## Introduction

The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System [2] includes several patient-completed questionnaires that contain more than 250 questions. It was developed to measure health-related quality of life (HRQOL) of patients with cancer and other chronic illnesses. The FACIT has been translated into more than 40 languages.

The Functional Assessment of Cancer Therapy-General scale (FACT-G) [2] is the core questionnaire of the FACIT system. It contains four subscales to assess major HRQOL domains such as physical, social, emotional, and functional concerns of patients with specific health problems. The Japanese version of the FACT-G was developed and validated by Fumimoto et al. [6] in 2001.

The FACT-Anemia scale (FACT-An) [1] consists of FACT-G plus Anemia subscale to assess anemia-related HRQOL concerns and was developed in 1994. The Japanese version of the FACT-An was validated by Yoshimura et al. [10] in 2004.

To validate FACT-An, Yoshimura et al. examined test–retest reliability, factorial validity, construct validity, and internal consistency. However, the design of the study was cross-sectional; clinical validity was defined only with correlations to performance status ratings: the important clinical indicator for anemia, hemoglobin level, was not used, and the sample included only lung cancer patients. In this study, we examined the clinical validity of the Japanese version of the FACT-An in relation to hemoglobin level (1) among a larger group of patients, (2) receiving various treatments for a range of cancers, and (3) at two time points of 3 months apart.

## Materials and methods

### The Functional Assessment of Cancer Therapy-Anemia scale (FACT-An)

The FACT-An is an extension of the FACT-G questionnaire. The FACT-G consists of a core set of 27 generic QOL questions. The core questions measure four major aspects of QOL: physical well-being (PWB, seven items), social–family well-being (SWB, seven items), emotional well-being (EWB, six items), and functional well-being (FWB, seven items). The FACT-An consists of these four FACT-G subscales and a 20-item FACT Anemia subscale. Of the 20-item FACT Anemia subscale items, 13 relate to fatigue [1]. Each FACT-An item is scored on a 0-to-4-point Likert scale, giving a range of scores from 0 to 188. Higher scores indicate better HRQOL.

The FACT Trial Outcome Index-Anemia (FACT TOI-An) is a scale that includes the PWB subscale and the FWB subscale, from the FACT-G, and the Anemia subscale. This scale was developed exclusively for clinical trials of anticancer drugs, in which physical and functional domains and symptoms were thought to be more important than emotional and social domains. Total scores of FACT TOI-An range from 0 to 136. In addition to testing the validity of the FACT-An questionnaire, we determined which of the scales (FACT-G, FACT-An, Anemia subscale, or FACT TOI-An) was the most sensitive to anemia as defined by hemoglobin levels.

### Patients

Patients were recruited from eight hospitals throughout Japan. All of them spoke Japanese and were asked to complete the questionnaire at baseline and at 3 months.

The study included patients who were receiving, or who were planning, to receive cancer treatment. Treatments included chemotherapy, hormonal therapy, radiation therapy, or a combination. Patients who had surgical treatment were not included, but patients who received adjuvant treatments 3 months after the surgery were included. Epoetin alpha was not used for these patients as the drug is not approved in Japan.

Other inclusion criteria were: age older than 20 years old, an Eastern Cooperative Oncology Group Performance Status of 0 to 2, creatinine level $\leq$2.0 mg/dl, and expected survival of 3 months or more. Patients who had hemorrhagic lesions or nontreatment-related anemia, such as iron deficiency anemia or hemolysis, were excluded. Patients who were unable to participate in the study because of unfavorable health conditions, as suggested by the physician, were also excluded.

Demographic, disease, and treatment information were gathered from clinical records. All patients gave written informed consent after receiving a thorough verbal explanation of the protocol. The study conformed to the principles in the Declaration of Helsinki and was approved by the ethics committee of each institution.

### Statistical methods

Data collection, management, and monitoring were coordinated by the Comprehensive Support Project for Oncological Research (CSPOR) data center of The Japan Clinical Research Support Unit (J-CRSU).

To examine the clinical validity of the HRQOL questionnaire, FACT-An scores were correlated with patients' hemoglobin measurements at baseline and at 3 months using Pearson's correlation coefficient. We also analyzed the data by FACT-G, Anemia subscale, and FACT TOI-An scores.

Internal consistency was determined by Cronbach's alpha coefficient. Factor analysis using Promax rotation was used to confirm the subscale structure of the FACT-An scale.

**Table 1** Baseline demographic and clinical characteristics of 227 cancer patients participating in a validation study of the Functional Assessment of Cancer Therapy-Anemia scale

| Characteristic | Mean±SD (range) | Patients | |
|---|---|---|---|
| | | *n* | Percentage |
| Age, years | 59.0±12.1 (27 to 84) | | |
| Sex | | | |
| Male | | 126 | 55.5 |
| Female | | 101 | 44.5 |
| Cancer-related complications | | | |
| Yes | | 77 | 33.9 |
| No | | 150 | 66.1 |
| Cancer type | | | |
| Lung | | 98 | 43.2 |
| Breast | | 60 | 26.4 |
| Stomach | | 3 | 1.3 |
| Colon | | 4 | 1.8 |
| Liver, bile, pancreas | | 3 | 1.3 |
| Lymphoid gland | | 32 | 14.1 |
| Leukemia | | 24 | 10.6 |
| Others | | 3 | 1.3 |
| Hemoglobin levels (g/dl) | 11.4±1.8 (4.5 to 15.6) | | |
| <11.0 | | 92 | 40.5 |
| <8 | | 13 | 5.7 |
| 8–9 | | 6 | 2.6 |
| 9–10 | | 25 | 11.0 |
| 10–11 | | 48 | 21.1 |
| ≥11.0 | | 135 | 59.5 |
| 11–12 | | 38 | 16.7 |
| 12–13 | | 60 | 26.4 |
| >13 | | 37 | 16.3 |

Severe anemia was defined as a hemoglobin level <11.0 g/dl [5]. We tested the ability of the eight FACT scales to discriminate between patients with lower (Hb <11.0 g/dl) and higher (Hb ≥11.0 g/dl) hemoglobin levels using Student's *t* test. First, the ability of FACT scales to discriminate patients between these two ranges of anemia was examined in the two assessment points. Next, simple regression analysis was used to determine the relationship between changes in QOL scores and changes in hemoglobin levels over 3 months. Linearity was assessed with an analysis of residuals.

All missing values were treated according to the FACT scoring instructions. All analyses were performed with SAS for Windows, version 8.02; (SAS Institute, Cary, NC, USA). *P* values less than 0.05 were considered to be statistically significant unless indicated otherwise.

## Results

Between October 2003 and May 2004, 227 patients were recruited. At baseline, the rate of patients completing the questionnaire was 99.1% (225/227). At 3 months, 18 had dropped out. Reasons included voluntary withdrawal ($n$=2), transfer to another hospital ($n$=2), death ($n$=10), and others ($n$=4). Of the remaining 209 patients, 204 (97.0%) completed the questionnaires. For each item in the questionnaire, the frequency of missing data was less than 2% at baseline and less than 4% at 3 months, except for item 16 of FACT-G scale which asked about sexual satisfaction; this question went unanswered in 51.5 and 54.1% of the questionnaires at baseline and at 3 months, respectively. Demographic data and HRQOL scores did not show any difference except for cancer type and treatment method.

The sample represented a broad spectrum of cancer diagnoses (Table 1). About 40% of the patients had the lower range of hemoglobin level (Hb<11.0 g/dl) at baseline. The mean (SD) hemoglobin levels at baseline (11.4±1.8) and at 3 months (11.4±1.7) were not different. However, at 3 months, values were improved in 41% of patients ($n$=86), unchanged in 21% ($n$=43), and worse in 38% ($n$=80).

