Measuring health-related quality of life in clinical trials that evaluate the role of chemotherapy in cancer treatment

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Abstract

Quality of life is a subjective multidimensional concept that can be assessed by means of validated questionnaires completed by patients. The psychological effects of a diagnosis of cancer and the physical effects of the disease and its treatment have a major impact on a patient's health-related quality of life. Much cancer treatment, especially chemotherapy for metastatic disease, is given for palliation. Palliation implies improvement in either the duration or quality of life remaining. However, treating patients with common metastatic tumours to prolong life is generally unsuccessful, so improving quality of life is a more realistic goal. Most trials involve evaluating shrinkage of a tumour (i.e., tumour response), which does not imply a benefit to the patient. Few trials have assessed quality of life directly, although several validated instruments, described here, are available to quantify quality of life in cancer patients. These instruments represent a wide scope, from evaluating general health to assessing the quality of life of patients with specific types and stages of cancer. They respond to changes in clinical state and are strongly predictive of survival. Measures of quality of life should be incorporated in all clinical trials where treatment is palliative, and a simple, relevant measure of quality of life should be used as a (or the) primary outcome measure. Other measures of quality of life are important to ensure that gains in one area do not occur at the expense of others. A few large trials incorporating these principles have shown that chemotherapy can provide palliation for patients with advanced cancer.

Résumé

La qualité de vie est un concept multidimensionnel subjectif qu'il est possible d'évaluer au moyen de questionnaires validés remplis par des patients. Les effets psychologiques d’un diagnostic de cancer et les effets physiques de la maladie et de son traitement ont une incidence importante sur la qualité de vie d’un patient en ce qui a trait à la santé. De nombreux traitements contre le cancer, et particulièrement la chimiothérapie administrée contre les métastases, servent à des fins palliatives. On entend par palliation un prolongement de la période de vie qui reste ou une amélioration de sa qualité. Les traitements administrés à des patients qui ont des métastases ordinaires afin de prolonger leur vie échouent toutefois en général et c’est pourquoi l’amélioration de la qualité de vie constitue un objectif plus réaliste. La plupart des études portent sur l'évaluation de la régression d’une tumeur (c'est-à-dire sur la réaction tumorale), ce qui ne sous-entend pas nécessairement un avantage pour le patient. Rares sont les études où l’on évalue la qualité de vie directement même si plusieurs instruments validés, décrits ici, sont disponibles pour quantifier la qualité de vie chez les patients atteints du cancer. Ces instruments ont un grand champ d’application allant de l’évaluation de l’état de santé en général à celle de la qualité de vie des patients qui ont des types particuliers de cancer ou dont la maladie a atteint certains stades. Ils réagissent aux changements d’état clinique et constituent de solides prédicteurs de la survie. Il faudrait intégrer des mesures de la qualité de vie à toutes les études dans le cadre desquelles le traite-
The psychological effects of a diagnosis of cancer and the physical effects of the disease and its treatment have a major impact on a patient's health-related quality of life. Treatment may provide a cure, prolong life or control symptoms, but it also usually has toxic effects. In only limited situations is chemotherapy given to cure disease. Most patients with potentially curable diseases (e.g., tumours in children, lymphoma in adults, testicular cancer and early-stage breast cancer) will accept a temporary and even severe decrease in quality of life for a potential increase in survival.1

More commonly, chemotherapy is given for palliation of patients with metastatic cancer. The most widely used measure of treatment effect in oncology has been the shrinkage of the tumour, which is not necessarily an indicator of palliation. Rather, palliation is achieved by an increase in either the duration or quality of life remaining. Because chemotherapy has only a minimal impact on duration of survival in this group of patients,2 the main effect is likely to be on quality of life. Chemotherapy may improve quality of life by reducing symptoms, or it may reduce quality of life because of therapy-related toxic effects. Next to prolonging life, the most important objective of treatment is improving quality of life.3,4 A major goal of studies of palliation should therefore be the evaluation of quality of life.

