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Quality of Life Assessment in the Adjuvant Setting: Is It Relevant?

R. D. Gelber[1,2,4], M. Bonetti[1,2], B. F. Cole[3], S. Gelber[4], and A. Goldhirsch[5] for the International Breast Cancer Study Group*

[1] Department of Biostatistical Science, Dana-Farber Cancer Institute, Boston, MA 02115, USA
[2] Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts, USA
[3] Department of Community and Family Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USA
[4] Frontier Science and Technology Research Foundation, Brookline, Massachusetts, USA
[5] Department of Medical Oncology and Radiation Oncology, European Institute of Oncology, Milan, Italy, and Department of Medical Oncology, Ospedale Civico, Lugano, Switzerland, and International Breast Cancer Study Group, Bern, Switzerland

Introduction

In this paper we address a question concerning quality-of-life assessment in the adjuvant setting: is it relevant? Like the science of quality-of-life evaluation itself, the answer to this question is multifaceted. The most direct answer is yes, but only if there is a well-defined question of importance for patient care. This requires a specific hypothesis and an appropriate methodology to test it.

The assessment of quality of life in cancer patients was first introduced by Karnofsky et al. in 1948. Initial considerations were given to the patients with advanced disease. Clearly the disease process as well as the treatments had an influence on the patients' quality of life in this setting.

The situation in the setting of postsurgical adjuvant therapy is different. Following local treatment, patients are otherwise well as they begin on the road to recovery from the shock of the diagnosis and initial therapy. Patients' adaptation to their situation substantially influences the reported quality of life as the disease-free survival interval increases. A critical question also concerns the impact of adjuvant therapy on quality of life.

One perspective could be that patients simply want to live as long as possible, with only secondary consideration given to the quality of life. This is supported by evidence from patients who would be willing to repeat a previously completed course of toxic adjuvant therapy even if they would gain relatively little additional survival time (Simes et al. 1989; Lindley et al. 1998).

* See Appendix for participants and authors.

However, the current evidence concerning the effectiveness of adjuvant therapies (Early Breast Cancer Trialists' Collaborative Group 1992) is sufficient to routinely prescribe chemotherapy and tamoxifen for all patients, if these therapies could be given free of charge and were not associated with any toxic side effects. Given that cost considerations are not overwhelming factors in determining oncology therapies, one must presume that the concern for side effects is the main reason physicians are reluctant to prescribe chemoendocrine therapy for all patients. Therefore, despite the evidence that survival is of primary concern, aspects of quality of life remain important for treatment decision-making.

In this paper we discuss several reasons why the assessment of quality of life in the adjuvant setting is relevant. We illustrate how quality-of-life considerations can be incorporated into an overall evaluation of the quality and quantity of survival in this setting. The current controversy concerning the worth of adding adjuvant chemotherapy to tamoxifen for postmenopausal patients serves as an example.

What Is Quality-of-Life Assessment?

Quality-of-life assessment has been defined as the measurement of multiple domains including physical, mental, social, psychological dimensions using valid and reliable instruments. There are two approaches to this measurement: health status and utility assessment. The first approach describes patient experience in the major domains of health, while the second approach elicits patient preferences (utilities) for particular health states. Utilities are usually measured on an interval scale from 0.0 (death) to 1.0 (perfect health). These values can be incorporated in quality-adjusted survival and cost-effectiveness analyses.

Reasons for Quality-of-Life Assessment

There are several reasons why one might conduct quality-of-life assessments in clinical trials in the adjuvant setting. An obvious goal is to describe the subjective quality-of-life differences between treatment groups being compared. This is useful to inform patients and clinicians about what to expect with respect to quality-of-life issues. Another reason is to indicate situations in which psychosocial interventions might be useful (Ganz et al. 1998). A third reason is to provide an additional measure with prognostic significance. Coates et al. (1992) found that baseline quality-of-life measures were significant predictors of subsequent survival for patients with metastatic breast cancer. A fourth objective is to document patient adaptation to their diagnosis and treatment. A recent study by the International Breast Cancer Study Group (IBCSG) of node-positive patients reported that the initial decrease in quality of life (during adjuvant chemotherapy) was of lower magnitude than the subsequent improvement in quality of life associated with patient adaptation (Hürny et al. 1996). A fifth reason to incorporate quality-of-life considerations in the adjuvant setting is to assess the tradeoffs between quantity and quality of life. A relevant question is whether the gain in disease-free survival and overall survival balance the decreased quality of life that might be associated with the use of adjuvant therapy following local management of operable breast cancer. A quality-of-life oriented endpoint designed to address this question is the Q-TWiST method. A controversial area of treatment decision-making for which quality-of-life considerations are particularly relevant concerns the worth of chemotherapy added to tamoxifen for postmenopausal patients.