### Validation

FACT-An scores were correlated with hemoglobin levels both at baseline ($r$=0.24, 95% CI=0.10 to 0.36; $n$=225) and at 3 months ($r$=0. 24, 95% CI=0.10 to 0. 36; $n$=204).

All the subscales of the FACT-An had high internal consistency. At baseline, Cronbach's coefficient alpha was between 0.79 and 0.84 for each domain of the FACT-G and

**Table 2** Validation characteristics for the HRQOL scales

| Scale | Baseline scores ($n$=227) | | | 3-Month scores ($n$=209) | | |
|---|---|---|---|---|---|---|
| | Mean | SD | Cronbach's alpha | Mean | SD | Cronbach's alpha |
| FACT-G (27 items); scores range from 0 (low) to 108 (high) | 70.8 | 14.7 | 0.86 | 70.1 | 15.1 | 0.87 |
| FACT-An (47 items); scores range from 0 (low) to 188 (high) | 126.3 | 25.0 | 0.92 | 125.6 | 26.5 | 0.93 |
| Anemia subscale (20 items); scores range from 0 (low) to 80 (high) | 55.6 | 12.9 | 0.90 | 55.4 | 14.0 | 0.92 |
| FACT TOI-An (34 items); scores range from 0 (low) to 136 (high) | 91.8 | 21.3 | 0.93 | 91.5 | 22.9 | 0.94 |

*HRQOL* Health-related quality of life, *FACT-G* Functional Assessment of Cancer Therapy-General, *FACT-An* Functional Assessment of Cancer Therapy-Anemia, *FACT TOI-An* Trial Outcome Index-Anemia

**Table 3** Ability of HRQOL scales to discriminate between patients with lower (Hb <11.0 g/dl) and higher (Hb ≥11.0 g/dl) hemoglobin levels at baseline

| Scale | Degree of anemia at baseline | | | | *F* | *P* |
|---|---|---|---|---|---|---|
| | Hb <11.0 g/dl | | Hb ≥11.0 g/dl | | | |
| | n | mean (SD) | n | mean (SD) | | |
| FACT-G | 91 | 67.5 (14.4) | 134 | 73.0 (14.6) | 7.92 | 0.005 |
| FACT-An | 91 | 120.2 (24.9) | 134 | 130.5 (24.3) | 9.39 | 0.003 |
| Anemia subscale | 92 | 52.6 (13.3 | 135 | 37.2 (9.2) | 8.51 | 0.004 |
| FACT TOI-An | 92 | 86.0 (21.6) | 135 | 95.7 (20.2) | 11.92 | <0.001 |

*HRQOL* Health-related quality of life, *FACT-G* Functional Assessment of Cancer Therapy-General, *FACT-An* Functional Assessment of Cancer Therapy-Anemia, *FACT TOI-An* Trial Outcome Index-Anemia

0.90 for the Anemia subscale. At 3 months, Cronbach's coefficient alpha was between 0.82 and 0.86 for each FACT-G domain and 0.92 for the Anemia subscale (Table 2). These results indicate that items in each domain or scale measured a unidimensional concept. Factor analysis also showed good factor validity for FACT-An (data not shown.)

All HRQOL subscales used in this study differentiated anemia appropriately, where higher QOL scores were associated with higher hemoglobin levels (Tables 3 and 4). FACT TOI-An discriminated anemia most efficiently both at baseline and at 3 months.

Simple regression analyses showed that changes in scale scores over 3 months correlated linearly and positively with changes in hemoglobin level. The results suggest that these HRQOL scales are sensitive to changes over time (Table 5).

## Discussion

Anemia is an important concern when treating cancer patients. Interventions to reverse fatigue and anemia using growth factors, such as epoetin alfa, have shown benefits in Western countries [4, 5, 7, 9]. These interventions have not been studied in Japanese patients, and these drugs have not been approved in Japan. Therefore, we did not use any of these drugs for our study. Developing a reliable and valid scale to properly measure HRQOL in Japanese cancer patients with anemia is important to conducting such studies.

We validated the FACT-An in cancer patients by its feasibility, reliability, and factor validity and revealed the clinical usefulness of FACT-An in discriminating the severity of anemia as measured by hemoglobin levels. Our results showed that the FACT-An and the Anemia subscale in Japanese version were clinically valid instruments for measuring the subjective symptoms of anemia and other general HRQOL aspects among patients with different cancers.

A previous validation study [1] defined anemia with different hemoglobin levels. We set 11 g/dl as the cutoff point for lower or higher levels of anemia in cancer patients. The greatest change in HRQOL scores occurred in patients with hemoglobin levels between 11.0 and 13.0 g/dl. Crawford et al. [5] showed that when Linear Analog Scale Assessment was plotted against hemoglobin level on a sigmoid curve, the steepest slope of HRQOL curve was seen at around 11.0 g/dl. Moreover, we consider 11.0 g/dl a clinically valid value to define anemia, especially when examining both men and women together.

When conducting the current study, the purpose and method of this study were explained by nurses and clinical staff. With that, we achieved excellent completion rate for almost all items (more than 98%). On the other hand, item

**Table 4** Ability of HRQOL scales to discriminate between patients with lower (Hb <11.0 g/dl) and higher (Hb ≥11.0 g/dl) hemoglobin levels at 3 months

| Scale | Degree of anemia at 3 months | | | | *F* | P |
|---|---|---|---|---|---|---|
| | Hb <11.0 g/dl (*n*=92 patients) | | Hb ≥11.0 g/dl (*n*=135 patients) | | | |
| | *n* | Mean (SD) | *n* | Mean (SD) | | |
| FACT-G | 72 | 67.8 (14.6) | 132 | 77.3 (15.3) | 2.45 | 0.119 |
| FACT-An | 72 | 120.1 (25.2) | 132 | 128.6 (26.9) | 4.85 | 0.030 |
| Anemia subscale | 75 | 52.1 (13.8) | 132 | 37.3 (10.3) | 6.95 | 0.009 |
| FACT TOI-An | 75 | 85.1 (22.4) | 132 | 95.0 (22.5) | 9.28 | 0.003 |

*HRQOL* Health-related quality of life, *FACT-G* Functional Assessment of Cancer Therapy-General, *FACT-An* Functional Assessment of Cancer Therapy-Anemia, *FACT TOI-An* Trial Outcome Index-Anemia

**Table 5** Regression coefficients for predicting changes in HRQOL scores from changes in hemoglobin levels over 3 months

| Scale | Regression coefficient | 95% CI | $r^2$ | $P$ |
|---|---|---|---|---|
| FACT-G | 0.18 | 0.05–0.31 | 0.0340 | 0.007 |
| FACT-An | 0.23 | 0.09–0.35 | 0.0517 | 0.002 |
| Anemia subscale | 0.22 | 0.08–0.34 | 0.0472 | 0.002 |
| FACT TOI-An | 0.22 | 0.09–0.34 | 0.0479 | 0.004 |

*HRQOL* Health-related quality of life, *FACT-G* Functional Assessment of Cancer Therapy-General, *FACT-An* Functional Assessment of Cancer Therapy-Anemia, *FACT TOI-An* Trial Outcome Index-Anemia, *95% CI* 95% confidence interval for the regression coefficient (the slope of the regression line), $r^2$ Coefficient of determination; as a measure of predictive ability of the regression model, it indicates the proportion of the variability in changes in hemoglobin levels, which is explained by knowing the change in HRQOL scores

16 of FACT-G had the highest nonresponse rate both at baseline and at 3 months. Item 16 asked about "sexual satisfaction with one's partner". We believe that the high nonresponse rate for this item is related to the Japanese culture. The similar nonresponse rate was seen in previous studies of the same instrument in Japan [8].