Canadian clinicians have made substantial contributions to the development, validation and use of several instruments that document and quantify the quality of life of patients with cancer.5–11 Measures of quality of life have been used as primary goals in a small number of clinical trials.8 There is also evidence that quality of life has a role in determining prognosis; in fact, quality of life is often a better indicator of prognosis than factors relating to the disease or its treatment. In this article the determinants of health-related quality of life and the structure of the most common instruments used to assess it will be described. Examples will be given to show how quality-of-life measures can be used to evaluate therapeutic benefit in clinical trials.

Defining health-related quality of life

A widely accepted definition of quality of life is a person's own sense of well-being, as derived from his or her current experience of life as a whole.12 The impact of a disease and its treatment can be explored by assessing the person's health-related quality of life.5 Quality of life is subjective and can only be measured by the patient. Assessment by health care professionals is not only inappropriate but also inaccurate, and studies of concurrent assessments of quality of life by physicians and patients with cancer have demonstrated considerable disparity.14,15 Subjective evaluation does not imply soft or nonreproducible data. In fact, quality-of-life data are at least as reproducible as tumour-response data and sometimes more so.16

The determinants of quality of life can be divided into 3 categories: those related to general health (physical, social and psychological), those related to the disease and those related to treatment. Some components of

<table>
<thead>
<tr>
<th>Table 1: Some components of health-related quality of life</th>
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<tbody>
<tr>
<td><strong>Related to general health</strong></td>
</tr>
<tr>
<td>Physical functioning</td>
</tr>
<tr>
<td>Mobility within and outside the home</td>
</tr>
<tr>
<td>Activities of daily living</td>
</tr>
<tr>
<td>Recreational activities</td>
</tr>
<tr>
<td>Time spent in bed or chair</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Ability to work</td>
</tr>
<tr>
<td>Social supports</td>
</tr>
<tr>
<td>Relationship with family and friends</td>
</tr>
<tr>
<td>Emotional support</td>
</tr>
<tr>
<td>Impact on family, social life</td>
</tr>
<tr>
<td>Intimate relationships</td>
</tr>
<tr>
<td>Psychological aspects</td>
</tr>
<tr>
<td>Level of anxiety, fear, depression</td>
</tr>
<tr>
<td>Level of coping</td>
</tr>
<tr>
<td>Ability to concentrate</td>
</tr>
<tr>
<td><strong>Related to disease</strong></td>
</tr>
<tr>
<td>General symptoms</td>
</tr>
<tr>
<td>(e.g., pain, nausea, vomiting)</td>
</tr>
<tr>
<td>Disease-specific symptoms</td>
</tr>
<tr>
<td>(e.g., lymphedema in breast cancer or dysphagia in head and neck cancer)</td>
</tr>
<tr>
<td><strong>Related to treatment</strong></td>
</tr>
<tr>
<td>Side effects of systemic chemotherapy</td>
</tr>
<tr>
<td>(e.g., nausea, mucositis, hair loss)</td>
</tr>
<tr>
<td>Side effects of medications to control symptoms</td>
</tr>
<tr>
<td>(e.g., drowsiness, constipation, confusion with opiates)</td>
</tr>
</tbody>
</table>

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these categories are described in Table 1, although there is considerable overlap.

**Instruments for measuring health-related quality of life**

Instruments for measuring quality of life consist of a series of questions or items grouped within domains of related attributes. An optimal instrument should have domains pertaining to physical, social and emotional well-being. Attention has recently been placed on the existential domain, which assesses patients’ concerns about death, isolation and the meaning of life. Although these concerns are important determinants of quality of life, they have been neglected in most instruments.

The ideal quality-of-life instrument should satisfy the following criteria. Its scope should be appropriate to its intended use. To assess quality of life, aspects of quality of life that are important to the patients being studied should be included and those that are irrelevant should be omitted. To encourage a high level of compliance an instrument must be simple enough to be understood and completed by all patients. The instrument must also be validated.

**Scope**

The scope of various instruments differs, thus influencing their applicability to patients with different types and stages of cancer. The first attempts to measure quality of life were made with unidimensional scales completed by physicians, such as the Karnofsky Performance Scale, now largely replaced by the simpler Eastern Cooperative Oncology Group (ECOG) Performance Scale. However, performance status, or level of function, measured by a physician with one of these scales, while providing information relevant to prognosis, does not provide many useful details about the patient’s quality of life.