A Complementary Outcome in the Adjuvant Setting (Q-TWiST)

Q-TWiST stands for Quality-adjusted Time Without Symptoms of disease or Toxicity of treatment (Goldhirsch et al. 1989; Glasziou et al. 1990; Gelber et al. 1995). The Q-TWiST method has been previously applied to evaluate treatments for cancer and AIDS, with a number of analyses conducted to compare adjuvant therapies for breast cancer (Gelber et al. 1991, 1992). To use the Q-TWiST method to evaluate adjuvant chemotherapy for breast cancer we start by defining three clinical health states through the course of the disease: TOX is the period of time when chemotherapy patients experience toxicity, REL is the period of time after relapse, and TWiST is the period of relatively good quality of life following the completion of treatment, if given, and before a recurrence. Second, using the data from the clinical trial and Kaplan-Meier plots for disease-free survival (DFS) and overall survival (OS), we partition the overall survival time for each treatment separately into the clinical health states of TOX, TWiST, and REL. This provides estimates of the average amount of time that patients spend in each of these health states. The quality-adjusted survival relative to TWiST (Q-TWiST) is then defined as

$$\text{Q-TWiST} = u_{\text{TOX}} \times \text{TOX} + \text{TWiST} + u_{\text{REL}} \times \text{REL},$$

where u_{TOX} and u_{REL} are weights which can take on values between zero and one, with values of one being equivalent to TWiST (i.e., no loss in quality of life) and values of zero being equivalent to death.

Finally, using a threshold utility plot, treatment groups can be compared with respect to the amount of Q-TWiST they provide for a range of possible values for u_{TOX} and u_{REL}. This plot illustrates the utility values for which each treatment provides more Q-TWiST. In this way, the relative worth of the treatments can be assessed with adjustments for possible influences on quality of life. Note that the average DFS is simply Q-TWiST with the utility for TOX set equal to one and the utility for REL set equal to zero, i.e., treatment toxicity carries no disutility, but postrelapse survival has the same quality

weight as death. Similarly, average OS is obtained from the equation by setting both utilities equal to one. Thus, estimates of the average amounts of DFS and OS are obtained as specific endpoints in a Q-TWiST analysis.

International Breast Cancer Study Group (IBCSG) Trial VII

Trial Design and Analysis of Disease-Free Survival and Overall Survival

Between July 1986 and April 1993, the IBCSG enrolled 1212 postmenopausal patients with node-positive breast cancer into a two-by-two factorial clinical trial evaluating chemoendocrine treatment versus endocrine therapy alone for postmenopausal breast cancer patients. As previously reported (International Breast Cancer Study Group 1997), the patients were randomized to receive one of four adjuvant regimens: tamoxifen alone for 5 years; tamoxifen plus three early single cycles of cyclophosphamide, methotrexate, and fluorouracil (CMF) on months 1, 2, and 3; tamoxifen plus delayed single courses of CMF on months 9, 12, and 15; tamoxifen plus early and delayed CMF on months 1, 2, 3, 9, 12, and 15. Estrogen-receptor (ER) status was known for all patients and was used to stratify the randomization. Tumors with hormone receptor concentrations above or aqual to 10 fmol/mg cytosol protein were considered positive, and those with lower values negative.

The median age was 60 years. Twenty-three percent of patients had primary tumors classified as ER-negative. Twenty-four percent had surgery with breast preservation. Sixty-two percent had fewer than four axillary lymph nodes involved, and the median number of involved nodes was three. Treatment groups were balanced according to age, race, type of primary surgery, number of positive nodes, and tumor size.

Date of relapse was defined as the time when recurrent disease was diagnosed or, if confirmed later, when it was first suspected. DFS was defined as the length of the time from the date of randomization to any relapse (including ipsilateral breast recurrence), the appearance of a second primary cancer (including contralateral breast cancer), or death, whichever occurred first.

In this paper, we focus on the comparison of two of the four treatment arms: tamoxifen plus three early cycles of CMF chemotherapy (tamoxifen plus early CMF) versus tamoxifen alone. At 5 years median follow-up, there was a significant difference in DFS favoring the chemoendocrine therapy (Fig. 1A). The 5-year DFS was 64% for tamoxifen plus early CMF versus 55% for tamoxifen alone ($p = 0.02$).

This difference might be considered enough evidence to recommend that chemotherapy should be added to tamoxifen for postmenopausal, node-positive patients. However, at this analysis there was no difference in OS between the two arms (5-year OS: 74% versus 77%; $p = 0.56$; Fig. 1B).

When the treatments are compared with respect to DFS separately for the prospectively stratified subpopulations of patients defined according to ER status of the primary tumor, the magnitude of effect appears to be larger for

the ER-positive cohort (Fig. 2). It is important to recall that all patients are assigned to receive 5 years of tamoxifen and the 3 cycles of early CMF are given currently with the first three months of tamoxifen. No OS differences were observed even for the ER-positive group that had the best response in terms of DFS.