We described whether changes in hemoglobin level predicted changes in QOL scores over 3 months in our study. We must note, however, that the $r$-square values for all scales are small in our analysis. QOL is greatly influenced by a variety of individual factors such as personal social events or individual understanding of HRQOL. As hemoglobin level is just one of such factors, using only hemoglobin level as a clinical indicator to explain or predict QOL variation has its limitation. In our study, we only showed that a change in hemoglobin level could be a predicting factor of QOL because it was one of the statistically significant explanatory factors.

FACT TOI-An is a scale that measures HRQOL related to the physical and functional domains, as well as anemia. Our study showed that FACT TOI-An best differentiated the anemic status of cancer patients categorized into lower (Hb <11.0 g/dl) and higher (Hb ≥11.0 g/dl) hemoglobin levels when compared with other scales. When Cella et al. [3] validated HRQOL measures of lung cancer patients using the FACT-L, they constructed the 21-item TOI-L by combining the scores of PWB and FWB. The Cronbach's alpha for the TOI-L was high, suggesting that little information was lost when combining the domains and subscales into one. They showed that TOI was the most precise indicator of patient-reported HRQOL for lung cancer patients in a clinical trial. In contrast to Cella's result, the change seen in our study was small. This is because the PWB condition of patients at baseline influences the scores of FACT TOI-An to a great extent. Because our study was noninterventional, we would expect an interventional study using FACT-An to show a larger difference.

## Conclusions

The Japanese version of the FACT-An has higher clinical validity and can be used to appropriately assess HRQOL among Japanese cancer patients with anemia.

**Acknowledgments** This study was part of the Health Outcomes Research (HOR) project (HOR 04) established in 2003 by the Comprehensive Support Project for Oncology Research of Breast Cancer (CSPOR-BC) and was supported by a grant from the CSPOR-BC. We thank Tomoko Shishida, Shitomi Kudo, Narikazu Boku, Shozo Ohsumi, Morihiko Kimura, Takashi Seto, Yoshiaki Ogawa, Masaru Kuranami, Hiroshi Isobe, Masato Koseki, and others who helped us in patient recruitment. We also thank Ann C. Tang and Tom Lang for their assistance in preparing the manuscript. Finally, we are grateful to all patients who participated in the study.

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Breast Cancer
Vol. 14 No. 1 January 2007

# Review Article

# Current Status of Health Outcome Assessment of Medical Treatment in Breast Cancer

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Recent research has shown the importance of the patient's point of view on the goals of medical care, and now health-related quality of life (HR-QOL) has become an important endpoint of clinical studies. However, as HR-QOL is essentially a subjective, personal concept determined from the viewpoint of the patient, it is fundamentally important to understand the concept and use the HR-QOL assessment, to express both the subjective and qualitative concept of HR-QOL in an objective and quantitative way that meets the patient's true needs, and also to obtain high-quality information about HR-QOL. In this article, we describe the concept of HR-QOL, the purpose of HR-QOL measurement, the approach to the HR-QOL assessment, instruments used in the measurement of HR-QOL, and general principles of HR-QOL measurements. We also review the current status of HR-QOL assessment of medical treatment in breast cancer.

*Breast Cancer 14:74-80, 2007.*

Key words: Health outcome, Quality of life, Breast cancer, Medical treatment

Health outcomes are measures or events that define the medical, personal or social consequences of an illness and its treatment[1]. In the field of oncological research, the focus has usually been on assessing the outcomes of cancer treatment and care through the use of objective measures such as length of survival, clinical or pathological response and toxicities. Potential consequences of treatment, such as severe toxicity, patient discomfort, and infrequent mortality, are often viewed as acceptable risks. Since, however, the World Health Organization defined health as being not only the absence of disease and infirmity but also the presence of physical, mental, and social well-being[2], it has become increasingly important to assess the patients' perspective of their symptoms and their impact on the daily life as a tool for determining treatment and a means to assess the outcome of the chosen treatment. This review aims to give a comprehensive insight in the health outcome assessment, especially the health-related quality of life (HR-QOL) of medical treatment in breast cancer.

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Abbreviations:
CSP-HOR, Comprehensive support project for health outcome research; CSPOR, Comprehensive support project for oncological research of breast cancer; EORTC QLQ, European organization for research and treatment of cancer quality of life questionnaire; EQ-5D, EuroQol 5 dimension; FACT, Functional assessment of cancer therapy; GOG-Ntx, Gynecologic oncology group-neurotoxicity; HR-QOL, Health-related quality of life; HOR, Health outcome research; N-SAS BC, National surgical adjuvant study of breast cancer; PNEF, Physician neurotoxicity examination form; PNQ, Patient neurotoxicity questionnaire; PRO, Patient-reported outcome; QOL, Quality of life; QOL-ACD, Quality of life questionnaire for cancer patients treated with anticancer drugs

## Concept and Methods of HR-QOL Assessment

### *Concept of HR-QOL*

Quality of life (QOL) is essentially a subjective, personal and multidimensional concept, determined from the viewpoint of the patient. The fundamental domains include physical, functional, psychological or mental, social, and spiritual aspects, but most of these domains are interrelated and cannot be clearly separated, and are influenced by a person's experiences, beliefs, expectations, and

perceptions. Among them, the physical, functional, psychological, and social aspects are usually referred to as HR-QOL, and so far health outcome research (HOR) in cancer patients has focused on the assessment of these domains with the use of profile (questionnaire)-type QOL instruments. Measurements of spiritual aspects of QOL are difficult and there is some concern as to whether medical intervention can bring improvements in this area[3].

### *Purpose of HR-QOL Measurement*

The clinical studies on HR-QOL can be categorized as basic studies or clinical application studies[4]. The former aim to investigate the reliability and validity of instruments, to develop the instruments for HR-QOL assessment, and to cross-culturally validate the instruments after translation into various languages, while the latter includes observational or interventional studies evaluating the effect and net balance of new therapeutic strategies on HR-QOL. To provide the information that patients require when treatment decision are being made, detailed data about HR-QOL needs to be collected using well-validated instruments in an era when patients are meant to be offered more opportunities to be partners with their health-care providers in therapeutical decision-making.

On the other hand, the measurement of an individual patient's HR-QOL can be used in clinical practice to help decision making, to facilitate detection of unexpected physical or psychological problems, to monitor disease and treatment over time, and thus improve the delivery of medical care. This approach might provide useful information to care providers, and facilitate communication[5,6]. However, so far a number of practical, methodological and attitudinal barriers have limited the use of patient-based measures of health within routine practice[7,8]. For example, many questionnaires are lengthy and repeated measures may be a burden for both patients and physicians. There are also logistic and financial barriers to data collection, and their analysis in an understandable manner with prompt feedback. Moreover, the effectiveness of the formal provision of information about perceived health status to the clinician in practice remains unclear. In fact, in a systematic review by Espallargues *et al.*[8], prompt feedback led to an increase in the diagnosis of conditions and the use of health services and referrals, while the health status of the patients was similar to that of patients whose physicians were not provided with such information. Thus, there is still need for a more through evaluation of this type of intervention.

### *Approach to HR-QOL Assessment*

HR-QOL is a measurement of health status filtered by the subjective perceptions and expectations of the individual[9]. In this sense, HR-QOL measurement represents a radical realignment between the objective and subjective elements of clinical medicine[10]. However, each domain of HR-QOL has many components, and there is an almost infinite number of states of health, all with differing qualities, and all quite independent of longevity[1]. Moreover, since expectations regarding health and the ability to cope with limitation and disability can greatly affect a person's perception of health and satisfaction with life, two people with the same health status may have different qualities of life. Therefore, the construct can be defined in a number of ways, and a consensus of what the term means has not been reached. Thus a challenge for clinicians and researchers has been knowing their patients' QOL[11].