Patient-based multidimensional instruments that evaluate general health can be used to assess patients with a range of types and severity of disease. The Sickness Impact Profile and the Medical Outcome Study Short-Form are examples of this type of instrument. Others are specifically designed for patients with cancer, such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core Module (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy — General (FACT-G) instrument. Some instruments are intended to assess specific types of cancer or specific types of treatment during specific stages of disease, for example, the Prostate-Specific Quality of Life Instrument for patients with advanced prostate cancer, and scales for adjuvant chemotherapy in early-stage breast cancer, advanced breast cancer, lung cancer and head and neck cancer.

**Nature of data recorded**

Quality of life is usually quantified using 1 of 2 methods. With a categorical or Likert scale, as shown here,

```
| Very poor | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Excellent |
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the patient uses a series of discrete categories to rate the intensity or frequency of an item. The visual or linear analogue self-assessment scale, as shown here,

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None ______________________________________ Extreme
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consists of a continuous horizontal line, usually 10 cm, anchored at either end by descriptive extremes of the item being measured. The patient indicates the degree of each item by placing a vertical mark across the line. The 2 methods have been shown to be equally valid, reliable and responsive to changes in clinical conditions. For both types of scale, patients are asked to give an assessment of each item for a specified time-frame, typically the preceding 24 hours or the preceding 7 days.

**Administration of instrument**

Ideally, quality-of-life instruments should be completed by patients after they have been given adequate unbiased instruction, although they are sometimes completed by trained interviewers after a face-to-face or telephone interview or by surrogate responders (e.g., relatives or caregivers). However, information provided by caregivers may not reflect the information that would be provided by patients.

**Compliance**

Low compliance rates produce doubts as to whether the results for patients who do complete an instrument are representative. To encourage compliance, forms should be as simple as possible. Compliance also depends on the commitment of the investigators: in Canada and many parts of Europe compliance rates of up to 90% have been achieved, but in the United States the rates are generally much lower.

**Validation**

An instrument is valid if it measures what it is intended to measure. Because no gold standard exists, indirect methods of validation have been established. The following criteria are important components of the validation process are described below.
Face or construct validity. Does the instrument measure what is important to patients? Typically a prototype is generated by health care professionals and then undergoes modifications after evaluation by patients.\(^4\),\(^31\)

Test–retest reliability. Does the instrument give similar results when it is administered a second time after an interval of time short enough that changes in the patient’s clinical condition are unlikely but long enough that the patient cannot complete it from memory?\(^2\)

Convergent validity. Is there a correlation among data for items that measure related attributes?\(^4\)

Divergent validity. Do items designed to measure different aspects of quality of life distinguish between them?\(^2\)

Predictive validity. Does the instrument give similar results when it is administered a second time after an interval of time short enough that changes in the patient’s clinical condition are unlikely but long enough that the patient cannot complete it from memory?\(^2\)

Responsiveness. Does the scale of the instrument respond to changes in a patient’s condition?\(^4\) Quality-of-life scales must be responsive if they are to be used in clinical trials to evaluate the benefits of therapy. It is important to determine the smallest clinically meaningful differences in measures of health-related quality of life. The clinical significance of changes in quality-of-life scores has been evaluated among patients with chronic lung disease and congestive cardiac failure. In one study\(^38\) a 7-point Likert scale was used to assess dyspnea, fatigue and emotional functioning. A 7% difference in the score for any item reflected a small clinical effect, a 14% difference reflected a moderate clinical effect and a difference of more than 14% reflected a large clinical effect. This approach to quantifying the degree of effect has been used to evaluate changes in quality of life in trials assessing drug efficacy for patients with various chronic diseases\(^39\) and chronic airflow limitation.\(^40\) In both studies small, moderate and large changes in the scores had corresponding effects on overall quality of life.

