Aspects of health related quality of life in prostate cancer
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Citation for published version (APA):

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Chapter 2

Quality of life assessment:
genereal and methodological aspects
Introduction

Interest in health related quality of life (HRQOL) assessment in clinical research has been growing rapidly. It’s rather peculiar that this interest used to be small, given the fact that from the days of Hippocrates, the primary goal of a doctor is to improve the patient’s well-being, and not only an attempt to control his disease. In fact, Hippocrates even did go further, stating in his dictum: ‘primus est non nocere’ which means ‘first, do no harm’. Treatments given in an effort to control disease sometimes conflict with this goal. Therefore, it is clear that knowledge of a patient’s well-being, in other words assessment of a patient’s HRQOL, and insight how this is influenced by treatment, is an undisputable need in good clinical practice.

The term quality of life (QOL) was first used by Dwight Eisenhower’s Presidential Commission on national goals in 1960. However, its ethos was already clearly embodied in the constitution of the WHO in 1947, in which health was defined as not merely the absence of disease, but also a state of complete physical, social and mental well-being [1]. Since that time, quality and quality of life has become a hot issue, and not only in health care but in the society as a whole everything seems to revolve around the word quality. Much time has passed since then, but one problem remains. How to define quality and how to measure it? This is also true for defining and measuring the HRQOL.

In this chapter we will discuss what HRQOL assessment should involve, how it should be measured. We’ll address the issue of questionnaire development. We’ll give an overview of the questionnaires available for measuring HRQOL in prostate cancer. Finally we will discuss some methodological issues.

HRQOL – what it mean.

Most researchers agree that HRQOL involves a number of relatively independent domains, that at least include physical, functional and psychosocial aspects, and social well-being. So, it is a multi-dimensional concept, grouped under the broad headings of physical, functional, psychological, and social health. These domains are formed and influenced by several factors. In this view physical health is related to symptoms, e.g. pain, fatigue, gastrointestinal problems, urinary problems and so on. Functional health is related to mobility, role activities, self care, and physical activities. Psychosocial health is related to cognitive function, psychological distress, and psychiatric morbidity. Finally, social health is related to social activities and interpersonal relationships [1,2].

Some researchers also emphasize other areas, such as spiritual aspects and satisfaction with health care [3]. However, the widely accepted model aims to identify different dimensions that may influence HRQOL. Until now relatively little attention has been paid to the relationship between these domains. How do they influence each other? For example, the individual judgement of the impact of the same symptom may vary widely and is most probably related to other personal factors (coping) as well as sociocultural factors and several resources (among others, economic resources, social support, and appropriate health care)[4]. This may hamper a good interpretation of HRQOL data, and may limit the usefulness of HRQOL data as an outcome measure in cancer treatment. Therefore, there’s a need for research programs which investigate the relationship between the different domains. If the outcome in one domain is influenced by the nature of another domain, the final HRQOL outcome should be corrected accordingly. As a result new models may be needed that can provide the proper corrections in these assumed relationships. On the other hand, this research may produce models that identify and link independent variables to patient-assessed individual patient’s factors with HRQOL assessment.

Such models will facilitate the development of interventions that incorporate individual patient’s factors with HRQOL assessment. These models are more likely to give a sound view of the real impact of the disease and its treatment on HRQOL.

HRQOL – the way it should be assessed

HRQOL assessments obviously involve capturing patients’ own perceptions of their health and ability to function in life. So, patients themselves had to be questioned accordingly. There exist, however, several ways to do so. One can use an interview or a questionnaire, taken or presented by the patient’s own physician, an independent investigator, or the patient can administer the questionnaire himself. It can be done prospectively and retrospectively, in the hospital or at home, anonymously or not, and so on. It has been demonstrated that physicians tend to underestimate the symptoms and their burdens experienced by prostate cancer patients [5-7]. This is probably because they are not likely to hear the
true impact of the given therapy. On the other hand, patients might underestimate their problems when speaking directly to the primary caregiver. Fossa et al, however, concluded in their study that physicians tend to overestimate the impact of the disease and its treatment on patients' HRQOL [6]. One way or the other, HRQOL assessments performed by physicians are unreliable. The best way to assess HRQOL is through instruments which are self-administered by the patient. This administration should be done at the moment the investigator wants to be informed about the patients' HRQOL. In HRQOL research one can not do this retrospectively. Litwin et al demonstrated that men undergoing radical prostatectomy for early-stage prostate cancer do not accurately recall their pre-treatment HRQOL when asked several months or years later. This recall bias is constant throughout a period of 6 months to 3 years after surgery. Moreover, it is reported that patients anonymously rate their HRQOL worse compared to a not anonymous assessment [8,9].

