the use of internet technologies seems feasible, it is not known whether internet reporting of QOL data directly to health care professionals will result in positive clinical outcomes in all situations, particularly
when patients become seriously ill. For instance, local computer and/or server malfunctions, breaches of confidentiality, inability on the part of the health care professionals to retrieve real-time reports in a timely manner, or an unwillingness on the part of patients to enter sensitive information into a web-based program may lead to breakdowns in patient-provider communication.

Mixed results have been reported in studies investigating the potential value of standardized HRQOL assessments in terms of communication, problem detection, patient management, and health outcomes. Of particular relevance to the current thesis are four studies conducted in oncology settings. In a non-randomized study, Taenzer and colleagues [2000] sequentially recruited 53 patients with lung cancer to either a control condition or to an experimental condition in which patients were asked to complete a cancer-specific HRQOL questionnaire, the EORTC QLQ-C30 on a single occasion, immediately prior to an outpatient appointment with their oncologist. Based on patients’ self-report, statistically significant between-group differences were noted in the frequency with which HRQOL-related problems reported by the patients were actually discussed during the visit, and in the number of HRQOL-related notations in the medical records. No significant group differences were found in patient satisfaction or in the number of HRQOL-related actions taken.

McLachlan and colleagues [2001] carried out a prospective, randomized study of 450 patients with heterogeneous cancer diagnosis being treated on an outpatient basis in a specialized cancer center in Australia. All patients completed an electronic (computer touchscreen) version of the Cancer Needs Questionnaire-Short Form (CNQ), the EORTC QLQ-C30 and the Beck Depression Inventory immediately prior to an outpatient visit. For patients randomly allocated to the experimental group, a one page summary of the patients’ responses to these questionnaires was made available to the treating physician and coordinating nurse. Subsequently, an individualized management plan was formulated based on issues raised in the summary report and on pre-specified psychosocial guidelines. All patients completed the same battery of computer-based questionnaires 2 and 6 months after randomization for purposes of assessing changes in their cancer needs, HRQOL and depression levels over time. These latter questionnaires were used for evaluation purposes only; i.e., the results were not shared with the health care team. For the total patient sample, no statistically significant between-group differences over time were found in self-reported psychological needs, informational needs, HRQOL or depression. However, for the subgroup of patients who reported moderate to severe levels of depression at baseline, there was a significant
reduction in depression at the 6 month follow-up for the intervention group relative to the control group 39.

Detmar et al. [2001] employed a prospective, randomized (cross-over) design to investigate the value of standardized HRQOL assessments as a routine part of the outpatient palliative chemotherapy clinic of a specialized cancer hospital in the Netherlands in terms of two primary outcomes: (1) facilitating doctor-patient communication; and (2) increasing physicians’ awareness of their patients’ physical and psychosocial health problems. Secondary outcomes included patient management activities, patients’ and physicians’ satisfaction with their medical interactions, and changes in patients’ self-reported HRQOL over time. The study sample included 214 patients and 10 medical oncologists. All patients were followed for 4 consecutive outpatient visits. The first visit served as a baseline. Patients randomly assigned to the intervention group completed a paper-and-pencil version of the EORTC QLQ-C30 immediately prior to 3 consecutive outpatient visits. The results were computer-scored and summarized in a graphic profile, a copy of which was provided to the treating oncologist at the time of the visit. Structured content analysis of audiotapes of the consultations were used to evaluate doctor-patient communication. Physicians’ awareness of their patients’ HRQOL-related problems was assessed by comparing patients’ and physicians’ ratings on the COOP/WONCA charts. The results indicated that the patients’ physical and psychosocial functioning and symptoms were discussed significantly more frequently in the intervention group than in the control group. Physicians in the intervention condition identified a significantly greater percentage of patients with moderate to severe HRQOL problems in a number of HRQOL domains as compared to those in the control condition. A significant, albeit modest salutary effect favoring the intervention group was noted for some patient management activities (i.e., counseling and advise-giving), patients’ satisfaction with the emotional support received from their physician, and improvement over time in self-reported mental health and role functioning 21.