A recent study\(^41\) of EORTC QLQ-C30 results assessed the significance of changes in quality-of-life scores to patients with cancer. The EORTC QLQ-C30 instrument and a Subjective Significance Questionnaire (SSQ), which measures perceived changes in physical, emotional and social functioning and global quality of life, were completed by patients at the same time. The degree of change in the scores of the EORTC QLQ-C30 dimensions corresponded with the degree of changes in quality of life reported on the SSQ.

Instruments in common use in cancer clinical trials

In the field of oncology there is no instrument that meets all the ideal criteria.\(^17\) Each instrument in common use has its strengths and weaknesses. The characteristics of these instruments are summarized in Table 2.

Karnofsky and Eastern Cooperative Oncology Group performance scales

The Karnofsky Performance Scale\(^19\) was developed in the 1940s and is completed by a physician or nurse. It assesses 3 dimensions of health status (activity, work and self-care), but there is no instruction on how to obtain the data needed to categorize the patient.\(^42\) The scale has not been validated\(^17\) and under repeat testing its reliability has been relatively poor.\(^43\)

The ECOG Performance Scale\(^20\) is a briefer version of the Karnofsky scale. It has a structure similar to that of the Karnofsky scale, consisting of levels of physical functioning with 5 response categories, but it also has the same deficiencies.\(^2\) These scales are useful for providing prognostic information about a patient’s response to treatment and survival but, because they are based on physician-reported ratings, offer little insight into the factors that determine a patient’s quality of life.

Table 2: Characteristics of the instruments commonly used to measure health-related quality of life\(^*\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Karnofsky or ECOG</th>
<th>FLIC</th>
<th>EORTC QLQ-C30</th>
<th>FACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target population</td>
<td>Cancer patients</td>
<td>Cancer patients</td>
<td>Cancer patients</td>
<td>Cancer patients</td>
</tr>
<tr>
<td>Assessor</td>
<td>Physician</td>
<td>Patient</td>
<td>Patient</td>
<td>Patient</td>
</tr>
<tr>
<td>No. of items</td>
<td>1</td>
<td>22</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>Dimensions (% of total)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>100</td>
<td>37</td>
<td>64</td>
<td>43</td>
</tr>
<tr>
<td>Psychological or emotional</td>
<td>0</td>
<td>36</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Social</td>
<td>0</td>
<td>14</td>
<td>10</td>
<td>32</td>
</tr>
<tr>
<td>Global health perception</td>
<td>0</td>
<td>13</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>No. of possible responses to each item</td>
<td>10 (Karnofsky)</td>
<td>7</td>
<td>Variable</td>
<td>5</td>
</tr>
</tbody>
</table>

*Karnofsky = Karnofsky Performance Scale,\(^19\) ECOG = Eastern Cooperative Oncology Group Performance Scale,\(^20\) FLIC = Functional Living Index — Cancer\(^6\), EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core Module,\(^23\) FACT = Functional Assessment of Cancer Therapy.\(^24\)
Functional Living Index — Cancer Scale

The Functional Living Index — Cancer Scale (FLIC) is a cancer-specific instrument developed by Schipper and colleagues. It is a 22-item instrument covering physical, social and psychological functioning, general health perceptions, and nausea, pain and hardship. The items are measured using a linear analogue self-assessment scale with a variable time frame (from 1 day to 1 month). Scores are provided for each dimension and are summed to yield a total. This instrument has met the criteria for validity and is responsive to changes in a patient’s clinical condition. In several clinical trials the FLIC has been used as an ancillary outcome measure.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire

The EORTC core questionnaire was developed to provide an integrated instrument to assess the quality of life of patients participating in international clinical trials. It has been field-tested internationally and progressively modified into its current form. It consists of 30 items, 24 of which are grouped into 9 dimensions: 5 functional dimensions (physical, role, cognitive, social, emotional), 3 symptom dimensions (nausea, pain, fatigue) and a global quality-of-life dimension. The 6 other items evaluate dyspnea, difficulty sleeping, anorexia, constipation, diarrhea and perceived financial difficulties. Categorical scales (referring to the previous week) are used for 23 of the items and dichotomous (yes or no) questions are used for the other 7 items. A score is calculated for each of the 9 dimensions by summing the responses to items for that dimension. The EORTC QLQ-C30 instrument is cancer-specific, discriminatory and responsive. It was validated initially for patients with cancer of the lung, breast and ovary. Disease-specific modules have been developed to supplement the core module for head and neck, breast and prostate cancer. The core questionnaire has been translated into several European languages.

Functional Assessment of Cancer Therapy Scale

