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Invited articles

Q-TWiST to assess the quality of life in cancer patients

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Quality of life has recently become an important outcome that has to be included and measured in prospective trials. There are many different ways to measure quality of life. This review discusses in detail one method, the Quality-Adjusted Time Without Symptoms or Toxicity (Q-TWiST). Variations of this method and its limitations, too are discussed in this review. Practical examples of the use of this method in melanoma, breast and colon cancer in the literature are outlined. Its use also lends itself to economic analysis of cost-effectiveness, which is increasing in importance as health care funding becomes more scarce.

Parametr Q-TWiST (jakość życia i przeżycie wolne od objawów chorobowych i toksyczności) w ocenie jakości życia chorych z nowotworem

W ostatnich latach jakość życia stała sie istotnym elementem, uwzględnianym w toku oceny wyników badań prospektywnych. Istnieje wiele metod oceny jakości życia. Niniejsza praca przedstawia dokładny opis jednej z nich – jakości życia oraz przeżycia wolnego od objawów chorobowych i toksyczności (Q-TwiST – Quality-Adjusted Time Without Symptoms or Toxicity). Przedstawiamy również różne odmiany tej metody i jej ograniczenia oraz opisy jej zastosowania w praktyce u chorych z czerniakiem, rakiem piersi i rakiem jelita grubego. W pracy uwzględniono również aspekty ekonomiczne, pozwalające na dokonywanie realnych oszczędności, co jest szczególnie istotne w dobie ograniczania nakładów na opiekę zdrowotną.

Key words: quality of life, clinical trial
Słowa kluczowe: jakość życia, badania kliniczne

What is quality of life (QOL)?

Quality of life includes psychological and social functioning as well as physical functioning and incorporates positive aspects of well-being as well as negative aspects of disease and infirmity. Health-related quality of life (HRQL) often refers to a subset of specific QOL endpoints which relates to the health of the patient. HRQL is a relatively new outcome, which has been considered for incorporation into randomized, controlled clinical trials since the 1990s. Different methods have been proposed for evaluating clinical interventions for treatments of cancer in terms of their effects on disease-related outcomes, social cost and quality of life. Patient preference, too, has to be included in the evaluation.

This review aims to describe and to examine different methods for assessing quality of life. Examples are taken from the literature in order to show the application to different cancer sites.

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Why measure QOL?

The goals of cancer treatment and cancer prevention are the extension of life expectancy and the improvement of quality of life in the years prior to death. Usually, outcomes of cancer treatment are evaluated in terms of survival times. Although quality of life is often measured, interpretation of these measurements in relation to mortality is difficult. Survival analysis places each individual into one of two categories: alive or dead. Among those alive, all individuals are considered equivalent. Thus a patient confined to bed with severe symptoms is scored the same as someone who is active and asymptomatic. Clinical oncology is always evolving. Newer chemotherapeutic agents or regimens, and advances in radiation technology are being examined in clinical trials to improve survival. To a patient and a caregiver, the total duration of being alive may not be most important. A new treatment regimen may increase the three-year survival from 11% to 23% [1], thus more than doubling the odds of survival compared with survival after conventional treatment but the new regimen may disrupt seriously a patient's life or may cause significant treatment morbidity and mortality.

More intensive regimens tend to have a negative impact on QOL because of increased physical symptoms, such as fatigue or the inconvenience of frequent attendances at the clinic, however, if the more intensive regimens can be given over shorter periods of time, they may still be worthwhile [2]. These facts are summarized in Table I.

Table I. Reasons why quality of life assessment is important

Different treatments may have similar survival
Treatment may improve survival but may have severe side effects
Treatment may have no effect on survival but may improve quality of life

How to measure QOL?

Different instruments for measuring QOL include patient or physician-administered questionnaires. Instruments that detect different aspects of HRQL include health profiles and utility measurements [3]. Health profiles are highly responsive to change over time but are not easily comparable between studies. On the other hand utility measurements are not as responsive to change, but their numerical values are more readily comparable between studies. With the increasing number of multidimensional instruments available for measurement of the quality of life, investigators have to be careful that they select instruments which are reliable and which have been validated for incorporation into clinical trials. In addition, investigators have to choose an instrument or instruments which are best suited to detect the primary HRQL outcomes which are of interest for a specific population.