Considering these issues, one approach might be to apply the techniques of qualitative research. This is an interpretative, naturalistic approach that involves making sense of phenomenon in terms of the meanings people bring to them; to understand thoughts, feelings and experiences of individuals, focusing on direct face-to-face knowledge of patients as human beings coping with their condition and treatment in any setting. This approach sets out without a hypothesis, does not use a control group, a fixed design or any minimum number of subjects, does not attempt objectivity and does not rely on statistical analysis. Thus, qualitative research provides a different type of evidence from quantitative research[12], and can help clinicians to understand the patient's experience of being diagnosed and treated for breast cancer as an individual.

On the other hand, quantitative research as a method holds that both the natural and social sciences strive for testable and confirmable theories that explain phenomena by showing how they are derived from theoretical assumptions, and attempts to reduce social reality to a variable in the same manner as physical reality. This approach places numerical values on HR-QOL to produce a single item score, a scale or a composite index,

and requires psychometric properties such as reliability, validity and responsiveness to change to tightly control the variable in question to see how other variables are influenced. As it is often hard to establish a cause-and-effect relationship on QOL issues for individual patients, conclusions are usually drawn for a group of patients, not an individual.

***Instruments used in HR-QOL Assessment***

Instruments to measure HR-QOL are commonly classified as generic instruments and disease- or condition-specific instruments. The former are generally applied to assess the QOL of people who suffer no daily illness or patients with benign disease. They are also used occasionally to assess cancer survivors who have gone for a long period without a cancer recurrence. Generic instruments are further classified as those that allow calculation of utility, and the health profile type. The advantage of these instruments is that they allow comparison of QOL beyond the confines of the disease or condition. However, these generic instruments usually lack information specific to the disease or treatment.

Disease- or condition-specific instruments are no different from generic ones in terms of including the main domains of HR-QOL, but the contents are more closely matched to each disease. For example, cancer-specific instruments commonly include items on loss of appetite, weight loss, nausea, and hair loss. In addition, subscales or modules for additional concerns which include questions specifically for the treatment or type of disease have been developed as options to be used with the general scale or core questionnaire in disease- or condition-specific instruments. Using these instruments, it is easy to obtain clinically useful information, while it is virtually impossible to compare QOL not specifically related to the disease or condition, and bias in the measured domains of QOL cannot be denied.

***General Principles in HR-QOL Measurement in Clinical Application Studies***

In clinical application studies, it is fundamentally important to adopt a questionnaire for which the reliability and validity have been confirmed, to express both the subjective and qualitative concept of HR-QOL in an objective and quantitative way that meets the patient's true needs, and to obtain high-quality information about HR-QOL. In addition, as a true measure of HR-QOL needs to assess not only the occurrence of or ability to experience a given symptom or phenomenon, but also satisfaction and concern about the area[13], more detailed questions regarding treatment-related symptoms, level of satisfaction with treatment, body image and sexual function can be included to obtain instructive information.

Moreover, considering the recent increase in the opportunities for international collaboration in clinical trials, it is also important to adopt the instruments after rigorous translation work if they have been developed in a foreign language. For the cross-cultural validation, the first key matter to compare differences between countries and cultures is the translation of materials to accurately convey meaning in the language of each country. At present, several QOL instruments developed in Western countries such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ), the Functional Assessment of Cancer Therapy (FACT) scale and the EuroQol 5 Dimension (EQ-5D) are available in Japanese[14-16]. Table 1 lists the currently available HR-QOL instruments for breast cancer currently available in Japanese[3, 4, 17]. Of them, the Japanese version of the EORTC QLQ-C30, FACT-G and FACT-B, and the Quality of Life Questionnaire for Cancer Patients Treated with Anticancer Drugs (QOL-ACD) have been verified in terms of reliability and validity[3, 17, 18]. The others, such as the EORTC QLQ-BR23 and FACT-Taxane, are now being verified for reliability and validity.

For accurate HR-QOL assessment, one should take into account several sources of bias, which may influence the results of the analysis in oncological research. These include not only the medical status such as disease progression and existing treatments but also age, marital status, occupation, level of education, and family income. In addition, one should make every effort to minimize missing data, and the cause of missing data should be identified before analyzing the data collected, as the analytical technique will differ according to the reason for the missing data[19]. Missing data can be broadly classified qualitatively as missing completely at random, missing at random, missing not at random, and missing data tend to increase particularly in HR-QOL assessments in advanced cancer patients. Therefore, it is important to consider these issues as fully as possible

**Table 1. Currently Available Japanese Versions of Health-Related Quality of Life Instruments and Psychological Measures for Breast Cancer**

| |
|---|
| Health-related QOL instruments |
| Generic instruments (Health profile type) |
| Medical Outcome Study Short Form (SF-36) |
| World Health Organization Quality of Life Assessment questionnaire (WHO/QOL-26) |
| Disease/condition-specific instruments for cancer patients |
| European Organization for Research and Treatment of Cancer Quality of life Questionnaire (EORTC QLQ) |
| I: Core questionnaire: C30 |
| II: Modules specific to tumor site, treatment modality, or a QL dimension: EORTC QLQ-BR23 (Breast cancer), CIPN20 (Chemotherapy-induced peripheral neuropathy) |
| Functional Assessment of Cancer Therapy (FACT) scale |
| I: General instrument: FACT-G |
| II: Subscales for cancer-, symptom-, or treatment-specific concerns: FACT-B (Breast cancer), An (Anemia), F (Fatigue), Taxane (Taxane toxicity), GOG/Ntx (Gynecologic Oncology Group-Nerotoxicity), Sp (spirituality), ES (Endocrine-related symptoms), Pal (Palliative care) |
| Quality of Life Questionnaire for Cancer Patients Treated with Anticancer Drugs (QOL-ACD) |
| I: General instrument: QOL-ACD |
| II: Subscale for breast cancer: QOL-ACD-B |
| Psychological measures |
| The Center for Epidemiologic Studies Depression Scale (CES-D) |
| General Health Questionnaire (GHQ) |
| Hospital Anxiety and Depression Scale (HADS) |
| Profile of Mood States (POMS) |
| Self-rating Depression Scale (SDS) |
| State-Trait Anxiety Inventory (STAI) |

before the start of the survey. This is especially true in the longitudinal study, as the treatment baseline is an essential survey point.

## Current Status of Clinical Application Studies of HR-QOL Assessment in Breast Cancer

Recent studies evaluating treatment and intervention outcomes in breast cancer are increasingly including some measurement of HR-QOL[20]. According to the systematic review of Shimozuma *et al.*[4], the most common setting of clinical application studies in breast cancer has been postoperative, followed by advanced or recurrent disease. There have been few studies focusing on medical examination, prevention, or terminal stage breast cancer. As for interventions, the most common were chemotherapy and/or endocrine therapy, followed by surgery, nursing/care/counseling/rehabilitation, and radiotherapy and medical testing.