The Functional Assessment of Cancer Therapy (FACT) Scale, developed by Cella and colleagues, is a 28-item questionnaire with 5 dimensions: physical, functional, social and emotional well-being and satisfaction with treatment. Each item consists of a 5-point categorical scale that applies to the previous 7 days. It provides a total score for overall quality of life and subscale scores for each dimension. It was evaluated initially by 135 patients with various types of cancer and found to be valid and to have uniformly high responsiveness. It can discriminate among patients on the basis of disease stage and performance status. A module specific to breast cancer has also been developed.

Use of quality-of-life instruments in trials that evaluate cancer chemotherapy

Quality of life is not relevant to all clinical trials. It is generally not relevant in most early trials of drug development, where the aim is to determine the maximum tolerated dose or to assess biological activity. Similarly, quality-of-life assessment is not relevant in trials evaluating new therapies that are reasonably expected to increase chance or duration of survival or where the new therapies would not be instituted unless they increase a patient’s duration of survival (e.g., stem cell transplantation for metastatic breast cancer). In these cases, patients are likely to accept a temporary reduction in quality of life to increase the chance of prolonged life. However, in most trials that evaluate the palliative effect of chemotherapy (e.g., that given to adults with metastatic cancer) the most important measure should be quality of life.

Quality-of-life assessment should be incorporated in the following settings: (1) randomized trials where the new treatment is not likely to influence long-term survival but might improve palliation through improved quality of life (e.g., most phase III trials for metastatic cancer); (2) trials where the specific goal is to improve quality of life, including many trials of symptomatic therapy and (3) phase II trials that assess the activity of new agents in poorly responsive malignant lesions, such as renal cell carcinoma, melanoma and refractory colorectal cancer (information about quality of life can complement data such as tumour response and may influence the selection of agents for testing in phase III trials).

In clinical trials where quality of life is relevant, its assessment must be either a primary or secondary goal and should reflect which aspects have the most palliative benefit to the patient. An objective in a trial might be to measure a patient’s global quality of life (possibly with the global scale of the EORTC QLQ-C30) or to measure the dominant symptom, such as pain in patients with prostate cancer. A hypothesis must be formulated to address the magnitude of difference in these measures that will be considered clinically important, and the sample size should be appropriate to detect this change (or not) with confidence. The number of measures should be limited to avoid multiple statistical comparisons. Other scales of the same instrument (or other instruments) may be used to support the main instrument, for example to ensure that relief of pain has not been achieved at the expense of toxic effects that detract from global quality of life.
Quality of life as a primary measure in clinical trials

Two recent randomized controlled trials have demonstrated the potential utility of quality-of-life assessment by using quality of life as a main measure. Their results were accepted as the primary evidence for licensing the relevant drugs by the US Food and Drug Administration, stimulating interest in the use of quality-of-life measures in clinical trials.

In a Canadian multi-institution phase III randomized trial, 161 patients with hormone-refractory prostate cancer were randomly selected to receive either chemotherapy with mitoxantrone and prednisone or prednisone alone (control). Mitoxantrone was chosen as a gentle anticancer drug that was expected to be well tolerated by elderly patients. The primary outcome measure was a decrease in pain: success was defined as a 2-point decrease in pain (assessed on a 6-point pain scale) with no increase in analgesic medication. The secondary outcome measure was a 50% reduction in analgesic medication without an increase in pain. Each decrease had to be maintained on 2 consecutive visits at least 3 weeks apart. Supportive information about other aspects of quality of life was collected from the Prostate-Specific Quality of Life Instrument (a series of 9 linear analogue self-assessment scales together with the pain intensity and analgesic consumption scale) and from the EORTC QLQ-C30 and a disease-specific module.

A successful response as measured by the primary endpoint (a decrease in pain without an increase in analgesic medication) was observed in 29% of patients in the mitoxantrone and prednisone group and 12% in the control group ($p < 0.001$). The total response rates assessed by the primary and secondary endpoints (a decrease in pain or analgesic medication without increases in the other) were 38% for the patient group and 21% for the control group ($p = 0.025$). The palliative effects of chemotherapy lasted significantly longer than the effects of prednisone alone ($p < 0.001$). Most of the patients who experienced palliative effects also reported improvements in most domains of quality of life and a significant improvement in overall well-being.

