Abstract. Health-related quality of life (HRQoL) is a multidimensional concept, encompassing all aspects of patient health and used widely as an outcome measure in clinical trials. In this review, the current status of HRQoL assessment in clinical studies of gastrointestinal cancer is examined and the various instruments proposed for this purpose are considered and compared. The cancer-specific questionnaires, among them the Spitzer Quality of Life Index, the Rotterdam Symptom Check List, the Functional Living Index-Cancer, the Functional Assessment of Cancer Therapy General (FACT-G) and the Quality of Life Questionnaire of the European Organization for Research and Treatment in Cancer (EORTC), provide essential information about particular concerns of cancer patients and are most sensitive in detecting changes over time. The domain-specific questionnaires, among them the Multidimensional Fatigue Inventory, the McGill Pain Questionnaire, the Hospital Anxiety and Depression Scale and the Anorectal Sphincter-Conservative Treatment Questionnaire, are designed to assess one specific domain of quality of life. The core-module cancer-specific questionnaires combine a core questionnaire for use in any type of cancer with a module questionnaire which assesses specific issues in cancer patient subgroups. Such core-module instruments have been evaluated for colorectal, pancreatic, hepatobiliary, oesophageal and gastric cancer. The most valid and standardized instruments for HRQoL assessment in cancer patients are the EORTC and the FACT questionnaires, which are widely used in Europe and around the world. Data provided by these specific instruments complement clinical outcomes and may help to evaluate the costs and benefits of different treatment options, thus being essential to further improvement of treatment and care of cancer patients.

Objective tumor responses and overall survival have traditionally been the main outcome used to assess the effectiveness of therapy in cancer patients, especially in clinical trials. Despite the use of new chemotherapeutic agents and the administration of more effective combination regimens, tumors of the gastrointestinal tract are serious, often fatal. Therefore, the principal goals of treatment remain relief of tumor-related symptoms, palliation, substantial prolongation of survival and improvement of the general well-being.

Health-related quality of life (HRQoL) has become, over the last 20 years, an important component of the evaluation of new therapeutic modalities such as novel chemotherapeutic regimens. HRQoL data provide robust assessments of the patients' perception of the benefit of therapy. Therefore, accurate HRQoL measurements through valid, standardized questionnaires are crucial to ensure that data are clinically useful.

During the last decade, several instruments have been constructed and clinically applied in order to compare treatment outcomes. The purpose of this review is to critically present the existing instruments for quality of life assessment in patients with gastrointestinal cancer.

Materials and Methods

A bibliographic search of the Medline database was conducted for published papers from 1980, with the key words "oesophageal cancer", "gastric cancer", "pancreatic cancer" "colorectal cancer" and "quality of life". The search was limited to articles written in English. The following criteria should be fulfilled for the selection of questionnaires: i) validity: that is the extent to which the questionnaire measures what it purports to measure. As there is no "gold standard" for HRQoL, the aspect of validity of such questionnaires which is usually assessed is the construct validity, namely the ability to correlate with other generally accepted 'proxy' measures (e.g. other independently validated general health instruments, visual analogue scales or performance status). Another aspect of the validity of a questionnaire is the ability to produce consistent results across items in the same dimension (purporting to measure the same trait). This is called internal validity or internal consistency. ii) reliability: that is the degree of agreement (consistency) between two administrations of the questionnaire to the same patients under similar conditions (general and clinical) on two different occasions; this is also called

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Key Words: Quality of life, gastrointestinal, oesophageal, gastric, pancreatic, colorectal cancer.
test-retest reliability or reproducibility iii) responsiveness-sensitivity to change: this is the degree the instrument can detect clinically meaningful changes which are important for the subject involved.

The instruments selected were tested for the above parameters and proved to have acceptable validity, reliability and sensitivity to change.

Results

The instruments selected according to the above criteria could be grouped into three categories: generic instruments, disease-specific and symptom-specific questionnaires.

Generic instruments. Generic instruments provide comparison across groups and interventions. They may be used to detect similarities or differences between patient groups, but they are not sensitive enough to detect changes after therapy in the same group of patients or may lack particular specific relevant subscales (e.g. issues of relevance to colorectal cancer patients). Examples of widely used, well validated generic instruments are the Short-Form 36 questionnaire (1,2), the Sickness Impact Profile (3,4) and the Nottingham Health Profile (5).