Finally, Velikova et al. [2004] conducted a randomized controlled trial of patients (n=286) attending the medical oncology outpatient clinic of a university hospital in the United Kingdom. Patients were randomly assigned to one of three groups: (1) an intervention group that completed HRQOL via a touchscreen computer, the results of which were fed back to the physicians; (2) an attention control group that completed the same HRQOL questionnaires, without the results being fed back to the physicians; and (3) an usual care control group (no HRQOL assessments). The HRQOL questionnaires including the EORTC QLQ-C30 and the Hospital Anxiety and Depression Scale (HADS), were completed before each outpatient visit for a
period of approximately 6 months. Patient outcomes were measured after the study baseline encounter, after three on-study encounters, after 4 months, and at study end (approximately 6 months). Process-of-care outcomes were evaluated from audio-taped encounters. Physicians’ perceptions of clinical usefulness of the data for individual encounters were assessed. Positive HRQL effects were observed for patients in both the intervention group and in the attention-control group, as compared to the control group. A positive effect on emotional well-being was associated with feedback of the HRQL data (intervention group), but not with HRQL questionnaire completion only (attention control group). A larger proportion of intervention patients showed clinically meaningful improvement in HRQL. More frequent discussion of chronic, non-specific symptoms was found in the intervention group, without prolonging the length of the clinical encounters. There was no detectable effect on patient management. In the intervention patients, HRQL improvement was associated with explicit use of HRQL data, and particularly discussion of pain, and role function.

In summary, the results across these four studies provide consistent support for the effect of standardized HRQL assessments in terms of enhancing provider-patient communication about HRQL-related issues. In the one study in which it was measured [Detmar et al. 2001], a positive effect was also found on physicians’ awareness/detection of their patients’ functional problems and symptoms. In two of the three studies in which it was assessed, some support was found for improved patient management. No or only modest benefit was observed across studies in patient satisfaction, probably due to a ceiling effect (i.e., high background levels of satisfaction), and in patients’ self-reported HRQL over time.

It is important to note some of the limitations of these studies. First, one of the four studies [Taenzer] reviewed had a very small sample size and/or did not include an appropriate control group. Results from such a study can, at best, be suggestive and requires replication in a more rigorous research setting.

Second, in two of the four studies reviewed [Taenzer, McLachlan], the standardized HRQL assessments were made at a single point in time. This may not have provided sufficient opportunity for the health care providers to incorporate such information into their daily practice. Additionally, one of the most potentially attractive features of routine, periodic HRQL assessments is that they yield a temporal record, allowing for tracking of individual patients’ HRQL profiles over time.

Third, three of the four studies employed a questionnaire (the QLQ-C30) designed to assess
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the HRQOL of cancer patients, in general. There is increasing evidence that more detailed, condition-specific questionnaires (e.g., for patients with lung cancer, breast cancer, colorectal cancer, etc.) are particularly useful in documenting functional limitations and symptoms associated with a specific diagnosis and/or treatment. The availability of computer-based questionnaires can facilitate tailoring HRQOL data collection to the specific situation of individual patients.

Fourth, with the exception of the study by McLahlan et al., the intervention was directed at the treating oncologist only, rather than at the health care team as a whole. Given their increasingly important role in the treatment and care of patients with cancer, nurse specialists may also profit significantly from having standardized HRQOL information made routinely available to them.

Fifth, only in the study of Detmar et al. were the patients themselves provided with summaries of their responses to the HRQOL that they had completed. Such a procedure might be useful in familiarizing patients with the types of reports their health care providers are receiving, and may encourage patients to assume a more active role in their contacts with their providers.

Finally, all four studies were conducted in specialized cancer treatment centers or university hospitals. Given the large numbers of cancer patients treated in community hospitals, it is important to determine if these types of HRQOL assessments can be successfully incorporated in the daily clinical routine in such community settings with equal (or greater) effectiveness.

Outline of this thesis: Part one

The first part of this thesis (Chapters 2 and 3) addresses many of the issues outlined above, and thus provides additional empirical evidence regarding the value (and limitations) of standardized HRQOL information in daily clinical oncology practice.

We first conducted a methodologically oriented pilot study to determine the validity of patient self-report data about HRQOL topics actually discussed during medical outpatient visits. This is important because, in the larger, randomized clinical study that we were planning, it was not possible to actually observe (or record) conversations between nurses and their patients due to logistical limitations, and thus it was necessary to rely on the patients’ self report. To investigate the validity of patient self-report data on HRQOL-related communication, comparisons were made with data obtained via observer-raters. Given that patient characteristics may influence self-reports, we also examined whether the level of agreement between the self-reported and observed communication was associated with various sociodemographic and clinical characteristics, including age, education, sex, and treatment intent.
The results of this pilot study are reported in **Chapter 2** of this thesis.