The second study was a multicentre North American randomized trial of patients with symptomatic untreated advanced pancreatic cancer, in which the benefits of the new drug gemcitabine were compared with those of 5-fluorouracil. The primary goal was defined prospectively as a clinically beneficial response. There were 3 components of clinical response: pain (assessed as pain intensity on the Memorial Pain Assessment Card and by analgesic consumption), functional impairment (Karnofsky performance status assessed by 2 independent observers) and weight gain. Patients had to experience a sustained improvement for at least 4 weeks to be classified as having received clinical benefit. Clinical benefit was observed in 24% of patients treated with gemcitabine and 5% treated with 5-fluorouracil.

Palliative benefit in this trial did not correlate with response as measured by radiographic results in either drug group. This may reflect difficulty in assessing the radiologic response of primary pancreatic masses because of their retroperitoneal location and the associated inflammatory reaction. An alternative explanation is that chemotherapy had an effect on the tumour — or host-derived biochemical mediators responsible for pain or malignant cachexia. Instruments measuring quality of life may make it possible to assess these aspects of systemic chemotherapy.

Prognostic role of quality of life in clinical trials

As well as providing an appropriate objective in clinical trials, measuring quality of life may provide prognostic information relevant to both response to treatment and survival. Trials of patients with breast cancer, melanoma and prostate cancer have demonstrated that scores on both performance status and patient-based quality-of-life scales are strong (dominant) predictors of survival in a multivariate analysis.

The multicentre Canadian trial of prostate cancer demonstrated that the use of quality-of-life assessment scales and the GLQ-8 instrument, and by physicians, who used Spitzer's Quality-of-Life Index. On multivariate analysis, overall quality of life together with the QL Index and the linear analogue self-assessment scale for appetite and mood were significant predictors of survival ($p < 0.05$ for each score) and were independent of other prognostic factors.

The multicentre Canadian trial of prostate cancer de-
scribed earlier also assessed the association between performance status, quality-of-life measures and duration of survival. Multivariate analysis indicated that performance status, the intensity of pain and one other patient-based measure of quality of life were powerful independent predictors of duration of survival.

A recent multicentre trial evaluated the prognostic association of quality-of-life scores among patients with advanced tumours in routine practice. In all, 735 patients with advanced disease from 12 institutions in 10 countries completed the EORTC QLQ-C30. Single-item quality-of-life scores for overall physical condition, overall quality of life and the global and social functioning scales were found to be independently prognostic after controlling for variations in performance status scores, age and metastatic site.

All studies described here show the prognostic importance of quality of life. Future clinical trials for advanced cancer should stratify patients by performance status and a patient-based measure of quality of life, which appear to be the most important prognostic factors for survival.

**Measurement of quality of life in routine clinical practice**

Patient-derived quality-of-life measures might be used in general clinical practice to assess the response and toxic effects of palliative systemic therapy. They might also be used to select or stratify those patients who would benefit from palliative therapy. However, there are some problems associated with the general use of quality-of-life scales. Physicians are reluctant to accept palliative responses to therapy over tumour responses, despite the fact that palliative effects are more beneficial to the patient. It must be difficult to choose which of the several instruments available are most appropriate and to compare the results obtained with different instruments. Effort is required by the patient to complete the instrument and by the medical staff to ensure compliance. Instruments being used in a nonresearch setting must be brief, validated, required by the patient to complete the instrument and by the medical staff to ensure compliance. As clinicians, we are finally listening to our patients. As clinicians, we are finally listening to our patients.

**Conclusions**

As clinicians, we are finally listening to our patients. We are hearing what impact a disease has on the whole individual instead of relying solely on laboratory tests or imaging for our information. Quality of life will be used increasingly to describe therapeutic outcome and as a powerful prognostic indicator. The next step will be to go beyond clinical trials and consider the quality of a patient’s life when making treatment decisions.

**References**


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