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Quality of life in oncology: Why and how can we evaluate this aspect in cancer care?

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Since it has been recognised that QoL is an important outcome in medicine this field of research has grown rapidly. In the past decade increasing attention is being given to more systematic and quantitative ways to evaluate explicitly the impact of diseases and medical interventions on QoL. A substantial part of this research pertained to the field of cancer where cure is not always possible and treatments are mostly intrusive. The general purpose of QoL assessment in medicine is to provide more accurate evaluations of the wellbeing of individuals or groups of patients, and of the benefits and losses that may result from medical interventions. The focus of study can be to describe, to measure changes over time, to compare different populations, or to predict future outcomes. If QoL is to be evaluated, a number of decisions have to be made concerning the methodology of measurement. These decisions relate to: a) the design of the study; b) the components of QoL that will be evaluated; c) the instrument(s) to measure the relevant components; d) the subjects and e) the timing of assessment. In recent years it has become more acceptable to include QoL (mostly as a secondary) outcome measure in cancer clinical trials. Since missing QoL forms or missing data are, by definition, irretrievable, logistics and organization of the study require special measures to ensure good quality of data up-front. As QoL research is a rather new field of research there is not yet a large data base available to compose reference scores which can be used to calculate sample size and to facilitate the interpretation of results. In cancer clinical trials QoL is mostly evaluated between treatment arms in a longitudinal design. But what are significant changes over time? Surely statistical significance is not identical to clinical significance. A clinically meaningful change is statistically significant, but a statistically significant change is not always clinically meaningful. This presentation will focus on and discuss the basic principles of QoL assessment in general and in oncology in particular. Examples will be used from both the literature and current practice in the European Organization for Research and Treatment of Cancer (EORTC).

Key words: neoplasms; quality of life

Introduction

Historically, the main purpose of oncology has been to cure cancer, and, if cure is not possible to prolong life. Regardless of the tremendous progress in medicine in general and in oncology in particular, many patients still cannot be cured of their cancer. New treatment modalities seldom lead to revolutionary improvements of tumour control and life expectancy. On the other hand, cancer requires treatments that are mostly highly intrusive in character and often cause considerable side-effects in terms of morbidity.

Although implicitly QoL (QoL) always has been an important goal, it is only quite recently that we have come to accept that there are limitations to the strictly biological approach to evaluate cancer treatment outcomes in terms such as overall or disease free survival. Especially when two treatment options offer comparable biomedical advantages, the principal differences may lie in associated features like

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QoL. Therefore, increasing attention is being given to more systematic and quantitative ways to evaluate the impact of cancer and its treatments on QoL.

What is QoL?

It has been agreed upon that QoL is not a directly observable and measurable entity, but that it is a construct which has to be specified and defined. Without a definition a concept cannot be measured. However, despite the increasing interest and applications of QoL evaluation, still no consensus has been reached among researchers concerning the definition of this concept. Definitions of QoL are numerous and widely divergent. Nevertheless there are some issues regarding the concept of QoL that researchers in this field have agreed upon. The first agreement is that QoL is a *subjective* evaluation. It is generally accepted among QoL researchers that patients themselves are the best judges of their own QoL. However, there are circumstances in which it is difficult or even impossible that patients rate their own QoL. In these cases patients' QoL has to be assessed from the perspective of the family (e.g., partner, parents) or the caretaker (e.g., physician, nurse).

The second issue researchers have agreed upon is that QoL is not a static, but a *dynamic* entity. QoL changes as a function of time, susceptible to numerous external as well as internal influences. In other words QoL is more a transient time-dependent process than a final outcome.

The third agreement is that QoL is a *multidimensional* concept. The four basic components of the concept of QoL are physical and psychological well-being, social relations and functional capacity. Although additional components (e.g., role performance, economic status, and spirituality) or subcomponents (e.g., sexuality, body-image, self-esteem) to the main components are often being suggested, these four are generally considered to provide the core elements of the conceptual framework of QoL research.

Purpose of QoL evaluation

The general purpose of QoL assessment in medicine in general and in cancer more specific is to provide more accurate assessments of the well-being of individuals or groups of patients and of the benefits and losses that may result from medical treatment. The focus of study can be to describe QoL in individuals or in certain populations, to measure changes in QoL over time, to compare QoL in different populations, or to predict future QoL outcomes.