It is beyond the scope of this paper to provide a full review of these studies. However, it should be noted that some adverse events that affect HR-QOL are often underestimated or unrecognized by clinicians if assessed using several questionnaires[21], indicating that the manner in which all the adverse events associated with drugs are collected is not always reliable. It is also important to note that, in recent years, there has been a trend toward increasing HR-QOL and other patient-reported outcomes (PROs) claims in regulatory documents for the approval of new pharmaceutical products by the European Medicines Agency [22]. Docetaxel was the first case in which HR-QOL data appeared in product regulatory documents registered at the European Medicines Agency. The impact of docetaxel on HR-QOL was measured by EORTC QLQ in a large phase III study of locally advanced or metastatic breast cancer in which docetaxel was used in combination with doxorubicin, and the HR-QOL results were discussed both under the efficacy and safety sections of the Scientific Discussion as well as in the summary of product characteristics document, stating "In both arms, QOL measured by EORTC questionnaires was comparable and stable during treatment and follow-up." This experience with HR-QOL in the authorization process has served as a baseline for a review of the use of HR-QOL in regulatory submission in European between 1995 and 2003. However, it has been stated that health

**Table 2. Summary of Clinical Studies of Comprehensive Support Project for Health Outcome Research Assessing HR-QOL in Breast Cancer**

| Study | Clinical setting | Study design | Intervention | Instruments |
|---|---|---|---|---|
| HOR 01-2 | Postoperative adjuvant hormone therapy for postmenopausal patients | Longitudinal study (non-controlled study) | Tamoxifen, anastrozole | FACT-G, FACT-ES, Kupperman Menopausal Index, VAS for hot flash, QOL-ACD-B, Original scale |
| HOR 02 | Metastatic breast cancer | Longitudinal study (non-controlled study) | Weekly paclitaxel | FACT-G, FACT-Taxane, PNQ, PNEF |
| HOR 04-1* | Under treatment | Longitudinal study (non-controlled study) | Chemotherapy, hormone therapy, radiation | FACT-An |
| HOR 06 | Preoperative chemotherapy in operable breast cancer | Longitudinal study (non-controlled study) | Anthracycline and taxane | WAIS-R, HAM-D, POMS, EORTC QLQ-C30, EORTC QLQ-BR23, SF-8 |
| HOR 07 | Under treatment | Longitudinal study (non-controlled study) | Taxane | PNQ |
| N-SAS BC 02 | Postoperative adjuvant chemotherapy | RCT | AC followed by taxane vs taxane | FACT-G, FACT-B, FACT-Taxane, EQ-5D, PNQ, PNEF |
| N-SAS BC 03 | Postoperative adjuvant hormone therapy | RCT | Tamoxifen vs tamoxifen followed by anastrozole | FACT-G, FACT-B, FACT-ES, CES-D |
| N-SAS BC 04 (TEAM-Japan) | Postoperative adjuvant hormone therapy | RCT | Tamoxifen vs exemestane vs anastrozole | FACT-G, FACT-B, FACT-ES, CES-D |
| SELECT BC | Metastatic or recurrent breast cancer, hormone refractory and HER-2 negative | RCT | Taxane vs TS-1 as first line chemotherapy | EORTC QLQ-C30, PNQ, EQ-5D, PHRS-SCL (SF), CES-D |

*Various types of cancer were included.
Abbreviations: AC, doxorubicin and cyclophosphamide; An, anemia; B, breast; BR23; Breast Cacner Module 23; C30, Core Questionnaire 30; CES-D, The Center for Epidemiologic Studies Depression Scale; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQol 5 Dimension; ES, endocrine-related symptoms; FACT, Functional Assessment of Cancer Therapy; G, general; HAM-D, Hamilton Depression Rating Scale; HER-2, human epidermal growth factor-2; HOR, Health outcome research; N-SAS BC, National Surgical Adjuvant Study of Breast Cancer; PHRS-SCL (SF), Public Health Research Foundation Stress Checklist (Short Form); PNEF, Patient Neurotoxicity Examination Form; PNQ, Patient Neurotoxicity Questionnaire; POMS, Profile of Mood States; QOL-ACD-B, Quality of Life Questionnaire for Cancer Patient Treated with Anticancer Drugs; RCT, randomized control trial; SF-8, Short Form 8-item of SF-36; WAIS-R, Wechsler Adult Intelligence Scale-Revised.

researchers need to better justify the inclusion of these outcomes in clinical trials and highlight the added value of PRO data for more efficient utilization of HR-QOL and PROs.

Under these circumstances, the Comprehensive Support Project for Health Outcome Research (CSP-HOR) in the Public Health Research Foundation has conducted several health outcome studies in healthy individuals as well as in patients with various types of cancer in Japan. The aims of these studies are to verify the reliability and validity of existing instruments, to assess the effect of interventions on HR-QOL and to develop instruments. For example, the HOR 01 has developed a scale for endocrine-related symptoms in postmenopausal patients with breast cancer undergoing endocrine treatment (Table 2). HOR 02 aims to assess the effects of weekly paclitaxel (80-100 mg/m$^2$ per week) on HR-QOL in patients with advanced or metastatic breast cancer. The measures being used in that study are FACT-G, FACT-Taxane including FACT-Gynecologic Oncology Group-Neurotoxicity (GOG/Ntx), Patient Neurotoxicity Questionnaire (PNQ), and the Physician Neurotoxicity Examination Form (PNEF)[23], and the primary endpoint is to evaluate the frequency and severity of neurotoxicity caused by weekly paclitaxel[24]. As a secondary endpoint, HR-QOL and the feasibility, reliability and validity of these questionnaires will be evaluated.

Concurrently, CSP-HOR has supported the health outcome studies in the Comprehensive Support Project for Oncological Research of Breast Cancer (CSPOR-BC). Among them, the National Surgical Adjuvant Study of Breast Cancer (N-SAS BC) 02 is planned to investigate HR-QOL as a secondary endpoint along with survival time, adverse events and cost. This randomized controlled trial compares four cycles of doxorubicin and cyclophosphamide (AC) followed by four cycles of taxanes (docetaxel or paclitaxel), and eight cycles of either taxane, and the comparison of docetaxel and paclitaxel is planned in a two-by-two factorial design. The measures used in this study are FACT-G, FACT-B, FACT-Taxane and EuroQol 5 Dimension (EQ-5D). For analysis of documented patient neurotoxicity symptoms and functional assessment, PNQ and a PNEF are also included. Thus, several health outcome studies are now investigating HR-QOL of medical treatment using several criteria in Japan.

## Conclusion

This review has outlined the concept and use of HR-QOL assessment in the medical treatment of breast cancer. As HR-QOL is essentially a subjective, personal concept determined by the viewpoint of the patient, it is fundamentally important to understand the concept and use of HR-QOL assessment, to express both the subjective and qualitative concept of HR-QOL in an objective and quantitative way that meets the patient's true needs, and also to obtain high-quality information about HR-QOL. This will enable us to provide the information that patients require when treatment decisions are being made in an era when patients are meant to be offered more opportunities to be partners with their health-care providers in decision-making.

## Acknowledgement

The authors thank Tomoko Moriya for providing information about the health outcome studies and N-SAS BC conducted by CSP-HOR.

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Breast Cancer
Vol. 14 No. 1 January 2007

# Review Article

# Economic Evaluation of the Prevention and Treatment of Breast Cancer-Present Status and Open Issues

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***Background***: More effective methods of preventing and treating breast cancer are being sought by clinicians every day, and new drugs and interventions for overcoming this cancer are being energetically evaluated. At present, there are wide treatment options and many different objectives for breast cancer. These circumstances led us to seek information about the relative costs of the different medical options for the prevention and treatment of breast cancer and to try to ascertain whether one course of action is more efficient than other courses. Economic evaluation of healthcare is indispensable for selection of the best alternatives among medical interventions which are becoming more diverse day after day. The total medical expenditure continues to rise each year and some sort of evaluation from an objective and external viewpoint is required to provide the information with which to suppress this rise.

***Methods***: This paper surveys the three major reports published on this topic to date, for the purpose of demonstrating the importance and necessity of performing an economic analysis of the treatment and prevention of breast cancer. The three reports to be surveyed pertain to: (1) cost-effectiveness analysis of adjuvant chemotherapy for patients with lymph node negative breast cancer, (2) cost utility analysis of first-line hormonal therapy in advanced breast cancer, namely comparison of two aromatase inhibitors to tamoxifen, and (3) cost-effectiveness analysis of tamoxifen in the prevention of breast cancer. In addition, this paper discusses the advantages, limitations and perspective for the future of the economic evaluation of healthcare for breast cancer.