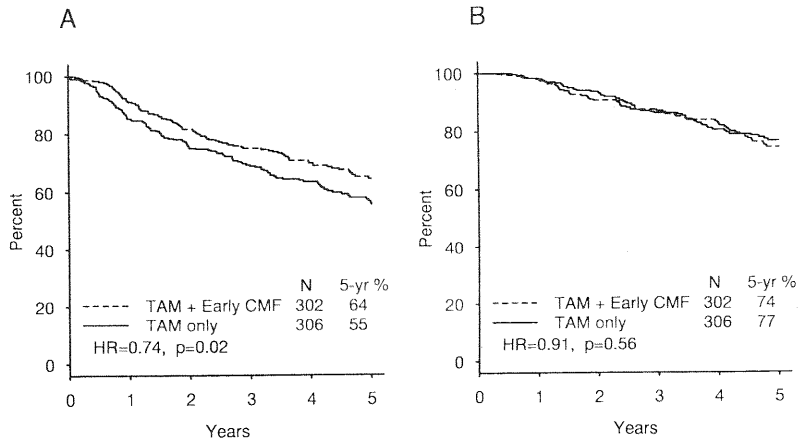

Fig. 1. Disease-free survival (**A**) and overall survival (**B**) according to treatment group (tamoxifen plus early CMF versus tamoxifen alone) for 608 postmenopausal, node-positive patients enrolled in International Breast Cancer Study Group Trial VII. Median follow-up is 5 years *HR*, Hazards ratio

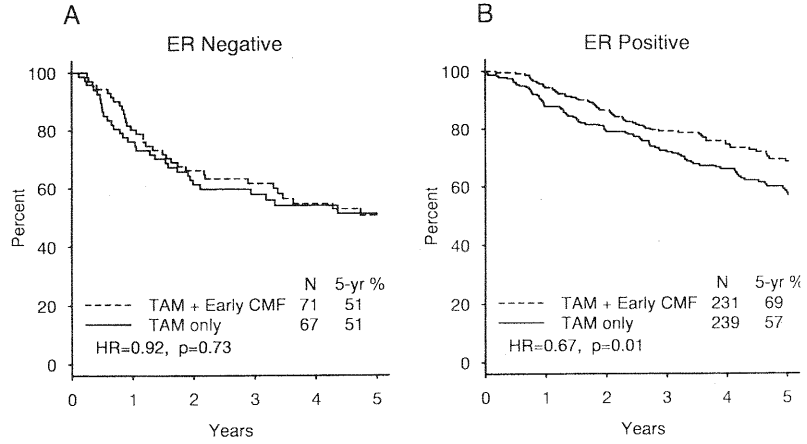

Fig. 2. Disease-free survival for 138 patients with ER-negative tumors (**A**) and for 470 patients with ER-positive tumors (**B**) according to treatment group in IBCSG Trial VII at 5 years' median follow-up. *HR*, Hazards ratio

Because OS gains are minimal at best, the treatment decision can be synthesized based on quality-of-life considerations. In fact, adding chemotherapy is beneficial because it reduces the risk of disease relapse, which has quality-of-life implications. But this benefit needs to be balanced against the reduced quality of life associated with the toxicity of the treatment. The Q-TWiST methodology allows us to explore which of the two arms is to be preferred with respect to such tradeoff between quantity and quality of life for the two treatment groups.

A Q-TWiST Analysis of IBCSG Trial VII at 5 Years of Follow-up

To be conservative in comparing the toxic effects of tamoxifen plus CMF versus tamoxifen alone, no TOX period was assigned to patients who received tamoxifen alone. Instead these patients began in TWiST at the time of randomization. For the TOX health state for patients who received tamoxifen plus CMF, only symptomatic toxicities – those that have an impact on quality of life – were considered. These were primarily nausea/vomiting, alopecia, stomatitis/mucositis, eye disorders, and diarrhea. The entire duration of CMF treatment was included in TOX for any patient who experienced any of these toxicities. An additional 3 months was added for alopecia and weight gain to allow for recovery.

Figure 3 shows the partitioned survival plots for the tamoxifen plus early CMF group and for the tamoxifen alone group separately. The average number of months patients spend in the Q-TWiST health states – the areas between the partitioning Kaplan-Meier curves in Fig. 3 – are shown in Table 1. Patients in the chemoendocrine group spend an average of 3.3 months in TOX, 44.8 months in TWiST, and 5.2 months in REL within 60 months of follow-up. This is compared with zero months, 44.7 months, and 8.9 months for tamoxifen alone, respectively. The average OS time is the sum of the times spent in each of these three health states: 53.3 months for tamoxifen + CMF and 53.6 months for tamoxifen alone, out of a possible 60 months if everyone survived for 5 years.