Although the broad area of potential applications seems to imply that QoL assessment is indicated in most medical studies, it is obvious that QoL data are more relevant in some cases than in others. The European Organisation for Treatment and Research of Cancer (EORTC) considers QoL to be a possible relevant outcome parameter in randomised phase III studies if:

1) important improvements of overall, recurrence-free, or systemic disease-free survival realistically cannot be expected to occur as a result of treatment, but significant changes or differences in at least one aspect of QoL are expected to occur;

2) one treatment demonstrates a better survival, but produces more severe toxic effects;

3) with or without treatment the disease site is associated with an extremely poor prognosis;

4) a treatment is known to be burdensome for patients;

5) a new (invasive) treatment is to be evaluated.

Measurement of QoL

If QoL is to be evaluated in a clinical study, a number of decisions have to be made concerning the design and methodology of measurement.

Design of the study

There are three main designs to evaluate the effects of treatment on QoL: by means of a cross-sectional study, a prospective cohort study, and a randomised clinical trial. The first consists of a single point evaluation at a certain interval after intervention. Although this method is relatively quick, easy, and inexpensive to conduct, it also has a number of drawbacks since the type of information obtained is limited due to the fact that data are obtained in a single point assessment. It will neither provide insight into the dynamics of the concept, nor into the magnitude of the changes or the differences between the populations. As it is now generally acknowledged that QoL changes as a function of time, a prospective cohort study is to be preferred over a cross-sectional, single point assessment. Obvious-

ly, when QoL is measured to evaluate and compare therapeutic efficacy, a randomised clinical trial is the preferred strategy. Although a few years ago QoL assessment in randomised clinical trials was more the exception rather than the rule, at present it is becoming a well accepted outcome measure.

Relevant components

As stated earlier, QoL assessment includes the evaluation of minimally four components (functional status, physical, psychological, and social well-being). In addition, other components or subcomponents can be considered relevant outcomes, depending on the specific context and the objectives of the study. The selection of these additional (sub)components can be based on expert opinions, patient interviews, reports in the literature, or can be selected based on their face validity.

Instruments of measurement

Although criteria for QoL assessment in general and selection of proper QoL instruments in particular have been formulated in the literature, the important feature remains that no gold standard exists. Instruments that have proved to meet all criteria when applied in one application may be less appropriate or even inappropriate in another. Nevertheless, there is consensus about some general criteria an instrument has to meet.

First, the instrument should have proven, good psychometric properties with respect to validity, reliability, and responsiveness to change. The latter refers to a combination of both reproducibility (i.e., identical scores in stable subjects over time), and sensitivity (i.e., the ability to demonstrate changes when the subject's state of health improves or deteriorates) (Guyatt *et al.*, 1987). Second, it should be simple, brief, and easy to administer. The rationale behind this second criterion is that these properties enhance both participation and compliance, and that they reduce both patient and staff burden. It is mainly for practical and economic reasons that a self-assessment questionnaire is preferred to a person-to-person interview.

Broadly speaking, there are three basic types of instruments: generic, disease specific and domain specific. Generic instruments focus on the main components that constitute QoL, and they are intended to be applied in a wide range of health states. This last characteristic is at the same time the main advantage of generic instruments. However, generic instruments have the disadvantages that they may not be very responsive to changes in clinical status, and they may not always focus on the most critical health outcomes of interest (Revicki & Kaplan, 1993).

Disease specific instruments have been developed especially to detect subtle, disease related effects. However, these instruments have the disadvantages that comparison of results can only be made across studies in specific populations.

Domain specific questionnaire are even more limited in their scope since they focus on one particular aspect of QoL. Examples of such questionnaires are body image, sexual functioning, or treatment related side-effects.

Timing of measurement

Since QoL is a dynamic process the timing of the assessments must be carefully scheduled. Both the number and timing of assessments have to be decided upon at a case-to-case base. They largely depend on the research question, the characteristics of the population and circumstances such as logistics and finances available. However, in broad terms it can be stated that a minimum of three assessments is usually required in randomised clinical trials to capture relevant changes in QoL over time. The first assessment is to serve as a baseline measurement and should take place prior to the start of treatment and preferably also prior to randomisation. A second assessment is performed during treatment to capture the side-effects of treatment. The timing of this assessment is usually the moment at which the side-effects are expected to be at their height. A final assessment is performed at follow-up after treatment to account for long-term effects.