***Results***: (1) The authors concluded that if the average risk of all women of undergoing recurrence after this therapy is assumed to be 4% per year, adjuvant chemotherapy is definitely of benefit for node-negative, estrogen receptor-negative breast cancer patients. They additionally stated that this benefit decreases markedly if the changes in long-term survival are less than those in disease-free survival. In this connection, they pointed out that the benefit is considerably smaller among postmenopausal 60-year-old women. (2) The incremental cost per quality-adjusted progression-free life year (QAPFY) for letrozole and anastrozole, relative to tamoxifen, was Can $12,500-19,600, which was lower than the criterion level (US $50,000). On the basis of this result, the authors concluded that these two drugs are economically acceptable. Furthermore, when efficacy and cost effectiveness were analyzed together, it was concluded that letrozole is in fact preferable to anastrozole. (3) The model analysis of tamoxifen's cost effectiveness among women at increased risk for breast cancer yielded the following results. In the base-case analysis, involving the calculation of the costs and benefits of 5-year tamoxifen administration, the incremental cost effectiveness of tamoxifen was $41,372 per life-year gained for women age 35 to 49 years, whereas for women age 50 to 59 years and 60 to 69 years, these values were $68,349 and $74,981, respectively. For women who had undergone hysterectomy and thus had no risk of the onset of endometrial cancer, the incremental cost effectiveness of tamoxifen was $46,060 per life-year gained.

***Conclusion***: Medico-economic evaluation of breast cancer is very significant and valuable and is expected to stimulate efficient utilization of healthcare resources. It can provide important information to physicians, patients, insurers, pharmaceutical and other industries, healthcare policy planners, and others.

*Breast Cancer 14:81-87, 2007.*

Key words: Breast cancer, Economic evaluation, Cost-effectiveness analysis, Cost-utility analysis

Breast cancer is one of the leading causes of death in all developed countries, and expenditures connected with its treatment have been increasing year after year, until they now represent a large percentage of all medical expenditures in each nation[1,2]. More effective methods of preventing and treating breast cancer are being sought by clinicians every day, and new drugs and interventions for overcoming this cancer are being energetically evaluated. At present, there are wide treatment options and many different objectives for breast cancer[3,4]. These circumstances led us to seek information about the relative costs of the different medical options for the prevention and treatment of breast cancer and to try to ascertain whether one course of action is more efficient than other courses. Economic evaluation of healthcare is indispensable for selection of the best alternatives among medical interventions which are becoming more diverse day after day. The total medical expenditure continues to rise each year and some sort of evaluation from an objective and external viewpoint is required to provide the information with which to suppress this rise.

What constitutes the economic evaluation of healthcare? What purposes does such an evaluation serve? The economic evaluation of healthcare has two major purposes. One is to determine the cost of obtaining a given unit of health outcome. The cost per health outcome, e.g., the cost of caring for one low-birth-weight infant or the cost of the antihypertensive drugs to prolong the survival period by one year, is a piece of information needed not only by the financial officers of hospitals and pharmaceutical companies but also by governmental medical care policy planners. The other purpose is to conduct comparison of different courses of medical intervention, in addition to a separate analysis of each course of intervention. Healthcare resources are limited, and comparing the results of economic evaluations of different medical interventions will yield vital information about the most effective and efficient methods of allocating healthcare resources[5].

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Abbreviations:
QAPFY, Quality-adjusted progression-free life year; QOL, Quality of life; CER, Cost effectiveness ratio; QALY, Quality-adjusted life year; CMF, Cyclophosphamide methotrexate fluorouracil; RCT, Randomized clinical trial; BCPT, Breast cancer prevention trial

The prevention and treatment of breast cancer may be a good model of the application of economic evaluation, because we need cost-effective alternatives for dealing with this disease. In the economic evaluation of healthcare, we have to evaluate health outcomes in connection with the costs of a given health outcome[6]. Cost-effectiveness analysis is a representative technique used for this evaluation. When health-related quality of life (health-related QOL) is deemed to be a health outcome, the economic evaluation of healthcare is called "cost-utility analysis." This paper will survey the three major reports published on this topic to date, for the purpose of demonstrating the importance and necessity of performing an economic analysis of the treatment and prevention of breast cancer. The three reports to be surveyed pertain to: (1) cost-effectiveness analysis of adjuvant chemotherapy for patients with lymph node negative breast cancer[7], (2) cost-utility analysis of tamoxifen and 2 third-generation selective aromatase inhibitors[8], and (3) cost-effectiveness analysis of prophylactic tamoxifen therapy for women at elevated risk for breast cancer[9]. In addition, this paper will discuss the advantages, limitations and perspective for the future of the economic evaluation of healthcare for breast cancer (Table 1).

## Representative Reports on Economic Evaluation of Breast Cancer

### *Cost-Effectiveness Analysis of Adjuvant Chemotherapy for Patients with Lymph Node Negative Breast Cancer*

This paper, by Hillner and Smith in the United States, may well mark the start of the medico-economic studies of breast cancer that have been made over the past 15 years[7]. The data contained in this paper have been frequently cited since 1991 by other investigators in their medico-economic studies of breast cancer. This study may be one of the most excellent economic studies of breast cancer in the past 15 years. The study aimed at evaluating the efficacy of adjuvant chemotherapy for lymph node negative breast cancer at different levels of risk of recurrence and conducting a cost-effectiveness analysis of this therapy. The study was carried out after a clinical alert issued in 1988 by the American National Cancer Institute, which stated that "Chemotherapy can have a meaningful impact on the natural history of node-negative breast cancer patients."[10]. This

**Table 1. Summary of Representative Reports on Economic Evaluation of Breast Cancer**

| authors | patients | methods | Regimens | CER or CUR(unit) | Conclusion | conflict | level |
|---|---|---|---|---|---|---|---|
| Hillner BE, *et al.* (1991) | ER-<br>Stage I or IIa<br>N-, 45y.o. 60y.o.<br>N-, 45y.o. 60y.o. | · Markov meodel.<br>· The analysis evaluated different scenarios of the benefit of therapy: improved disease-free survival for five years, with a lesser effect on overall survival (base line; a lifelong benefit from chemotherapy; and a benefit in disease-free survival with no change in overall survival by year 10).<br>· Charges in 1989 at the Medical College of Virginia and estimates from Medicare data. | CMF<br>CMF<br>CMF<br>CMF | $15,400/QALY<br>(5 years of benefit)<br>$18,800/QALY<br>(5 years of benefit)<br>$5,100/QALY<br>(lifelong benefit)<br>$7,400/QALY<br>(lifelong benefit) | Chemotherapy substantially increases the quality-adjusted life expectancy of an average women at a cost comparable to that of other widely accepted therapies. This benefit decreases markedly if the changes in long-term survival are less than in disease-free survival. Given it uncertain duration, the benefit may be too small for many women to choose chemotherapy. | – | 2b |
| Dranitsaris G, *et al.* (2003) | Postmenopausal, ER+, PR+, first-line | · Decision model<br>· Clinical data were obtained from a meta analysis of modern (i.e., post-1990) randomized trials.<br>· Total hospital resource consumption was collected from the charts of 87 patients with advanced disease who had failed tamoxifen tehrapy.<br>· Quality of life data were got using Time Trade-Off technique, but utility of tamoxifen was not estimated. | letrozole and anastrozole vs. tamoxifen (control) | letrozole: incremental Can $12,500/QAPFY, anastrozole: incremental Can $19,600/QAPFY | Letrozole and anastrozole are both economically acceptable alternatives to tamoxifen in the first-line treatment setting. However, given the available clinical data and the findings of the current study, letrozole would be the preferred choice. | + | 2b |
| Noe LL, *et al.* (1999) | Age-groups (35-49, 50-59, 60-69, 35-69y.o.) defined cohorts of women who were at high-risk for developing breast cancer. | · BCPTresults, Markov mode<br>· Cost estimates were obtained from the published literature.<br>· Only direct medical care costs of treating observed events were included. | tamoxifen | 35-49 y.o. incremental $41,372/LYG<br>50-59 y.o. incremental $68,349/LYG<br>60-69 y.o. incremental $74,981/LYG<br>all ages incremental $46,060/LYG | The use of tamoxifen in high-risk women to prevent breast cancer in high-risk women may be cost effective, particularly in the 35-to-49 year-old age group and in those of any age who have had a hysterectomy. | + | 3a |