By varying the values of the weights (utilities), u_{TOX} and u_{REL}, one can explore how the treatment comparison changes according to the values associated to the various health states. We can compare the effect of chemoendocrine therapy relative to tamoxifen alone according to all possible values by looking at the threshold utility plot shown in Fig. 4. The vertical and horizontal axes show the utility coefficient values (ranging from 0 to 1) for TOX and REL, respectively. The solid line in the middle corresponds to utility values for which the Q-TWiST for tamoxifen + CMF is equal to the Q-TWiST for tamoxifen alone, i.e., it shows the set of the threshold values for the utilities. Utility values in the upper left region are those for which tamoxifen + CMF provides more Q-TWiST, while those in the lower right portion are those for which tamoxifen alone provides more Q-TWiST. Utility values in the extreme corners of Fig. 4A are those for which the differences in average

Q-TWiST are statistically significant. The upper left and upper right hand corners of the figure correspond to the utility values for average DFS and OS, respectively.

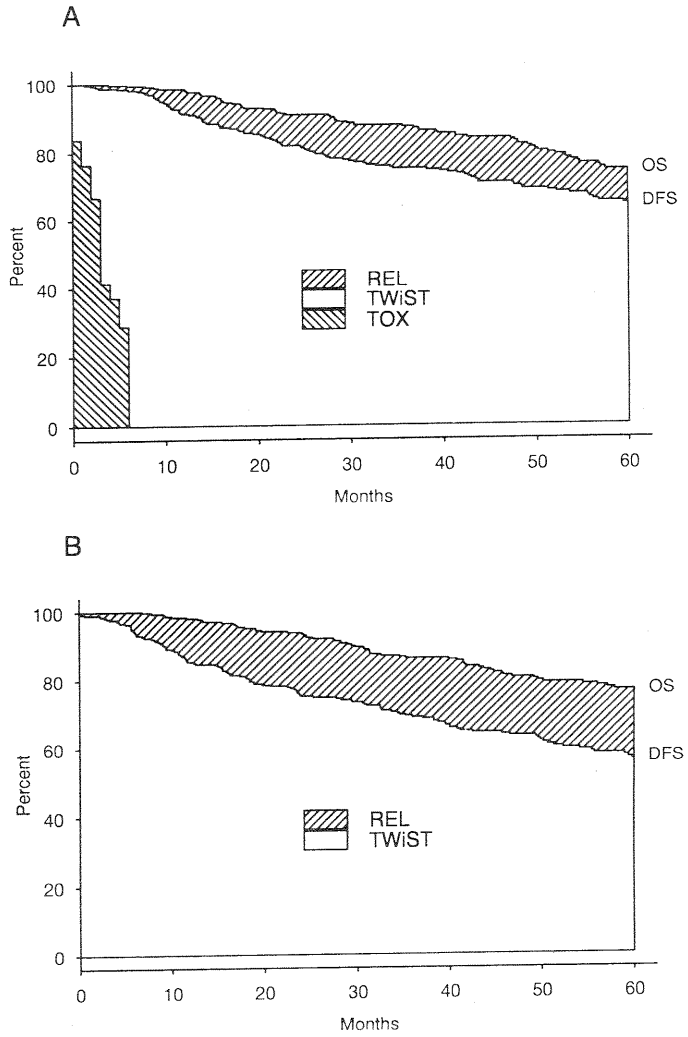

Fig. 3. Partitioned survival plots for tamoxifen plus early CMF (**A**) and for tamoxifen alone (**B**). The areas between the end of toxicity curve, the DFS curve, and the OS curve are the average amounts of time patients spend in the clinical health states TOX, TWiST, and REL within 5 years of follow-up (see Table 1 for values)

The threshold plot in Fig. 4B is the same as that in Fig. 4A, except that in addition to the bold threshold line showing utility values for which the Q-TWiST difference is zero, other lines are included to show utility values for which other specific average increases (decreases) in Q-TWiST occur between the two arms. This plot allows one to identify the amount of Q-TWiST gained or lost as the utility values change within the range of their possible values. The two ×'s shown in Fig. 4B indicate the two scenarios ($u_{TOX}=0.9$, $u_{REL}=0.5$) and ($u_{TOX}=0.5$, $u_{REL}=0.9$) illustrated in Table 1. These correspond to two situations in which the impact of toxicity is either not as severe as or worse than the impact of relapse. For instance, in the first scenario a woman would value time spent after a relapse as half as much as time in good health, while only assigning a slight decrement to time spent in TOX. In the second scenario a woman would value time spent with toxicity as half as much as time in good health, but would only give time after relapse a slight disutility. The use of chemotherapy

Table 1. Average months spent in the Q-TWiST clinical health states (within 60 months of follow-up) for patients assigned to tamoxifen plus early CMF versus tamoxifen alone in IBCSG Trial VII