In **Chapter 3**, we report the results of a sequential cohort study that evaluated the efficacy of incorporating standardized **HRQoL** assessments as a routine part of the outpatient treatment of cancer patients being treated with chemotherapy in a community hospital setting in terms of two primary outcomes: (1) facilitating nurse-patient communication; (2) increasing nurses' awareness of patients' **HRQoL**.

Additional outcomes included patients' and nurses' satisfaction with their interactions, patient management activities, and patients' **HRQoL** over time.

Specifically, it was hypothesized that eliciting standardized **HRQoL** information from patients and making this information available to nurses on a routine basis would increase significantly: (1) the likelihood that the physical, functional and psychosocial problems experienced by patients will be discussed during outpatient visits; and (2) nurses' awareness of the range of physical, functional and psychosocial problems confronting their patients.

In addition to these primary hypotheses, it was hypothesized that the intervention would increase significantly: (3) patients' satisfaction with the nurse-patient contact, in general, and the communicative aspects of that contact, in particular; and (4) nurses' satisfaction with outpatient consultations, particularly in terms of the extent to which the patients' problems could be identified and addressed. Of a more exploratory nature are the questions of whether the incorporation of **HRQoL** assessment as a routine part of outpatient oncology nursing care has a positive influence on: (5) nurse and medical chart notations relating to the patients' health problems and subsequent actions taken by the nurse and/or the physician around the time of the consultation; and (6) changes in patients' self-reported **HRQoL** over time.

**Aggregate level PRO data in clinical practice**

The availability of aggregate level **PRO** data in clinical practice can contribute to monitoring the effects of both standard and newly approved treatments when used routinely. It is well known that patients included in phase I-III clinical trials do not necessarily represent the larger population of patients encountered in daily clinical practice. For example, in many clinical trials, patients who are younger than 18 years of age, women of child-bearing potential, pregnant women, patients with hepatic or renal failure, the very old, those with comorbid health conditions, and those with previous treatment are typically excluded from participation. Thus, at the time of drug approval, there is usually little or no empirical evidence regarding drug safety and efficacy in the larger target population of interest 42.

The duration of treatment in clinical trials rarely exceeds 1 year, even if the disease under
study requires chronic therapy. At the time when a pharmaceutical manufacturer files for regulatory approval, about a few thousand patients may have been treated with the new drug. In studies in cancer patients these numbers are often even less. For this reason, many questions remain unanswered regarding the performance of a drug in routine practice. Post-authorization research and surveillance, also known as outcomes research or comparative effectiveness research, has become more and more important. Outcomes research seeks to understand the end results of particular health care practices and interventions. End results include effects that people experience and care about, such as change in the ability to function\(^{43}\). In particular, for individuals with chronic conditions – where cure is not always possible – end results often include HrQoL considerations. By linking the care people receive to the outcomes they experience, outcomes research has become the key to developing better ways of monitoring and improving the quality of care.

Outline of this thesis: Part two

In the second part of this thesis we focus on the use of pro’s in monitoring the quality of care in relation to two important side effects of chemotherapy treatment, i.e. fatigue and chemotherapy-induced nausea and vomiting.

Fatigue is a very common symptom among patients with cancer. When persistent, fatigue can seriously inhibit patients’ ability to participate fully in the roles and activities that make life meaningful. In Chapter 4 we investigated the association between clinical signs and symptoms of fatigue, and its treatment in daily clinical practice. This observational study was undertaken to: (1) document treatment for cancer-related fatigue (CRF) and cancer-related anaemia (CRA) in daily clinical practice; (2) determine the extent to which clinical practice reflects current evidence-based practice guidelines for CRF & CRA; and (3) identify factors influencing the choice of treatment and counseling.

Chapter 5 focuses on chemotherapy-induced nausea and vomiting (CINV). CINV are the most frequently reported adverse effects of anti-neoplastic chemotherapy and significantly affect patients’ daily functioning and HrQoL. This study was designed to: (1) determine the incidence of CINV during consecutive treatment cycles in daily clinical practice in general hospitals; (2) investigate the association between patient characteristics and types of antiemetics used and CINV; and (3) examine the influence of CINV on changes in antiemetic therapy, and specifically on adding antiemetics over multiple cycles of chemotherapy.

Finally, in Chapter 6 we summarize the results of these investigations, discuss their implications for clinical practice, and suggest directions for future research.