Cancer-specific instruments. Specific instruments are designed to address problems specific to a population. In contrast to generic instruments, cancer-specific instruments are more likely to provide essential information about particular concerns or worries of cancer patients and are most sensitive in detecting changes over time or after therapy. The specificity and the sensitivity of these measures allow the comparison of results across different populations (6) (Table I).

The Spitzer Quality of Life Index (QLI) is a 5-item questionnaire that is completed by the physician. The patient’s well-being is rated in the areas of health, activity, daily living, outlook and support with a 0, 1 or 2 for each item, resulting in a total score ranging from 0 to 10 (7).

The Rotterdam Symptom Check List (RSCL) consists of 38 items and an overall HRQoL question. This instrument measures psychological and physical distress in cancer patients. Patients are asked to indicate, on a four-point Likert scale (not at all, a little, quite a bit, very much), up to which point they have been bothered by the particular problem during the previous week (8).

The Functional Living Index-Cancer (FLIC) is a 22-item instrument, designed for easy, repeated self-administration. The questionnaire was validated against several generic instruments and was found to be valid and reliable. The instrument was applicable to clinical trials and, according to the authors, could provide additional functional information on which to analyze the outcome of clinical trials (9).

The Functional Assessment of Cancer Therapy-General (FACT-G) is a general cancer quality of life instrument for evaluating patients receiving cancer treatment. It consists of 28 items, divided into four subscales for physical, functional, social and emotional well-being (10). This instrument is considered appropriate for use in any type of cancer. Coefficients of validity and reliability were very high (10). The scale’s ability to discriminate among patients with different performance status was also significant and, additionally, it has demonstrated sensitivity to change over time (10). A longitudinal change of 5% in FACT-G score is considered to be clinically meaningful and significant (11).

Table I. Cancer-specific instruments for HRQoL assessment in patients with malignancies of the gastrointestinal tract.

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Year of publication</th>
<th>No. of items</th>
<th>Subscales</th>
<th>Method of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spitzer Quality of Life Index (QLI) (7)</td>
<td>1981</td>
<td>5</td>
<td>health, activity, daily living, outlook, support</td>
<td>Physician administered</td>
</tr>
<tr>
<td>Rotterdam Symptom Check List (RSCL) (8)</td>
<td>1990</td>
<td>38 and an overall HRQoL question</td>
<td>psychological and physical distress</td>
<td>Self administered</td>
</tr>
<tr>
<td>Functional Living Index-Cancer (FLIC) (9)</td>
<td>1984</td>
<td>22</td>
<td>physical, functional, social and emotional well-being</td>
<td>Self administered</td>
</tr>
<tr>
<td>Functional Assessment of Cancer Therapy-General (FACT-G) (10)</td>
<td>1993</td>
<td>28</td>
<td>five functional scales (physical, role, cognitive, emotional and social); three symptom scales (fatigue, pain and nausea/vomiting); a global health and quality of life scale</td>
<td>Self administered</td>
</tr>
<tr>
<td>European Organization for Research and Treatment in Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) (12).</td>
<td>1993</td>
<td>30</td>
<td></td>
<td>Self administered</td>
</tr>
</tbody>
</table>

2118
The European Organization for Research and Treatment in Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) is a 30-item cancer-specific questionnaire designed for use in clinical trials. The QLQ-C30 incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional and social); three symptom scales (fatigue, pain and nausea/vomiting); and a global health and quality of life scale. The score for each item ranges from 1 (not at all) to 4 (very much) for functional scales, or from 1 (very poor) to 7 (excellent) for symptom scales. The total score ranges from 0 to 100. For functional scales and global quality of life higher scores represent better quality of life, while for symptom-oriented scales higher scores mean more severe symptoms (12). Patients with a mean change in QLQ-C30 score of 5-10 points experience a small change in quality of life and disease-related symptoms, while “very much” change in HRQoL is demonstrated by changes in QLQ-C30 score greater than 20 points (on a 0-100 point scale) (13,14).