	Tamoxifen +early CMF	Tamoxifen alone	Months gained[a]	95% Confidence interval
For all 608 patients				
TOX	3.3	0.0	3.3	(3.1, 3.6)
TWiST	44.8	44.7	0.1	(−3.1, 3.3)
REL	5.2	8.9	−3.7	(−5.8, −1.6)
OS	53.3	53.6	−0.3	(−2.5, 2.0)
DFS	48.1	44.7	3.4	(0.2, 6.7)
Q-TWiST				
($u_{TOX}=0.9$; $u_{REL}=0.5$)	50.4	49.2	1.2	(−1.3, 3.8)
($u_{TOX}=0.5$; $u_{REL}=0.9$)	51.1	52.7	−1.6	(−3.9, 0.7)
For 138 patients with ER-negative tumors				
TOX	3.2	0.0	3.2	(2.7, 3.7)
TWiST	37.4	39.0	−1.6	(−9.2, 6.1)
REL	6.3	8.3	−2.0	(−6.2, 2.2)
OS	46.9	47.3	−0.4	(−6.5, 5.9)
DFS	40.6	39.0	1.6	(−6.0, 9.3)
Q-TWiST				
($u_{TOX}=0.9$; $u_{REL}=0.5$)	43.4	43.1	0.3	(−6.3, 7.0)
($u_{TOX}=0.5$; $u_{REL}=0.9$)	44.7	46.5	−1.8	(−7.9, 4.5)
For 470 patients with ER-positive tumors				
TOX	3.4	0.0	3.4	(3.1, 3.7)
TWiST	47.1	46.4	0.7	(−2.6, 4.0)
REL	4.9	9.1	−4.2	(−6.6, −1.8)
OS	55.4	55.5	−0.1	(−2.3, 2.0)
DFS	50.5	46.4	4.1	(0.8, 7.4)
Q-TWiST				
($u_{TOX}=0.9$; $u_{REL}=0.5$)	52.6	50.9	1.7	(−0.9, 4.1)
($u_{TOX}=0.5$; $u_{REL}=0.9$)	53.2	54.6	− 1.4	(−3.6, 0.7)

[a] Months in the tamoxifen plus early CMF group minus months in the tamoxifen alone group.

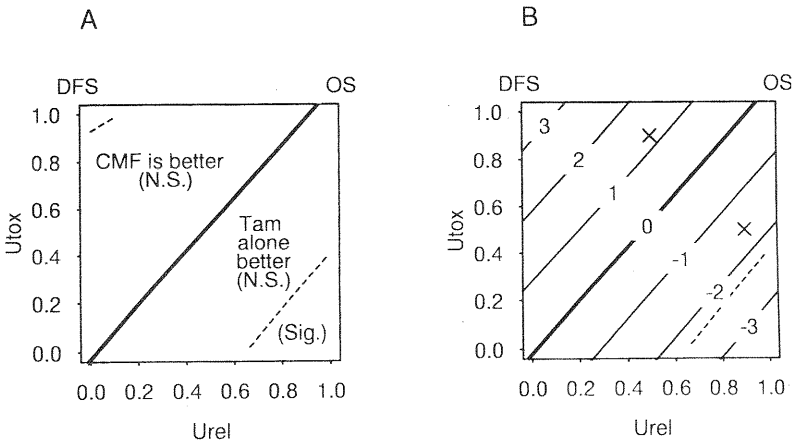

Fig. 4. Threshold utility plots comparing the amount of Q-TWiST gained for tamoxifen plus early CMF versus tamoxifen alone. Panel **A** shows the utility values for which one treatment is better than the other, with some differences reaching statistical significance (e.g., average DFS as shown in the *upper left* corner). Panel **B** shows the number of months of Q-TWiST gained within 5 years of follow-up for different pairs of utility values. The x-marks on panel B indicate the two scenarios described in the text

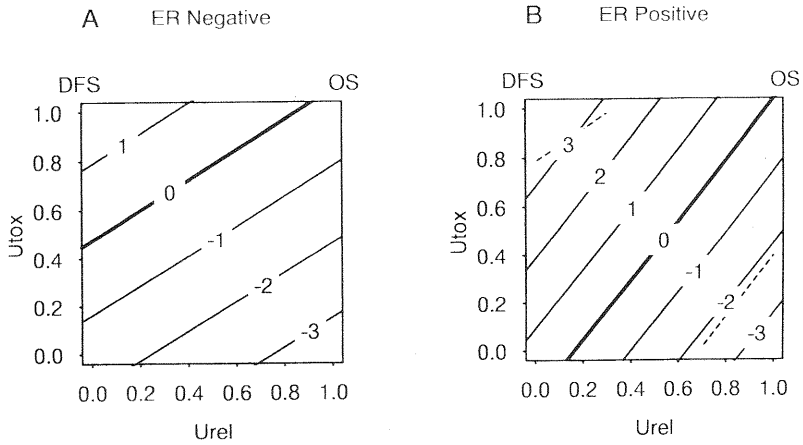

Fig. 5. Threshold utility plots comparing tamoxifen plus early CMF versus tamoxifen alone for patients with ER-negative tumors (**A**) and for patients with ER-positive tumors (**B**)

produced a gain of 1.2 months of Q-TWiST in the first scenario, and it was associated with a loss of 1.6 months of Q-TWiST in the second. Thus, the first patient described above should consider having chemoendocrine therapy, while the second might prefer tamoxifen alone.