A relatively new method for assessing the quality of life during different health states is the Quality-Adjusted Time Without Symptoms or Toxicity (Q-TWiST) statistic, introduced by Glasziou, Simes and Gelber [4]. This method combines toxicity, disease-free survival (DFS), and overall survival (OS) in order to assess the impact of treatments on the lives of patients. This methodology has received positive reviews from clinicians as being intuitive and useful and is used in many major clinical trials [5-7]. Usually Q-TWiST is measured for two or more treatment methods either prospectively or retrospectively. OS and DFS data are also obtained. The duration of the health states are obtained: toxicity (TOX) which may be divided into acute short-term toxicity (TOX1) and secondary toxicity (TOX2), time without symptom and toxicity (TWiST) and relapse (REL).

$$\text{Q-TWiST} = (u_{tox} \times \text{TOX}) + \text{TWiST} + (u_{rel} \times \text{REL})$$

where TOX, TWiST, and REL represent the durations of these health state;
u_{tox} and u_{rel} are utility coefficients which reflect the values of times in the health states TOX and REL, respectively.

The Q-TWiST method can be used in retrospective data is seen in the author's previous publication [8]. Areas under survival curves (AUC) can be retrospectively weighted according to QOL coefficients [5]. The weights assigned to each health state reflect their relative values in terms of quality of life and allow the weights to vary in a sensitivity analysis. The investigator can then combine the results of individual trials in a meta-analysis, using a multivariate regression model, in such a way that an overall sensitivity analysis could be performed easily. Individual patient-level data are not required in order to perform this meta-analysis if the individual Q-TWiST analysis result for each trial is available [9]. The goal of such meta-analysis is to provide an aid to clinical decision-making [5]. Murray et al reviewed aspects of the Q-TWiST method for analyzing data from clinical trials, and extended the method in order to accommodate multiple treatment arms [6].

Cole presented a parametric methodology for performing quality-of-life-adjusted survival analysis by use of multivariate censored survival data [10]. Cole's method represents a generalization of the nonparametric Q-TWiST method. The event times correspond to transitions between states of health that differ in quality of life. Each transition is governed by a competing risks model in which the health states are the competing risks. Overall survival is the sum of the amounts of time spent in each health state. The proposed method consists of defining a quality function that assigns a "score" to a life having given health state transitions. It is a composite measure of both quantity and quality of life. In general, the quality function assigns a low value to a short life with poor quality and a high value to a long life with good quality. The results are useful for simultaneously evaluating treatments in terms of quantity and quality of life.

The Kaplan-Meier product-limit method is used to estimate the mean duration of each health state [10]. These estimates provide the basis for quality-adjusted survival analysis. The survival curves are modelled using Cox's proportional hazards regression. Quality-adjusted survival is estimated with given sets of covariate values. This method permits the profiling of patients. Such results are useful for investigating how prognostic factors affect treatment benefits in terms of quality of life.

A General Health Policy Model is proposed in order to adjust life expectancy for diminished quality of life, which is measured using a standardized instrument known as the Quality of Well-being (QWB) scale [11]. This model expresses the effect of treatment in a unit known as a Well-Year or a Quality Adjusted Life Year (QALY). These units integrate side effects and benefits of treatment by combining into a single value, mortality, morbidity, and duration of each health state.

Using parametric models, another procedure for projecting survival estimates beyond the follow-up limits of a clinical trial has been developed [12]. The method consists of fitting an appropriate parametric model to the tail of a survival curve and then using the estimated model in conjunction with the Kaplan-Meier product-

limit estimate to produce a composite survival-function estimator. This estimator is especially useful whenever a parametric model is more easily fitted to the tail rather than to the entire survival curve. The resulting projected estimates of survival allow inferences to be made about long-term treatment effects in clinical trials. Thus, survival curves can be projected in order to estimate long-term treatment effects on quality-of-life-adjusted survival. This represents an extension of Q-TWiST, which evaluates treatments in terms of both quantity and quality of life. In a standard Q-TWiST analysis, the average time spent in each of a number of health states, which differ in quality of life, is estimated from clinical trial data. The health states are weighted according to the quality of life experienced, and the results are combined to produce an estimate of quality-adjusted survival. Such estimates, however, are restricted to the follow-up limit of the data. The extrapolation methodology provides longer range estimates of Q-TWiST.

The Gompertz extrapolation method is another technique that has been proposed for evaluating survival in cancer patients. The mathematical basis of the Q-TWiST method relies on estimating the area under the survival curve and partitioning this area into three components with different levels of quality of life (presence of toxicity, presence of symptoms, absence of symptoms and toxicity). The Gompertz method utilizes a curve-fitting procedure in order to extrapolate the survival curves to infinity. A published report [13] has described a combined application of the Q-TWiST method and the Gompertz approach called the "extrapolated Q-TWiST" method, which allows one to conduct a cost-utility analysis with the calculation of the cost per QALY gained.

While economic evaluation has often included quality of life within the concept of the QALY, determination of utilities within this concept has been highly variable and the validity of the QALY as a concept has been questioned. At the health policy decision-making level, controversy persists over how much society should pay for expansive new medical interventions and what boundaries for allocation should be established. Much work is still needed in order to improve comparability of HRQL results and to incorporate these results into clinical decision-making involving individual patients, physicians and health policy makers.