In conclusion HRQOL is best assessed in a prospective way with questionnaires or instruments self-administered by the patients and analysed in an anonymous manner.

Development of HRQOL instruments
The development of a questionnaire measuring HRQOL is a complicated process. At the end of this process the questionnaire in case must evidently possess the fundamental properties of reliability, validity and responsiveness [10].

Reliability refers to the extent to which the measure consistently produces the same result, particularly when applied to the same subjects at different times. Therefore it concerns the amount of error present in the assessment. The statistic used to quantify the internal consistency, or unidimensionality, of a scale is called Cronbach's coefficient alpha. According to generally accepted standards this should exceed 0.70 [11].

Validity is the degree to which the measure reflects what was intended to measure rather than something else. Again, generally accepted standards dictate that validity statistics should exceed 0.70 [11].

Responsiveness of a HRQOL instrument indicates its sensitivity to clinically significant change. In other words, it must be able to detect meaningful improvements or decrements in HRQOL during longitudinal studies.

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Group formulated guidelines for instrument development [12]. These guidelines also have been developed very precisely. The EORTC has great experience in instrument development and therefore its guidelines can be seen as the golden standard for sound instrument development. Summarising, these guidelines contain 4 procedures:

Construction. A team of physicians, nurses, patients and, if necessary, other participants formulate questions and construct a basic instrument addressing issues which are considered to be relevant for the population for which the instrument will be developed.

Translation. The questionnaire is submitted to a rigorous translation process, based on repetitive forward-backward procedures. The aim of the translation is to produce instruments which are: clear, expressed in ordinary language, and conceptually equivalent to the original instrument.

Pilot testing. For every language, each item of the questionnaire is tested by means of a structured interview of about 10 to 15 patients.

Field study. After corrections have been carried through, the questionnaire is tested in a large study in order to test the scale structure, reliability and validity as an outcome in clinical research.

When this procedure is followed and the field study has proved that the instrument has good psychometric properties with respect to validity, reliability and responsiveness to change, it is ready for use in trials assessing HRQOL.

Available HRQOL instruments
A spectrum of HRQOL instruments has been developed, ranging from general to disease-specific and ad hoc instruments that are specific to a single study [13]. General instruments are most applicable to health policy research and their advantage lies in examining a wide range of potential impacts of disease on mental and social functioning. They are designed for use in any group of illness or in any population to assess HRQOL. Cancer specific instruments on the other hand, have the advantage of addressing problems which are specific to a given cancer patient population, and may permit cross-
study comparison. In table 1 (page 24) validated general HRQOL instruments are listed, table 2 (page 25) shows validated cancer specific HRQOL instruments.

Cancer specific core instruments (a more focused type of general measurement) are supplemented with disease specific or treatment specific modules, aimed to come to a compact and useful instrument, combining the advantages of the general and cancer specific instruments. Examples include the European Organization for Research and Treatment QOL core questionnaire (EORTC QLQ-C30), supplemented by a lung cancer-specific module (QLQ-LC13), or the general Functional Assessment of Cancer Therapy Scale (FACT-G), supplemented by the ovarian cancer-specific module (FACT-Ovarian). Disease specific instruments developed in order to measure the specific problems of prostate cancer patients are listed in table 3 (page 25).

The choice of an QOL instrument is directly related to the trial structure and the questions to be answered. A broad and comprehensive approach is likely to be particularly useful for treatments at which little is known about potential effects on patients' well-being, and assessment in order to distinguish among treatments needs to be specific and sensitive. Other important factors in instrument choice are the patient population, the treatment, if known, and its potential toxicity's and, concerning the logistics, the resources of the investigators and the participating investigators. In addition the QOL questionnaire should be available in the appropriate languages in relation to potential participants in the study concerned [14].