The Q-TWiST analysis can be repeated separately for the ER-negative and ER-positive subgroups (see Table 1). Figure 5 shows the two corresponding threshold utility plots for these analyses. There is a wider range of utility coefficients for which adding chemotherapy is preferred for the ER-positive cohort than for the ER-negative group. In addition, the amount of time gained is larger for the ER-positive group.

How Do We Get the Utilities?

As with the majority of other Q-TWiST analyses conducted to date, the analysis reported above is summarized using the threshold utility plots without relying on specific values for the utility coefficients. The analysis highlights the extent to which different utility values between zero and 1 might influence the choice of therapy based on the amount of Q-TWiST gained for one treatment compared with another. Defining appropriate utility values to reflect patient preferences is complicated by adaptation of patients to their condition over time and differences in perspective concerning whose utilities to use.

Utilities measure the value of health states using standards such as time, money, or risk of death. There are four methods that can be used to obtain utility assessments from patients. The standard gamble and the time-tradeoff methods involve an iterative series of questions, which must be administered to the patient by an interviewer or conducted with the aid of a computer. The third method, the rating scale, is a single-item global health question presented on a 0 to 100 scale. The final method for eliciting utilities is based on the principles of multiattribute utility theory; it maintains the ease of administration of a traditional health status questionnaire, while also producing utility estimates appropriate for use in clinical and economic decision-making (Torrance et al. 1995). This system consists of two components: a simple patient-completed questionnaire and a formula that assigns a utility to each patient's set of responses to that questionnaire. Examples of multiattribute systems are the McMaster Health Utility Index (Feeny et al. 1995), the Euroqol (EuroQol Group 1990), and the Q-tility Index (Weeks et al. 1994). Several ongoing clinical trials that include a prospectively planned Q-TWiST analysis are collecting patient-derived utility values obtained from multiattribute utility systems.

Discussion

Assessment of quality of life can be very relevant for treatment decision-making in the adjuvant setting. The assessments must be made only when there are clear hypotheses to be tested and a well-defined methodology to evaluate the results. In this paper, we have described several specific purposes for such assessments. In addition, we presented an application of the Q-TWiST method to address questions involving tradeoffs between quality and quantity of life. We reported results from an analysis of the IBCSG Trial VII comparing 3 months of CMF chemotherapy plus tamoxifen versus tamoxifen alone for postmenopausal patients with node-positive breast cancer. This analysis indicated that the choice of whether or not to add chemotherapy should depend upon the relative utility weights or patient preferences assigned to periods of toxicity and periods of postrelapse survival.

In addition to the IBCSG trial, the National Surgical Adjuvant Breast and Bowel Project (NSABP) Trial B-20 recently reported a significant DFS and OS advantage for chemotherapy (MF or CMF for 6 months) given with tamoxifen compared with tamoxifen alone for patients with node-negative, estrogen-receptor-positive breast cancer (Fisher et al. 1997). The effects of chemotherapy were positive, but not statistically significant for patients aged 50 years of age or older. It would be interesting to conduct a Q-TWiST analysis to determine the extent to which patient preference might influence selection of 6 months of chemotherapy based on the B-20 data, which yielded 85% 5-year DFS and 94% 5-year OS for the tamoxifen alone group.

Some recently reported studies have demonstrated improved efficacy in terms of DFS and OS for more intensive (and more toxic) chemotherapy regimens compared with standard regimens. For example, Levine et al. (1998) reported a Canadian study showing that cyclophosphamide, 4-epidoxorubicin, and 5-fluorouracil (CEF) given in a CMF-like schedule (4-epidoxorubicin, and 5-fluorouracil given on days 1 and 8 every 4 weeks and cyclophosphamide given orally on days 1-14) was more effective than a "classical" CMF regimen. CEF had to be given together with antibiotics, which successfully reduced the incidence of febrile neutropenia. An ECOG/Intergroup trial showed that an intensive 16-week regimen provided more efficacy than standard CAF (Fetting et al. 1995), and a CALGB/Intergroup trial showed that adding taxol after completion of CA improved efficacy compared with CA alone (Henderson et al. 1998). For each of these randomized comparisons, a quality-of-life oriented question can be asked concerning the tradeoff between improved disease control on one hand and decreased quality of life due to treatment intensity and duration on the other. By summarizing treatment outcomes in terms of the amounts of time patients spend in the relevant clinical health states, the Q-TWiST approach provides a proper assessment of tradeoffs with respect to quality-of-life implications of more intensive therapies. For adjuvant therapy decision-making, quality-of-life assessment and evaluation of tradeoffs are indeed relevant.