FLIC, FACT-G and EORTC-QLQ-C30 questionnaires have been compared in a study of 310 patients (15). The acceptability of EORTC-QLQ-C30 and FLIC was found to be better than that of FACT-G due to a significantly lower rate of missing, confusing or upsetting items.

Domain-specific instruments. Domain-specific questionnaires are designed to assess one specific domain of HRQoL in detail. Examples of such instruments with adequate validity and reliability are the Multidimensional Fatigue Inventory (16), the McGill Pain Questionnaire (17), the Hospital Anxiety and Depression Scale (18) and the Anorectal Sphincter-Conservative Treatment Questionnaire (19), with the last two instruments being the most widely used in patients with gastrointestinal cancer.

The Hospital Anxiety and Depression Scale (HADS) is a self-administered instrument for detecting states of depression and anxiety in the setting of a hospital medical outpatient clinic (18).

The Anorectal Sphincter-Conservative Treatment questionnaire is an 18-item anorectal cancer-specific symptom scale which focuses on issues related to bowel habit (19).

Core-module assessment of HRQoL. There is a characteristic aspect of cancer-specific QoL questionnaires which distinguishes them from all other chronic disease QoL questionnaires. We can call it a “modular approach”. The modular approach in HRQoL assessment combines the administration of a cancer-specific instrument appropriate for use in any type of cancer (the “core” questionnaire) with a specific instrument (the “module” questionnaire), which assesses in great detail issues of relevance to specific cancer patients subgroups (e.g. colorectal or pancreatic cancer patients and so on), not adequately covered by the core questionnaire. The use of a module increases the specificity and the sensitivity to detect small, but clinically important changes in HRQoL. The cancer-specific questionnaires FACT-G (10) and QLQ-C30 (12) are such core instruments which can be supplemented by site- or treatment-specific modules (Table II).

The FACT-Colorectal quality of life instrument (FACT-C) is a questionnaire assessing quality of life concerns in colorectal cancer patients. It is a combination of the core FACT-G questionnaire with a 9-item Colorectal Cancer Subscale (CCS) module (20). The FACT-C demonstrated good validity and reliability, as well as an ability to discriminate patients with different functional status and extent of disease. The FACT-C was also found to be sensitive to changes in functional status. It is recommended that the entire FACT-C (instead of simple CCS) be used when studying patients with colorectal cancer in order to provide a comprehensive assessment of HRQoL (20).

The Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) questionnaire is a 45-item self-report instrument designed to measure HRQoL in patients with hepatobiliary cancers. This instrument consists of the 27-item FACT-G core questionnaire, combined with the recently validated 18-item Hepatobiliary Subscale (HS), which assesses disease-specific issues. All subscales and aggregated scores showed high validity and test-retest reliability. According to performance status, patients were divided into three groups: 0 (without symptoms, normal functioning), 1 (some symptoms but no extra rest required) and 2 to 3 (some degree of bed rest needed during the waking day). The 18-item HS subscale was able to discriminate these three groups to a degree comparable to the Physical and Functional Well-Being subscales of the FACT-G. Finally, as therapeutic interventions in these patients are themselves associated with some degree of disability and toxicity, patients were distinguished according

<table>
<thead>
<tr>
<th>Core questionnaire</th>
<th>Module questionnaire</th>
<th>Type of cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT-G</td>
<td>FACT-Colorectal Cancer Subscale (FACT-CCS)</td>
<td>Colorectal</td>
</tr>
<tr>
<td>FACT-G</td>
<td>FACT-Hepatobiliary (FACT-Hep)</td>
<td>Hepatobiliary cancer</td>
</tr>
<tr>
<td>EORTC-QLQ-C30</td>
<td>QLQ-oes24 (22)</td>
<td>Oesophageal cancer</td>
</tr>
<tr>
<td>EORTC-QLQ-C30</td>
<td>QLQ-STO22 (24;25)</td>
<td>Gastric cancer</td>
</tr>
<tr>
<td>EORTC-QLQ-C30</td>
<td>QLQ-PAN26 (26)</td>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td>EORTC-QLQ-C30</td>
<td>QLQ-CR38 (27)</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>EORTC-QLQ-C30</td>
<td>QLQ-LMC21 (28)</td>
<td>Colorectal cancer with liver metastases</td>
</tr>
</tbody>
</table>
to treatment status (two groups: on treatment and off treatment). Both the HS and the Fact-Physical Well Being (PWB) scale differentiated these groups (21).

