

review

Quality of life issues related to organ sparing

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The aim of organ sparing procedures is to maintain survival with a level of quality of life (QL) that is as high as possible. Methods are now available for evaluating QL in patients treated by quite different strategies and should be included as major endpoints, together with survival, in future clinical trials that investigate organ-sparing strategies. These methods will be useful in decision aiding for strategies leading to similar survival, and in framing choices between improved quality and improved quantity of survival.

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General features of quality of life assessment

There are two general methods for assessment of quality of life (QL) in patients included in clinical trials, or in patients receiving different types of treatment in the clinic: psychometric methods that are based on questionnaires completed by patients and utility-based methods that require patients to choose between different health states. In most settings it is appropriate to use a validated questionnaire that contains either discrete or continuous scales relating various

components of QL. In general, such questionnaires contain items related to symptoms of disease, symptoms that are caused by treatment, and general features of physical, psychosocial and emotional health. The provision of information about these separable components of QL provides an advantage when compared to utility-based measures. Most questionnaires either include an overall scale describing health-related QL or the individual scales can be summed to provide such an estimate. It is essential that the patients complete such questionnaires since physicians are often poor judges of the QL of their patients.¹⁻³ Caregivers may give better estimates but cannot substitute for the patients themselves.

Quality of life questionnaires vary between those that can be used very generally for patients with quite different diseases (e.g. the Sickness Impact Profile and the Medical Outcomes Short Form 36) to highly specific

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questionnaires that evaluate patients with a given type and stage of disease. In oncology, the most widely used questionnaires are those of the EORTC⁴ and the functional assessment of cancer therapy (FACT) devised by Cella and colleagues.⁵ Each of these questionnaires consists of a series of core questions (the EORTC QLQ C30 and the FACT-G) that can be used with an increasing series of modules that are specific for either given types of cancer, or for given types of symptoms (such as fatigue or endocrine symptoms). These questionnaires have been extensively validated and translated into multiple languages. There is no gold standard for validation, but in general, the development of a questionnaire requires that it have the following characteristics.^{4,5} There should be appropriate face or construct validity (does it measure what you want to measure?); related items should give related scores (convergent validity); unrelated items should give different scores (divergent validity); it should be reproducible (test-retest reliability); it should be responsive to change in clinical condition; and it should be predictive of outcome (predictive validity). In general QL scales are highly predictive of survival.⁶

Although QL scales are usually preferred for comparing aspects of QL among patients receiving different options of treatment, such comparisons may be difficult when treatments are radically different, as in trials of radical surgery versus an organ sparing approach. In such situations questionnaire-based approaches may be used to describe QL in patients who are treated by different modalities. These findings may then be used to describe to prospective patients the probable health state scenarios with or without radical surgery. Methods are then available which allow patients to assign a value to these health states; these values may vary between zero (equivalent to death) and one (equivalent to perfect health) and are called utilities.^{7,8}

Use of quality of life scales in clinical trials

Unfortunately, most clinical trials that have included QL assessments have done this in a rather poor way. In a typical trial, a large amount of information is collected at baseline and at some specified later time in the absence of any prior hypothesis about meaningful changes in one or more QL scales. Compliance in completing the questionnaires reflects the importance assigned to them by doctors and nurses involved in the trial: it is often poor in American studies (making analysis difficult) but may be high in European and Canadian studies. Some form of analysis is undertaken after the end of the trial, such as a comparison of mean or median QL scores for randomised groups of patients obtained at or close to a fixed time, say 3 months after treatment. The problems with this approach are that it is not driven by a hypothesis, does not establish *a priori* endpoints, and does not recognise that QL is a dynamic variable, which changes at different times in different individuals. Multiple comparisons are made, some of which will be significant by chance alone. It is analogous to measuring tumour response in a chemotherapy trial by measuring the average size of tumours in a group before treatment and at some fixed time after.

The inclusion of QL endpoints in clinical trials should be as rigorous as the inclusion of more traditional endpoints such as survival. This requires recognition that QL is a property of an individual, which will change with time. It also requires that a primary endpoint of QL be defined before the start of the trial. This might be either a measure of overall QL, or a measure of a dominant symptom such as pain. In trials of organ sparing, it should be a QL attribute related to the function of the organ that is either lost or spared, depending on treatment. Using this approach, the chosen QL endpoint should be measured for each patient at baseline and as a function of

time following treatment. For example, a scale representing the ability to communicate would be appropriate in comparing patients who had undergone laryngectomy or organ-conserving approaches for treatment of laryngeal cancer. A QL response may be defined by a predetermined level of improvement, by achievement or maintenance of a predefined level of function, or by a measure of deterioration. This may occur at different times in different patients. For example, function might improve as patients adapt to loss of an organ, and might deteriorate if the conserved organ suffers late damage following conservative treatment such as radiotherapy. The proportion of patients who attain a predetermined level in a chosen QL scale, or who have a predetermined deterioration in that chosen endpoint may then be assessed by following patients with time. Other measures of QL are supportive. It is important, for example, to ensure that the improvement in a single endpoint (e.g. a measure of pain or function) is not obtained at the expense of deterioration in other more global endpoints.