Summary

In the breast cancer adjuvant therapy setting, the critical issue to consider in treatment decision-making is the tradeoff between quality and quantity of life. The toxicities of adjuvant therapies, both acute and late, must be balanced against the potential benefits of delayed recurrence and improved survival. The question should be addressed concerning when quality-of-life assessment is relevant in the adjuvant setting. Such assessments can inform patients about what to expect from their treatment, describe quality-of-life differences between treatments, provide an additional baseline measure with potential prognostic significance, inform clinicians about their patients' experiences with toxicities, indicate situations in which psychosocial interventions might be useful, and document patient adaptation to diagnosis and treatment. The relevance of quality-of-life assessment in the adjuvant setting can be illustrated by investigating one of the most controversial questions of today: When should chemotherapy be added to tamoxifen for postmenopausal patients? Data from the International Breast Cancer Study Group (IBCSG) Trial VII showed that adding 3 months of CMF (cyclophosphamide 100 mg/m^2 orally days 1-14; methotrexate 40 mg/m^2 i.v. days 1, 8; fluorouracil 600 mg/m^2 i.v. days 1, 8; repeated every 28 days) to tamoxifen significantly improved disease-free survival compared with tamoxifen alone. The Quality-adjusted Time Without Symptoms of disease or Toxicity of treatment (Q-TWiST) method was used to compare the adjuvant therapies with respect to quality-adjusted survival. The analysis indicated that the decision to use adjuvant chemotherapy in this setting should be based on patient preferences concerning the relative importance of treatment toxicity versus disease recurrence.

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Appendix

International Breast Cancer Study Group Participants and Authors, Trials VI-IX

Coordinating Center, Bern, Switzerland	M. Castiglione, A. Goldhirsch (Studies Coordinators), K. Geiser, A. Berlinger, G. Egli (Data Management), R. Maibach, R. Pedowski
Statistical Center, Harvard School of Public Health and Dana-Farber Cancer Institute, Boston, MA, USA	R. Gelber (Group Statistician), K. Price, H. Peterson, M. Zelen, S. Gelber, A. O'Neill
Quality of Life Office, Bern, Switzerland	J. Bernhard, C. Hürny, H. Gusset
Pathology Office, Institute of Cancer Research, Royal Cancer Hospital, Sutton, UK	B. Gusterson, R. Bettelheim, R. Reed
Data Management Center, Frontier Science & Technology Research Foundation, Amherst, NY, USA	M. Isley, R. Hinkle
Auckland Breast Cancer Study Group, Auckland, New Zealand	R.G. Kay, V.J. Harvey, C.S. Benjamin, P. Thompson, A. Bierre, M. Miller, B. Hochstein, A. Lethaby, J. Webber
Centro di Riferimento Oncologico Aviano, Italy	D. Crivellari, S. Monfardini, E. Galligioni, A. Veronesi, A. Buonadonna, S. Massarut, C. Rossi, E. Candiani, A. Carbone, R. Volpe, M. Roncadin, M. Arcicasa, G.F. Santini, F. Villalta, F. Coran, S. Morassut
Spedali Civili & Fondazione Beretta, Brescia, Italy	G. Marini, E. Simoncini, P. Marpicati, A. Barni, P. Grigolato, L. Morassi
Groote Schuur Hospital, Cape Town, Republic of South Africa	D.M. Dent, A. Gudgeon, E. Murray, P. Steynor, J. Toop
West Swedish Breast Cancer Study Group, Göteborg, Sweden	C.M. Rudenstam, A. Wallgren, S. Ottosson-Lönn, R. Hultborn, G. Colldahl-Jäderström, E. Cahlin, J. Mattsson, S. Holmberg, S. Jansson, L. Ivarsson, O. Ruusvik, L.G. Niklasson, S. Dahlin, G. Karlsson, B. Lindberg, A. Sundbäck, S. Bergegårdh, H. Salander, C. Andersson, M. Heideman,