ER: estrogen receptor
CMF: cyclophosphamide, methotrexate, fluorouracil
CER: cost-effectiveness ratio
CUR: cost-utility ratio
QALY: quality-adjusted life years
QAPFY: quality-adjusted progress-free years
LYG: life years gained
conflict: +, supported by a pharmaceutical company
level: evidence level, from Oxford Centre for Evidence-Based Medicine Level of Evidence (http://cebm. net/)

alert was widely interpreted as a recommendation for adjuvant chemotherapy for such patients[11]. However, if this advice were faithfully followed, adjuvant chemotherapy would be given to many women who statistically would not have experienced a recurrence. For this reason, there has been much controversy on the value of this recommendation. According to the reports published to date, the efficacy of adjuvant chemotherapy can be affirmed if evaluated from the viewpoint of whether or not the disease-free survival period of node-negative breast cancer patients is prolonged, but the extent of prolongation is not very great. It was not clear whether or not the therapy had much effect in prolonging the patients' overall survival. It was also reported that, although there was little probability that the patients would die from the adjuvant chemotherapy, most patients had adverse reactions to the therapy and the estimated total cost of this chemotherapy amounted to as much as $338 million. These were serious considerations, and so the results of this study involving the cost-effectiveness analysis (by Hillner and Smith) had great importance.

The authors of this paper created a model containing such variables as risk of recurrence, efficacy of adjuvant therapy, duration of the benefit derived from adjuvant therapy, and quality of life (QOL). They calculated the expected survival period adjusted for QOL to analyze the cost-effectiveness of chemotherapy in the cohort of premenopausal 45-year-old women with node-negative breast cancer and the cohort of postmenopausal 60-year-old women with node-negative breast cancer. They thus developed a decision analysis model involving these two cohorts. For this model, the Markov process was used when calculating the cumulative outcome value for the cohort receiving adjuvant chemotherapy and the cohort without adjuvant chemotherapy. The analysis was conducted on the basis of the evaluation of various scenarios in which the patients enjoyed the benefits of the therapy. Specifically, it analyzed whether or not the therapy improved the disease-free survival for five years (the disease-free five-year survival rate?), whether or not it improved the life-long benefit expected from chemotherapy in general, and whether or not it improved the benefit related to disease-free survival while causing no change in overall survival by year 10.

The study revealed that for both the cohort of premenopausal 45-year-old women and the cohort of postmenopausal 60-year-old women, adjuvant chemotherapy given to node-negative breast cancer patients resulted in excellent results in terms of lifelong benefit and benefit of disease free survival for 5 years. The cost effectiveness ratio (CER) reflected these excellent results, showing a $15,000/quality-adjusted life year (QALY) for a 5-year benefit in the 45-year-old woman group, $18,800/QALY for a 5-year benefit in the 60-year old woman group, $5,100/QALY for lifelong benefit in the 45-year-old woman group and $7,400/QALY for lifelong benefit in the 60-year-old woman group. The drug used for this chemotherapy was probably CMF in most cases. However, since the report does not explicitly refer to the drug used, and because some other chemotherapeutic agents were noted in some source data, care is needed when interpreting the results of this study.

The authors concluded that if the average risk of all women of undergoing recurrence after this therapy is assumed to be 4% per year, adjuvant chemotherapy is definitely of benefit for node-negative, estrogen receptor-negative breast cancer patients. They additionally stated that this benefit decreases markedly if the changes in long-term survival are less than those in disease-free survival. In this connection, they pointed out that the benefit is considerably smaller among postmenopausal 60-year-old women, and that opting to use this therapy for women in this group should be based on a careful comparison of the cost-to-benefit ratio of adjuvant chemotherapy.

### *Cost Utility Analysis of First-Line Hormonal Therapy in Advanced Breast Cancer: Comparison of Two Aromatase Inhibitors to Tamoxifen*

This study, by Dranitsaris *et al.* in Canada, is based on an intensive effort to make a comprehensive evaluation of new drugs available for the treatment of breast cancer[8]. It involved not only the evaluation of responses and progression-free survival but also utility analysis, demonstrating how new anti-cancer agents used for the treatment of breast cancer should be evaluated. Tamoxifen has been serving as the standard first-line hormonal agent for women with advanced hormone-sensitive breast cancer. In recent years, however, a randomized clinical trial (RCT) comparing the conventional standard therapy using tamoxifen with a new regimen using third-generation selective aromatase inhibitors (anastrozole

and letrozole) demonstrated that the latter two drugs are at least comparable to tamoxifen in terms of efficacy[12, 13]. In view of these results from the RCT, we may say that anastrozole and letrozole should be considered viable alternatives to tamoxifen as first-line hormonal agents. In many countries however, and as a practical matter, the price of anastrozole and letrozole is higher than that of tamoxifen. For this reason, Dranitsaris *et al.* attempted to examine whether anastrozole and letrozole would have a better economic value, as compared with that of tamoxifen, when all clinical and economic factors were analyzed numerically. In addition, they undertook a cost-utility analysis to investigate whether treatment with anastrozole or letrozole would provide economically more attractive alternatives to tamoxifen therapy, in terms of the requirements of a publicly funded healthcare system.

In terms of methodology, this study can be viewed as an extremely sophisticated analysis. The decision model adopted for this study was developed and used to simulate and compare the outcome of ordinary treatment regimens. Clinical data for this study were derived from meta-analyses of RCTs conducted after 1990. The data pertaining to consumption of hospital resources were collected from the charts of 87 patients with advanced disease for whom tamoxifen therapy had failed. From these data, costs and benefits were calculated and linked together, to yield the incremental cost per quality-adjusted progression-free year (incremental cost/QAPFY).

The incremental cost per QAPFY for letrozole and anastrozole, relative to tamoxifen, was Can $12,500-19,600, which was lower than the criterion level (US $50,000). On the basis of this result, the authors concluded that these two drugs are economically acceptable. Furthermore, when efficacy and cost effectiveness were analyzed together, it was concluded that letrozole is in fact preferable to anastrozole.

Some limitations of this study are that it did not directly compare data on letrozole with data on anastrozole, that it did not take into account second-line hormonal therapy for non-responding patients, and that the analysis did not cover the costs of controlling drug-related reactions such as thromboembolic events.

### *Cost-Effectiveness Analysis of Tamoxifen in the Prevention of Breast Cancer*

If it is possible to completely prevent breast cancer, it is obvious that prophylactic interventional steps should be taken. However, the effectiveness of prophylactic intervention in breast cancer has not been fully demonstrated. Furthermore, prophylactic intervention involves the risk for adverse reactions and entails considerable expense. When deciding on the implementation of prophylactic intervention, the relationship between benefit and cost, i.e., the results of an economic evaluation, is the most important factor. However, the economic evaluation of prophylactic intervention against breast cancer is usually not simple[14, 15]. Precise measurement and evaluation of possible future health hazards and the cost of intervention to prevent such hazards is only possible either through interventional studies (which take a long time and huge amounts of money) or through the analysis of models, which involves the creation of theoretical frameworks based on hypotheses derived from the results of existing studies. Here, we will review a paper published by Noe *et al.* who adopted the latter approach (model analysis)[9].