Aim of HRQOL assessment.
Cella and Tulsky formulated three purposes for measuring HRQOL [15]:
1. to identify the full range of side effects and impacts of the treatments in order to assess rehabilitation needs;
2. to compare treatments in a trial;
3. to use HRQOL ratings as a predictor of response to future treatment.

Others emphasize that knowledge of the HRQOL may be important when the impact of a different treatment on the life expectancy is small. Beitz stated, based on the recommendations of the Oncological Drugs Advisory Committee, that beneficial effects on HRQOL and/or survival should be the basis for approval of new anti-cancer drugs, and that, from a regulatory point of view, for drugs that do not have an impact on survival, demonstration of a favourable effect on HRQOL is more important than most other traditional measures used to assess efficacy, such as objective tumour response [16].

Table 1: General Quality of Life instruments proven to have good psychometric properties

<table>
<thead>
<tr>
<th>Instrument</th>
<th>abbreviation</th>
<th>number of items</th>
<th>references</th>
</tr>
</thead>
<tbody>
<tr>
<td>EuroQol</td>
<td>EQ</td>
<td>15</td>
<td>[17]</td>
</tr>
<tr>
<td>MOS 12 – item Health Survey</td>
<td>SF 12</td>
<td>12</td>
<td>[18]</td>
</tr>
<tr>
<td>MOS 36 – item Health Survey</td>
<td>SF-36</td>
<td>36</td>
<td>[19]</td>
</tr>
<tr>
<td>Nottingham Health Profile</td>
<td>NHP</td>
<td>38</td>
<td>[20]</td>
</tr>
<tr>
<td>Quality of Well-Being scale</td>
<td>QWB</td>
<td>18</td>
<td>[21]</td>
</tr>
<tr>
<td>Sickness Impact Profile</td>
<td>SIP</td>
<td>136</td>
<td>[22]</td>
</tr>
</tbody>
</table>

*MOS = Medical Outcome Studies*
### Table 2: Disease (Cancer) Specific Quality of Life instruments proven to have good psychometric properties

<table>
<thead>
<tr>
<th>Instrument</th>
<th>abbreviation</th>
<th>number of items</th>
<th>references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Rehabilitation Evaluation System</td>
<td>CARES-SF</td>
<td>59</td>
<td>[23]</td>
</tr>
<tr>
<td>European Organization for the Research and Treatment of Cancer</td>
<td>EORTC-QLQ- C30</td>
<td>30</td>
<td>[24]</td>
</tr>
<tr>
<td>Functional Assessment of Cancer Therapy</td>
<td>FACT</td>
<td>28</td>
<td>[25]</td>
</tr>
<tr>
<td>Functional Living Index of Cancer</td>
<td>FLIC</td>
<td>22</td>
<td>[26]</td>
</tr>
<tr>
<td>Quality of Life index</td>
<td>QLI</td>
<td>34</td>
<td>[27]</td>
</tr>
<tr>
<td>Rotterdam Symptom Check List</td>
<td>RSCL</td>
<td>27</td>
<td>[28]</td>
</tr>
</tbody>
</table>