What are the difficulties when measuring and interpreting QOL?

What is meaningful to measure? Those responsible for making treatment recommendations – such as clinicians for individual patients, or health policy makers for groups of patients – must weigh the expected benefits of a treatment against its side effects, toxicity, inconvenience, and cost. This process requires a reasonably accurate understanding of the benefits and risks of alternative treatments. Typically, clinicians' enthusiasm for intervention decreases progressively as they see results presented in terms of relative risk reduction, absolute risk reduction, or the number needed to treat (NNT, the reciprocal of the absolute risk reduction) [14].

Single anchor (or an independent measure) [15] generally places great emphasis on a threshold that demarcates trivial from small but important differences: the "minimum important difference" or MID. One popular definition of the MID is " the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's (health care) management" [16].

A naive approach assumes that if the mean difference between treatment and control is less than the MID, the treatment effect would be trivial, and if greater than the MID, the treatment effect would be important. This ignores the distribution of results. For example, assume a MID of 0.5. A mean difference of 0.25 (trivial in a naive interpretation) may be achieved if 25% of the patients experience a benefit of 1.0 and 75% experience no benefit. Such a situation results in an absolute difference of 25% in the proportion of patients achieving improvement and an NNT of 4 [17].

The problem becomes more complex when one considers that patients may vary in the value they place on a particular benefit. Furthermore, the same patient may place a different value on the same benefit at different times depending on the patient's circumstances.

In addition, missing data due to dropout of patients may make interpretation of results difficult. Because the patients who drop out are likely to be experiencing poorer outcomes and thus poorer QOL, the methods of estimating change over time need to be carefully chosen in order to avoid bias. This is especially true when one is estimating changes in groups of patients with very different rates of dropouts [18]. One method is making the assumption that the data are missing at random (MAR) and then using all available observations; the results are obtained using a standard procedure for multiple inputation [19, 20]. Another method is making the assumption that the data are missing not at random (MNAR) and then relying on auxiliary information such as the time to disease progression and death. The rate of decline in QOL depends on the length of survival (specifically, the natural log of survival) [21]. Therefore when one reads an article, one should take careful note of the analytical techniques used for dealing with missing data, which cannot be ignored.

When can Q-TWiST be applied?

Evaluation of adjuvant treatment method

Adjuvant therapy has been studied extensively for every cancer. However, when adjuvant therapy is associated with significant toxic effects, the question whether the benefits of the treatment justify its quality-of-life costs for the individual patient may be raised. Cole reported on the use of the Q-TWiST concept in the individual decision

process about adjuvant treatment for each patient with resected cutaneous melanoma at high risk of recurrence [9]. Overall, the interferon (IFN) alpha 2b group had more quality-of-life-adjusted time than the observation group, regardless of the relative valuations placed on TOX and REL. This gain was significant ($P < 0.05$) for patients who consider TOX to have a high relative value and REL to have a low relative value. In contrast, the quality-adjusted gain for IFN alpha 2b was present though not statistically significant for patients who value TOX about the same as REL. An analysis stratified according to tumor burden indicated that the benefit of IFN alpha 2b was greatest in the node-positive strata. For patients with high-risk melanoma, the optimal treatment for an individual patient depends on the patient's tumor burden and preferences about toxicity and disease relapse.

Another example is the data from a North Central Cancer Treatment Group trial in which 204 patients with poor-prognosis rectal cancer were randomly assigned to receive either post-operative radiation therapy alone or post-operative radiation therapy plus fluorouracil-based chemotherapy [22]. A Q-TWiST analysis was used and took into account freedom from symptomatic disease and from early and late side effects of treatment. The combined therapy reduced the risk of relapse by 34% (95% confidence interval [CI] = 12%-50%; $P = 0.0016$) and reduced the overall death rate by 29% (95% CI =7%-45%; $P = 0.025$) in comparison with adjuvant radiation therapy alone. In the 5 years following assignment to treatment, despite an increase in the amount of time that individuals spent with early and late toxic effects, the Q-TWiST analysis indicated that the combined therapy conferred significantly greater benefit for a wide range of patient preferences about living with the toxicity of treatment or the symptoms of overt disease. Therefore, the use of combined chemotherapy and radiation therapy as an adjuvant to surgery for patients with resectable poor-prognosis rectal cancer is justified because the improved outcome in terms of delayed recurrence and increased survival more than balances the time spent with early and late toxic effects.

Adjuvant chemotherapy for premenopausal breast cancer patients with node-positive disease has been studied in a meta-analysis [23]. Within 6 years of follow-up, the benefits in terms of increased relapse-free and overall survival balanced the costs in terms of acute toxic side effects. This was true even for the extreme case in which a zero value was assigned to all 6 months during which patients might receive adjuvant cyclophosphamide, methotrexate, and 5-flurouracil (CMF) chemotherapy. Within 10 years of follow-up evaluation, treated patients gained an average of 1.5 years of relapse-free survival time, almost 1 year of overall survival time, and 1 year of time without symptoms and toxicity.