	Y. Hessman, O. Nelzén, G. Claes, T. Ramhult, J.H. Svensson, P. Liedberg
General Hospital, Gorizia, Italy	S. Foladore, L. Foghin, G. Pamich, C. Bianchi, B. Marino, A. Murgia, V. Milan
Sandton Oncology Center, Johannesburg, Republic of South Africa	D. Vorobiof, M. Chasen, G. Fotheringham, G. de Muelenaere, B. Skudowitz, C. Mohammed, A. Rosengarten
The Institute of Oncology, Ljubljana, Slovenia	J. Lindtner, D. Erzen, E. Majdic, B. Stabuc, A. Plesnicar, R. Golouh, J. Lamovec, J. Jancar, I. Vrhoved, M. Kramberger
Madrid Breast Cancer Group, Madrid, Spain	H. Cortés-Funes, D. Mendiola, C. Gravalos, Colomer, M. Mendez, F. Cruz Vigo, P. Miranda, A. Sierra, F. Martinez-Tello, A. Garzon, S. Alonso, A. Ferrero, C. Vargas
Anti-Cancer Council of Victoria, Melbourne, Australia	J. Collins, P. Gregory, P. Kitchen, S. Hart, S. Neil, M. Henderson, I. Russell, T. Gale, M. Pitcher, R. Snyder, R. McLennan, M. Schwarz, I. Burns, M. Green, R. Basser, R. Drummond, A. Rodger, G. Richardson, J. McKendrick, M. Chipman
Royal Adelaide Hospital, Adelaide, Australia	I. Olver, A. Robertson, P. Gill, M.L. Carter, P. Malycha, E. Yeoh, G. Ward, A.S.Y. Leong, J. Lommax-Smith, D. Hoosfall, R. D'Angelo
Sir Charles Gairdner Hospital, Nedlands, Western Australia	M. Byrne, G. van Hazel, J. Dewar, M. Buck, D. Ingram, G. Sterret
Australian New Zealand Breast Cancer Trials Group (ANZ BCTG), Mater Hospital, Waratah, Newcastle, Australia	J.F. Forbes, J. Stewart, D. Jackson, R. Gourlay, J. Bishop, C. Flower, A. Wilson, S. Cox, S. Ackland, A. Bonaventura, C. Hamilton, J. Denham, P. O'Brien, M. Back, S. Brae, A. Price, Muragasu, H. Foster, D. Clarke, R. Sillar, V. Clarke, S. Brew
University of Sydney, Dubbo Base Hospital and Royal Prince Alfred Hospital, Sydney, Australia	M.H.N. Tattersall, A. Coates, F. Niesche, R. West, S. Renwick, J. Donovan, P. Duval, R. J. Simes, A. Ng, D. Glenn, R.A. North, J. Beith, RG. O'Connor, M. Rice, G. Stevens,

	J. Grassby, S. Pendlebury, C. McLeod, M. Boyer, A. Sullivan, J. Hobbs
European Institute of Oncology, Milan, Italy	A. Goldhirsch, G. Martinelli, U. Veronesi, A. Luini, R. Orecchia, G. Viale, M. Colleoni, F. Nolè, F. Peccatori, A. Costa, S. Zurrida, P. Veronesi, V. Sacchini, V. Gallimberti
Ospedale Infermi, Rimini, Italy	A. Ravaioli, D. Tassinari, G. Oliverio, F. Barbanti, P. Rinaldi, E. Pini, G. Drudi
Ospedale S. Eugenio, Rome, Italy	M. Antimi, M. Minelli, V. Bellini, R. Porzio, E. Pernazza, G. Santeusanio, L.G. Spagnoli
Ospedale S. Bortolo, Vicenza, Italy	M. Magazu, V. Fosser, P. Morandi, G. Scalco, M. Balli, M. Gion, S. Meli, G. Torsello
Toronto Sunnybrook Regional Cancer Centre, Toronto, Canada	K. Pritchard, D. Sutherland, C. Sawka, G. Taylor, R. Choo, C. Catzavelos, K. Roche
SAKK (Swiss Group for Clinical Cancer Research):	
– Inselspital, Bern	M.F. Fey, E. Dreher, H. Schneider, S. Aebi, K. Buser, J. Ludin, G. Beck, H. Bürgi, A. Haenel, J.M. Lüthi, R. Markwalder, H.J. Altermatt, M. Nandedkar
– Kantonsspital, St. Gallen	H.J. Senn, B. Thürlimann, Ch. Oehlschlegel, G. Ries, M. Töpfer, U. Lorenz, O. Schiltknecht, B. Späti
– Ospedale San Giovanni, Bellinzona	F. Cavalli, O. Pagani, H. Neuenschwander, W. Müller, L. Bronz, C. Sessa, G. Martinelli, M. Ghielmini, P. Luscieti, E. Passega, T. Rusca, P. Rey, J. Bernier, S. Martinoli, E. Pedrinis, G. Losa, T. Gyr, L. Leidi, G. Pastorelli, A. Goldhirsch
– Kantonsspital, Basel	R. Hermann, J.F. Harder, O. Köchli, U. Eppenberger, J. Torhorst
– Hôpital des Cadolles, Neuchâtel	D. Piguet, P. Siegenthaler, V. Barrelet, R.P. Baumann
– Kantonsspital, Luzern	R. Joss
– Kantonsspital, Zürich	B. Pestalozzi, C. Sauter, V. Engeler, U. Haller, U. Metzger, P. Huguenin, R. Caduff

– Centre Hôpitalier Universitaire, Lausanne	L. Perey, S. Leyvraz, P. Anani, F. Gomez, D. Wellman, G. Chapuis, P. De Grandi, P. Reymond, M. Gillet, J.F. Delaloye
– Hôpital Cantonal, Geneva	P. Alberto, H. Bonnefoi, P. Schäfer, F. Krauer, M. Forni, M. Aapro, R. Egeli, R. Megevand, E. Jacot-des-Combes, A. Schindler, B. Borisch, S. Diebold
– Kantonsspital Graubünden, Chur	F. Egli, P. Forrer, A. Willi, R. Steiner, J. Allemann, T. Rüedi, A. Leutenegger, U. Dalla Torre
Swiss Cancer League, Bern, Switzerland	U. Metzger, W. Weber, G. Noseda

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