Tamoxifen is often given as a prophylactic intervention against breast cancer. Several trials on this kind of intervention have been made, but there are problems with the age distributions of the subjects, the sample sizes and the study designs. None of these studies has demonstrated that the intervention was effective in terms of modifying the incidence of breast cancer. Following these unsatisfactory results, British researchers attempted to evaluate its cost effectiveness in the prevention of breast cancer among women at increased risk of developing the disease. The model analysis, conducted during this study, used data on the risks and benefits of tamoxifen, collected in the Breast Cancer Prevention Trial (BCPT). The analysis was based on the assumption that high-risk women could be divided into three groups: (1) women aged over 60, (2) women between 35 and 59 years of age who have a history of lobular carcinoma *in situ*, and (3) women age 35 to 59 years with a breast cancer risk at least as great as that of women 60 years of age. The high-risk women received either 10 mg of tamoxifen twice daily or no therapy to prevent breast cancer. It was assumed that the prophylactic effect of tamoxifen would be exerted immediately after the start of this therapy and would remain throughout the

dosing period. The decision model was used to estimate the incremental cost effectiveness of tamoxifen compared with no intervention, as preventive therapy for the age-group defined cohorts of women who had a high risk of developing breast cancer.

The model analysis of tamoxifen's cost effectiveness among women at increased risk for breast cancer yielded the following results. In the base-case analysis, involving the calculation of the costs and benefits of 5-year tamoxifen administration, the incremental cost effectiveness of tamoxifen was $41,372 per life-year gained for women aged 35 to 49 years, whereas for women aged 50 to 59 years and 60 to 69 years, these values were $68,349 and $74,981, respectively. In the analysis of sensitivity, the benefit expected from 10-year prophylactic use of tamoxifen in these three cohorts was found to be $20,806, $36,421 and $41,621, respectively. The factors found to be most sensitive were discount rates, breast cancer mortality rates and medical costs. For women who had undergone hysterectomy and thus had no risk of the onset of endometrial cancer, the incremental cost effectiveness of tamoxifen was $46,060 per life-year gained.

Because model analysis involves calculations based on diverse assumptions, the results tend to be fragile in nature. Bearing this in mind, the authors of this paper conducted sensitivity analyses in an attempt to obtain more accurate results. Furthermore, taking into account possible adverse reactions to prophylactic interventions with tamoxifen, they affirmed the presence of evidence for the view that tamoxifen is associated with an increased risk of endometrial cancer. However, they also pointed out that the strategy of prophylactic intervention with tamoxifen among high-risk women may still be cost-effective. They added that this strategy would be particularly cost-effective in women in the 35-49 age group as well as among women of any age who had undergone hysterectomy.

## Discussion

Medico-economic evaluation of breast cancer is very significant and valuable and is expected to stimulate efficient utilization of healthcare resources. It can provide important information to physicians, patients, insurers, pharmaceutical and other industries, healthcare policy planners, and others. However, most of the economic evaluations of breast cancer conducted so far have utilized indirect data instead of direct data and have involved model analysis based on scenarios and assumptions. Clinical data with a satisfactorily high quality and volume concerning patients' QOL are difficult to obtain for use in economic evaluations. Many medico-economic studies have therefore relied on BCPT as a common source of data[16]. Thus, medico-economic evaluations have been conducted on a weak and unstable base, involving the danger of errors in all the evaluations in the same direction, if there has been some error in the common source of data. To avoid this and to achieve more solid analyses, databases for utilization by this kind of evaluation are greatly desired.

We should bear in mind that even when an economic evaluation has been carried out with utmost accuracy, there will be some limitations inherent in the information yielded from the evaluation. The information obtained gives nothing more than expenses per given unit or comparable values, i.e., it is information pertaining only to one aspect of the object. There are other types of social value (equality, justice, etc.) in addition to the one revealed by the evaluation. We should therefore consider medico-economic evaluation to be one of several sources of information available to us in the decision-making process. We should always be aware of both the advantages and limitations of this kind of evaluation.

In closing this paper, we would like to refer to the most crucial principle, which must be borne in mind by investigators attempting medico-economic evaluations. That is, the relationship between the investigator(s) and the sponsors providing the funds used for the analysis should be always made clear, and any financial relationships of the investigators to companies that manufacture or supply the drugs, methods of intervention and so on involved should be disclosed voluntarily. We would not say that medico-economic evaluation should be totally prohibited to investigators having a conflict of interest. However, we believe that investigators should always conduct research from a fair and neutral position.

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Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 4, pp. 1112–1121, 2006

0360-3016/06/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2005.09.027

**CLINICAL INVESTIGATION** **Esophagus**

# PROSPECTIVE TRIAL OF RADIOTHERAPY FOR PATIENTS 80 YEARS OF AGE OR OLDER WITH SQUAMOUS CELL CARCINOMA OF THE THORACIC ESOPHAGUS

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**Purpose: To assess the safety and efficacy of external beam radiotherapy for elderly patients with esophageal cancer.**
**Methods and Materials: A trial testing external beam radiotherapy (66 Gy within 6.5 weeks) as a single-modality treatment was performed for biopsy-proven squamous cell carcinoma of the thoracic esophagus clinically staged as Stage I and IIA (T1–T3N0M0, International Union Against Cancer, 1987) in patients aged ≥80 years.**
**Results: From January 1999 through December 2002, 51 evaluable patients (35 men and 16 women) with a median age of 83 years (range, 80–91 years) were enrolled from 22 institutions. Of the 51 patients, 18 (35%) had Stage T1 and 33 (65%) had Stage T2–T3 disease. Radiotherapy could be completed in 47 patients (92%) within 43–58 days (median, 49). The actuarial incidence of Grade 3 or worse cardiopulmonary complications at 3 years was 26%, with 3 early deaths, and correlated significantly with the size of the anteroposterior radiotherapy portals. The median survival time and overall survival rate at 3 years was 30 months and 39% (95% confidence interval, 25–52%), respectively.**
**Conclusion: The results of high-dose radiotherapy in octogenarians are comparable to those in younger patients, but meticulous treatment planning and quality control is required.** © 2006 Elsevier Inc.

**Esophageal cancer, Radiotherapy, Elderly, Quality control.**

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*Acknowledgments*—The authors are most appreciative of the kind cooperation they received from the following doctors: Takeshi Kodaira, M.D. and Minoru Kamata, M.D., Department of Radiation Oncology, Aichi Cancer Center, Nagoya; Atsuro Terahara, M.D., Department of Radiology, University of Tokyo Hospital, Tokyo; Sigeyuki Murayama, M.D. and Kei Muro, M.D., Divisions of Radiation Oncology and Medical Oncology, National Cancer Center Hospital, Tokyo; Keiko Shibuya, M.D., Department of Therapeutic Radiology and Oncology, Kyoto University Hospital, Kyoto; Michitaka Yamakawa, M.D. and Yuko Nakayama, M.D., Department of Radiation Oncology, Gunma University Graduate School of Medicine, Maebashi; Satoshi Uehara, M.D., Department of Radiology, National Hospital Organization Kyushu Medical Center, Fukuoka; Hiroo Sueyama, M.D., Department of Radiology, Niigata Prefectural Central Hospital, Niigata; Hisahiro Matsubara, M.D., and Yutaka Funami, M.D., Department of Frontier Surgery, Chiba University Graduate School of Medicine, Chiba; Hisanori Ariga, M.D., Department of Radiology, National Hospital Organization Mito Medical Center, Mito, and for all participants in the Japan Radiation Oncology Group (JAROG).

Received June 29, 2005, and in revised form Aug 23, 2005. Accepted for publication Sept 13, 2005.