An illustration of an adjuvant therapy that is not worthwhile can be drawn from the meta-analysis of quality-adjusted survival based on data from 3920 patients aged 50 years or older with node-positive breast cancer randomly assigned in nine trials that compared combination chemotherapy plus tamoxifen with tamoxifen alone. These nine trials were included in the worldwide overview conducted by the early breast cancer trialists' collaborative group (EBCTCG). The Q-TWiST method was used to provide treatment comparisons incorporating differences in quality of life associated with subjective toxic effects of treatment and with symptoms of disease relapse [24]. Within 7 years of follow-up the modest benefit of increased relapse-free survival (RFS) and overall survival (OS) for patients who received chemotherapy plus tamoxifen just balanced the costs in terms of acute toxic side-effects. Chemotherapy-treated patients gained an average of 5.4 months of RFS and 2 months of OS (neither statistically significant), but had to receive cytotoxic treatment for between 2 and 24 months to achieve these gains. No values of preference weights for time spent undergoing chemotherapy and for time after relapse gave significantly more Q-TWiST with chemotherapy plus tamoxifen than with tamoxifen alone. Thus better selection of chemotherapy regimens, different scheduling of chemotherapy and tamoxifen, and appropriate discriminative use of patient and tumor characteristics should be studied further in order to increase the therapeutic advantage of the combination treatment.

Comparison of different treatments

In prostate cancer, brachytherapy was compared to other treatment modalities by health questionnaires: external RT alone, external RT with brachytherapy, brachytherapy alone, radical prostatectomy [25-27]. Generally, urinary function was better in the brachytherapy group than in the prostatectomy group because of less urinary incontinence in the brachytherapy group. Brachytherapy group patients had more irritative urinary symptoms and worse bowel function than in healthy controls. Sexual function and bother were worse in prostatectomy group patients and in brachytherapy group patients than in healthy controls. Physical function, bodily pain, urinary function, bother and American Urological Association symptom index scores improved with time after brachytherapy. Patients who underwent brachytherapy after external beam radiation performed worse in all general and disease specific HRQOL domains compared with those who did not undergo external beam radiation therapy before brachytherapy. At an average of 7.5 months after treatment, the general HRQOL domains of patients undergoing brachytherapy with and without prior external beam radiation was similar to those of age matched controls, although urinary, bowel and sexual problems were still reported. These problems appeared to improve during the first year after radiation treatment [27].

Evaluation of costs

The QOL concept leads itself to estimations of the costs to the society of various treatments. Such cost estimation was preformed by the National Cancer Institute on the costs and benefits of combined levamisole and fluoro-

uracil as adjuvant treatments for patients with stage III colon cancer [28]. For a typical base-line patient, the calculated cost-effectiveness of such adjuvant treatment is a very favorable $2094 per year of life saved. Using a variety of less favorable assumptions, the calculated cost-effectiveness is still less than $5000 per year of life saved, again this is a favorable value. QOL adjustments have a negligible effect on the cost-effectiveness outcomes in this study. Under a wide range of different reasonable assumptions, adjuvant therapy for stage III colon cancer appears to be a very cost-effective treatment [28].

Another example of evaluation of costs may be obtained from the study of tamoxifen. This is the preferred adjuvant agent in postmenopausal women with breast cancer. Patients with node-positive, estrogen receptor-positive breast cancer have the most to gain from adjuvant tamoxifen therapy. Data from a decision-analysis model indicate that tamoxifen monotherapy has a cost-utility ratio ($US6000 per additional QALY, in 1989 dollars) which is 5 to 6 times lower than that cited as the cost-acceptability cut-off point in the US [29]. On the other hand a combined regimen of adjuvant chemotherapy and tamoxifen has a high incremental cost-utility ratio ($US58,000 per additional QALY, in 1989 dollars) compared with the cost of no adjuvant therapy in postmenopausal women with breast cancer.

What are the potential limitations of Q-TWiST?

Requirement for intelligent cooperative patients

Toxicity information has to be collected from patient-completed diaries so that the actual duration of each adverse event could be determined [30].

Scenarios when Q-TWiST may not apply too well

For patients who never achieve complete remission, the time following disease relapse (REL) should be regarded as zero.

One way of examining compromises between quantity and quality of life is by combining them into a single measure such as QALY. If censoring occurs, then estimation of QALYs presents some difficulties. The Q-TWiST approach is to define a series of health states and to use a 'partitioned' survival analysis in order to calculate the average time in each state, and then weight each state according to its QOL to calculate QALYs. Such health-state models are unhelpful, however, when the transitions between health states are unclear or when these transitions do not adequately reflect variations in QOL

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