### Table 3: Disease (Prostate) Specific Quality of Life instruments proven to have good psychometric properties

<table>
<thead>
<tr>
<th>Instrument</th>
<th>abbreviation</th>
<th>number of items</th>
<th>references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional Assessment of Cancer Therapy – Prostate</td>
<td>FACT-P</td>
<td>12</td>
<td>[29]</td>
</tr>
<tr>
<td>Prostate Cancer Specific QOL Instrument</td>
<td>PROSQOLI</td>
<td>10</td>
<td>[30]</td>
</tr>
<tr>
<td>Prostate Cancer Treatment Outcome Questionnaire</td>
<td>PCTO-Q</td>
<td>41</td>
<td>[31]</td>
</tr>
<tr>
<td>Radiumhemmets Scale of Sexual Function</td>
<td>RSSF</td>
<td>21</td>
<td>[32]</td>
</tr>
<tr>
<td>University of California, Los Angeles- Prostate Cancer Index</td>
<td>PCI</td>
<td>20</td>
<td>[33]</td>
</tr>
<tr>
<td>Expanded Prostate cancer Index Composite</td>
<td>EPIC</td>
<td>50</td>
<td>[34]</td>
</tr>
<tr>
<td>Prostate Cancer Quality of Life</td>
<td>PC-QOL</td>
<td>52</td>
<td>[35]</td>
</tr>
<tr>
<td>Dale instrument</td>
<td>Dale</td>
<td>23</td>
<td>[36]</td>
</tr>
<tr>
<td>Caffo instrument</td>
<td>Caffo</td>
<td>41</td>
<td>[37]</td>
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Finally, the European Organization for Research and Treatment of Cancer (EORTC) has defined criteria for the inclusion of quality of life issues in their phase III cancer clinical trials [38]. It is stated that theoretically HRQOL assessment can be a relevant endpoint if:
1. no improvement in overall, recurrence-free, or systemic disease-free survival is expected, but when significant changes or differences in (at least) one aspect of quality of life are expected;
2. one treatment results in a better survival but has more toxic effects;
3. the patients have an extremely poor prognosis with or without treatment;
4. treatment is known to be very burdensome to patients;
5. a new (invasive) treatment is to be evaluated.

So, in conclusion, generally, HRQOL assessment might be important in evaluating (relatively) new treatment modalities, when treatment itself has side effects (positive or negative) or when a new or different treatment has little or no impact on survival.

**Methodological issues related to HRQOL research**

Finally, we will discuss a few methodological issues related to HRQOL research. Firstly the compliance, secondly the issue of the clinical significance in HRQOL assessment, and finally we will address briefly the problem of how to use the results of HRQOL studies in daily practice and clinical decision making. One of the biggest problems in HRQOL research is the problem of the compliance. Compliance is mostly expressed in percentages, meaning the number of actually administered assessments divided by the number of expected assessments. Also, the term ‘missing data’ is used.

Two types of missing data are distinguished. Firstly, patients may fail to complete all items of a questionnaire, possibly by accident. In the scoring manuals of many validated instruments, elementary methods of calculating scalescores when items are missing, are described. Secondly, sometimes whole forms are missing. Several studies are less solid because of a low compliance [39]. Reasons for the low compliance may be physician as well as patient related. Not all physicians are aware of the importance of HRQOL assessment. As a result they are reluctant to administer the questionnaires to the patients. Moreover, it is time-consuming and some physicians don’t want to spent time on investigations in which they not fully believe, or maybe they really don’t have time. Other physicians argue that the results of HRQOL assessment nowadays don’t influence practical decision making and is therefore of relatively low or even no value. On the other hand, there are patients related reasons. Patients, especially older patients, sometimes don’t want to fill out all questions. That is one of the reasons why it’s so hard to get questionnaires concerning sexual issues validated. Patients, and especially those who are suffering from advanced disease, sometimes are in such a bad general condition that they’re physically not capable to reply, or because of their condition they are not very willing to administer questionnaires. It’s also possible that patients just feel fine but they see little point in replying. Sometimes there are just logistic reasons for bad compliance. However, the fact is that compliance in HRQOL studies is not always optimal. The question remains how to handle low compliance and how to interpret results of studies based on low compliance. How can one be sure that those patients with data are truly representative of the total sample recruited for that particular study? Are the results consequently biased? There is no widely accepted general rule for acceptable levels of compliance. It depends very much on the reasons for the missing data. If one can argue (and support empirically) that the data are missing at random, than from a methodological point of view it is not such a problem because it is acceptable to perform analyses on the available data. However, this is rarely the case. In fact, nowadays one can not easily eliminate bias when data are missing, and it should be emphasised that the results of analyses may be suspect and must be interpreted with caution whenever there are many missing data [14].