Problems and limitations

Although the field of QoL research is developing rapidly, there are also a number of problems and limitations to the present approaches and possibilities. Most cancer clinical trials are being conducted in a multicenter and often also in a multinational setting. These characteristics imply specific problems and require specific measures to ensure a good quality of the data. For instance instruments to measure QoL have to be available in the various languages and have to be validated in the different cultures. Also, the institutional settings differ high-

ly with respect to logistics and organisation which requires special measures to ensure good quality of data since missing forms or missing data are, by definition, irretrievable.

Another issue is the analysis and interpretation of results. As QoL research is a rather new field of research there is not yet a large data base available to compose reference scores. In cancer clinical trials QoL is mostly evaluated between treatment arms in a longitudinal design. But what are significant changes over time? Surely statistical significance is not identical to clinical significance. A clinically meaningful change is statistically significant, but a statistically significant change is not always clinically meaningful.

Many of these problems can be expected to be resolved in the near future as guidelines for datacollection and more data become available. However, the limitations are mostly inherent to the approach and hence more pertinent in character. Whereas in the earlier days of QoL research the main emphasis lied on the description of QoL within a certain context (i.e. disease and intervention), one can now observe a shift of study purpose towards evaluation and comparison of medical interventions. As a consequence of the growing medical possibilities and demands on one hand and limitations in health care expenditures on the other hand choices in health care are becoming inevitable in Western societies towards the 21st century. This necessity of making choices becomes apparent at three different levels: the macro level for policy making, the meso level for decisions related to the medical treatment of groups of patients, and a micro level for decisions concerning the individual patient.

An important consequence of the shift towards more decisional purposes of QoL evaluation is that the instruments of measurement have to meet other requirements. To compare treatment options (and eventually combine them with other parameters such as length of life and costs data) QoL has to be expressed in a single, numerical value that is a measure of the net effect balancing both positive and negative effects of treatment. Thus as such, it includes a valuation of the consequences.

Priorities for the near future

Although much progress has been made during the last decade, there is still a long way to go before QoL evaluation can be regarded as an integrated part of standard cancer clinical practice. The rapid growth of the number of studies that include QoL as an endpoint may reflect the increasing awareness and importance of the subject on the part of the investigators, but has also pointed out more clearly the flaws and shortcomings in this new field of research. The EORTC has set the following priorities for its activities related to QoL issues.

Good quality studies

It is extremely important to have a good infrastructure and a standard approach to the collection and analysis of QoL data. To ensure adequate rates of patient accrual, compliance, and data quality, there is an urgent need for a number of standard data management strategies. These include implementation procedures, detailed instructions for data collection, explicit instructions on the administration of QoL instruments, regulations on coding of data and interpretation of missing data and incomplete forms.

Analysis and interpretation of data

An important fact is that there is no optimal method for analysing QoL data. Several methods can be used and perhaps should be used to provide better insight into the data. However, each method has its advantages and disadvantages, and different models have different assumptions that are not always met.

The interpretation of results is impeded by the lack of standards concerning what can be considered as a clinically important change in any QoL score, and the absence of standard methods to define effect sizes and to calculate sample size requirements. An important step forward would be the availability of large datasets that can be utilised in future trials for the computation of expected differences and sample sizes.

A final methodological issue relates to the integration of different outcome measures. As stated previously, cancer clinical trials have a history of parameters, all related to length of life outcomes. Further development of methods to combine length of life with QoL data is both warranted and a major challenge. Since resources for health expenditure are becoming more restricted, health economic issues have become increasingly important, also in cancer clinical trials. Combining economic data with quality and length of life data will therefore become increasingly important.

Theoretical issues

Although it has become virtually impossible nowadays to keep up with the stream of publications of empirical studies on QoL issues, the theoretical foundation and framework on QoL is still rather weak. QoL is a dynamic concept like illness. However, the way and degree these two concepts interact with each other, and which other additional factors may have an influence is still largely unknown. One such additional factor is the unknown role culture plays in QoL issues.

Conclusion

In conclusion it can be stated that during the past few years much progress has been made in the field of QoL research. Sound instruments have been developed to measure QoL and guidelines have been made on the conduct of QoL evaluation in cancer clinical trials. However, there is still a long way to go before QoL assessment has become an integral part of cancer therapy evaluation.

As we move towards the 21st century, medicine in general and oncology in particular are facing major shifts in purpose of research and health care. The progress in medical technology and the parallel growing demand of health care lead to a continuing increase of costs that become more and more difficult to afford. Hence, making decisions, setting priorities, and allocation of health care resources become inevitable. To be able to make adequate decisions, information about illness and the expected consequences of treatment is a necessary prerequisites. In this context, information concerning the expected QoL as a medical outcome is highly relevant.

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