Specific issues related to organ sparing

It is not necessary to use complex QL scales to assess the obvious. If one is comparing, in a clinical trial, strategies that maintain major organ function with one that causes loss of that function, and survival is identical, one does not need a QL assessment to state that the first treatment is superior. Consider, for example, the results of the VA laryngeal study which showed that chemotherapy and radiation for patients with advanced larynx cancer led to the same survival as laryngectomy followed by radiation but with two-thirds of patients keeping their larynx.⁹ If the results of this study are confirmed, one does not need assessment of QL to know that the first strategy is superior. Quality of life scales are not necessary to know that a person who can

speak has better QL than one who cannot. Assessment of QL becomes more important when the loss of function is less severe, as in the comparison of mastectomy versus lumpectomy plus radiation therapy for breast cancer. Here there is substantial evidence for equivalent survival, but it is important to use QL scales to ensure that patients do not suffer undue anxiety because of concern about recurrence of tumour in the residual breast. Such studies have been undertaken: most have confirmed that patients had better QL with lesser surgery, especially in domains relating to body image.¹⁰⁻¹³

The situation becomes more complex when a patient may be faced with the choice between radical surgery, and an organ sparing procedure, where the latter may lead to some reduction in the probability of cure or long-term survival. For example, a meta-analysis of the 3 trials comparing surgery versus radiation and chemotherapy for locally advanced laryngeal and hypopharyngeal cancer suggests a non-significant trend to poorer survival for the organ-sparing approaches.¹⁴ If this is verified in further studies, the important question is whether patients are willing to accept a small reduction in the probability of cure or long-term survival in order to maintain speech and other important functions. A second example might relate to bladder cancer. Although data are lacking, cystectomy almost certainly gives better local control than radiation therapy (with or without chemotherapy) for muscle-invasive bladder cancer. In these situations, it is most appropriate to describe, as fully as possible, the probabilities of survival and function with the two options. Some patients will certainly accept a poorer probability of survival in order to maintain function, as demonstrated by McNeil and her colleagues, using a theoretical question about laryngectomy, many years ago.¹⁵ At present there are few data pertaining to patient choices of this type, especially those using realistic descriptions of health

states following modern treatment, and estimates of differences in survival following radical surgery or organ-sparing approaches obtained from well-designed randomised controlled trials. Studies of patients receiving adjuvant chemotherapy for breast cancer have shown that most patients will not accept improved QL (by avoidance of toxic treatment) for even a small deficit in survival.^{2,16,17} However, this might be quite different if patients were faced with more severe loss of function as would occur with laryngectomy or cystectomy.

The type of trade-off that is being made to patients in the above examples is similar to that which is used to measure utilities. A utility is a measure of QL for a given health state where perfect health has a utility of one and death has a utility of zero. The QL of a patient with a cystectomy and ileostomy is likely to be lower, in general, than the QL of a patient with a functioning bladder. If survival between the strategies that led to these two options were equal, almost all patients would accept having a functional bladder. By varying, in a theoretical presentation, the decrease in survival that would be acceptable to patients in order to retain their bladder, one can arrive at a utility for that state. For example, if patients could expect a long-term survival probability of 50% with cystectomy and were ambivalent in their choice between this option and that using a non-surgical approach with an expected long-term survival of 40%, then the utility for the state involving loss of a bladder would be 4/5 or 80%. Such utilities will vary from one patient to another, but can be useful in selecting appropriate treatments for future patients.

It is clear from QL studies that patients can adapt to loss of major function, and there are some apparent paradoxes where patients who have lost the function of a major organ may describe their overall QL as close to normal. This paradox probably occurs because of a frame-shift whereby the normal frame of ref-

erence for QL of a patient with a serious disease is different to that from a person that is healthy.¹⁸ These evaluations can be misleading unless one uses a quality of life scale that specifically relates to the function that has been lost.

In summary, the aim of organ sparing procedures is to maintain survival with a level of QL that is as high as possible. Methods are now available for evaluating QL in patients treated by quite different strategies and should be included as major endpoints, together with survival, in future clinical trials that investigate organ-sparing strategies. These methods will be useful in decision aiding for strategies leading to similar survival, and in framing choices between improved quality and improved quantity of survival.

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