How to interpret HRQOL research and its clinical significance are the last issues to be addressed. Most users of HRQOL instruments are unfamiliar with the particular scales, and do not know how to interpret the (mean) scores. Which interpretation should be given to a difference of 5 points on a scale running from 0 till 100. An example: the interpretation of the results of multivariate analyses from the CaPSURE database as reported by Litwin [40]. Using the UCLA- PCI (see table 3) sexual function 6 months after radical prostatectomy in patients who were operated nerve sparingly was 20 on a scale running from 0 till 100, in which 100 represents a good and 0 a bad function. In patients not operated nerve sparingly sexual function was calculated 14. With a p value of 0.006, this difference was statistically highly significant. However, statistical significance tells us whether the observed data can
be explained by chance fluctuations (such as selection of patients), but says nothing about clinical significance. So, what is the clinical significance and, what's more, what impact has a difference of 6 points on daily practice? Is such a difference big enough to be important? If a patient’s score changes by 6 points, would they even notice the change? One can argue that the difference in a score between 14 or 20 on a scale running from 0 till 100 has no clinical meaning or consequences. Both scores are bad. Does that mean that from a practical point of view the outcome of nerve sparing and not nerve sparing radical prostatectomy is equal? There are no straight answers to these questions. Osoba et al and King, among others, addressed this issue [41,42]. Osoba et al compared the outcome of the EORTC-QLQ C30 on two occasions. In addition, they asked the patients to rate their perception of change. He evaluated four scales (physical, emotional, social functioning and global QOL) [41]. It turned out that when these scale score changed by 5-10 points (on the 0-100 scale) patients described their change in condition as ‘a little’. Changes of 10-20 were rated as ‘moderate’ and changes over 20 points as ‘very much’. King used a different approach [42]. She collected data from 14 studies concerning patient groups who were expected to differ in terms of HRQOL (limited disease versus advanced disease). She concluded that for most scales a difference of 5 or less is a ‘small difference’, but the definition for a large difference varied for each scale. This was for example 16 for global QOL, 27 for physical function and 7 for emotional function.

In conclusion, the interpretation of results remains essentially quantitative. Clinical significance is subjective and a matter of opinion. Based on the present data and the variety of personal opinions it is unlikely that a single threshold value will be universally accepted as a cut-off point that separates clinically important changes from trivial and unimportant ones. However, many investigators agree that a change of 5-10 points on the 1-100 scale may be interpreted as clinically significant [14,43,44].

However, even if one knows how to interpret HRQOL data, it remains difficult to use this outcome in daily practice. How to incorporate this knowledge in therapeutic decision making for the individual patient? Especially when one must choose between prolonged survival with a worse HRQOL or shorter survival with a better HRQOL. How to handle this? Chapman constructed a model of prostate cancer patients’ preferences for health states [45,46]. The multi-attribute utility theory (MAUT) provides a way to model decisions involving trade-off among different aspects or goals of a problem. A study among 57 patients showed that patients’ preference judgements are moderately consistent and systematic. The model constructed appears to be a potentially feasible method for evaluating preferences of prostate cancer patients and may prove helpful in assisting patients make decisions regarding treatment [47]. These preferences are also called utilities and refer to the individual’s valuation of various health states. A state of perfect health is usually assigned as a utility of 1.0, whereas death or an extremely poor health is assigned as a utility of 0.0. Suboptimal states of health resulting from HRQOL impairment correspond to intermediate values between 0-1. By placing both survival and HRQOL (utilities) in the same equation, it is possible to determine the relative contribution of each. This allows the patient to incorporate his or her own preferences for various health states into the decision-making process.

An other way of combining survival and HRQOL is to use the term QUALY, Quality Adjusted Life Years. This is calculated by multiplying the survival with QOL. When for a certain treatment the survival is 4 years with an overall HRQOL of 0.6 the QUALY is 2.4. Resulted another therapy in a comparable patient group in a survival of 3 years but with a HRQOL of 0.9 the QUALY is 2.7. Notwithstanding the existence of these models, and in absence of a widely accepted golden standard, the incorporation HRQOL results in clinical decision making still remains difficult and will mostly depend on the personal view of the physician.

We will end with the words of Varricchio et al [48]. They stated that the results of HRQOL assessment in clinical oncology should focus on interventions to lessen the negative impact of cancer and its treatment on HRQOL, while the translation of HRQOL findings into valid, effective clinical applications must be of the greatest concern to modern-day researchers and clinicians. After all, it is important that HRQOL research continues to develop, and that cancer research questions of clinical importance will be addressed to patients.
References