Similarly, QLQ-C30 is used as a core instrument and can be supplemented with module questionnaires for the assessment of HRQoL in practically every type of gastrointestinal cancer. For HRQoL evaluation in patients with oesophageal cancer, the QLQ-C30 core instrument is combined with the QLQ-OES24 module. This module was developed as a 24-item questionnaire, conceptualised into six scales and five single items (22). Subsequent analyses refined the module to four scales and six single items (QLQ-OES18) (23). The questionnaire was well accepted, showing high compliance rates. Selective scales discriminate among clinically distinct groups of patients and clearly demonstrated treatment-induced changes over time (23).

The QLQ-STO22 module is developed for HRQoL assessment in patients with gastric cancer. This module contains 22 questions conceptualized into five scales and four single items, related to disease symptoms, treatment side-effects and emotional issues specific to gastric cancer (24,25).

For patients with pancreatic cancer the specific module is the QLQ-PAN26 questionnaire which includes 26 questions related to disease symptoms, treatment side-effects and emotional issues specific to pancreatic cancer (26). The questionnaire was able to detect small, but clinically significant disease- and treatment-related HRQoL changes in patients with pancreatic cancer.

In patients with colorectal cancer, the QLQ-CR38 questionnaire is the module that supplements the QLQ-C30 core instrument. The QLQ-CR38 contains 38 questions, of which 19 are completed by all patients, while the remaining 19 are completed by subgroups of patients (males, females, with and without a stoma). The items are combined in order to form subscales for the assessment of micturition problems, symptoms in the area of the gastrointestinal tract, chemotherapy side-effects, problems with defecation, stoma-related problems, male and female sexual problems, body image and future perspective (27). The module was proved to have adequate validity and reliability and was found able to clearly distinguish between patients differing in disease stage, initial and on-treatment performance status and the presence of a stoma (27).

Recently, a module for patients with colorectal cancer and liver metastases was developed. This instrument has been developed on the basis of input derived not only from the published literature, from health professionals dealing with these patients and, most importantly, from the patients themselves. The QLQ-LMC21 contains 21 items and provides essential HRQoL assessment in combination with the QLQ-C30. It could be used for the evaluation of new and existing treatments for colorectal hepatic metastases in future trials (28).

Conclusion

HRQoL has advanced from an indefinite and vague notion to a well-defined multi-dimensional concept, encompassing all aspects of patient health: physical, social and emotional aspects, as well as the impact of the disease on the patients’ daily function. HRQoL is implemented as an outcome measure in clinical trials and there is growing interest in its use for improvement of patient-physician interaction and facilitation of policy decision making.

A variety of instruments have been used for HRQoL assessment in several studies, leading to difficulties in cross study comparisons. One of the main issues in assessing HRQoL is the availability of reliable and robust instruments. HRQoL assessment should be based on standardised, valid and reliable instruments, capable of detecting small but clinically significant disease- and treatment-related HRQoL changes. These instruments should have also been tested across large groups of culturally diverse patients, in order to be employed in multinational clinical trials. Recognising this fact, the European Organization for Research and Treatment of Cancer has established a substantial research programme for developing such instruments, with particular relevance to cancer clinical trials, by creating the EORTC Quality of Life Group (29-32). The EORTC-QLQ-C30 questionnaire developed by this group is one of the most widely used questionnaires in Europe and around the world (32). The EORTC-QoL Group has continued this work by refining the EORTC-QLQ-C30 questionnaire (33), by constructing a range of additional modules and by initiating programs that explore aspects of HRQoL assessment, evaluation and interpretation.

Data provided by such instruments complement clinical outcomes and may help the clinicians as well as the patients to evaluate the costs and benefits of different treatment options. Furthermore, these data help to anticipate side-effects, thus making them essential for further improvement of the treatment and care of cancer patients.

References


Received December 19, 2003
Accepted April 24, 2004