Cost Effectiveness and Other Assessments of Adjuvant Therapies for Early Breast Cancer

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The 1992 metaanalysis of adjuvant therapies after surgery in early breast cancer summarizes the most extensively studied of all cancer treatments via randomized controlled trials. This study found overall benefits with use of adjuvant therapies, and their expanded use outside the clinical trial setting was assumed to be effective and implied to be cost effective. Thus, the primary remaining questions are which form of adjuvant therapy to use and how to identify which patients are unlikely to benefit. In British Columbia, the effectiveness of adjuvant therapy outside the clinical trial setting was reassuringly similar to the metaanalysis efficacy. Our decision analysis model of hypothetical cohorts of women with early breast cancer confirmed that the efficacy of adjuvant treatment is the primary determinate of its incremental cost effectiveness. Future cost-effectiveness and quality of life assessments should move from hypothetical cohorts assessed via models to prospective data collected within clinical trials or integrated health delivery system. [ONCOLOGY 9(Suppl):129-134, 1995]

Introduction

Economic and quality of life outcomes are major concerns in the management of early breast cancer. The potential clinical categories of early breast cancer amenable to economic, quality of life, and the general broad category of outcome assessments include screening primarily using mammography, evaluation of suspected lesions, primary surgical management, staging, adjuvant therapies, and monitoring. In this commentary, we restrict our discussion to the use of adjuvant therapies.

There is no shortage of data or recommendations related to the adjuvant treatment of early breast cancer. Except for studies in interventional cardiology, there is no area of medicine, and no other area in oncology, that has as rich a source of data to guide clinical treatments. The 1992 metaanalysis of all randomized trials initiated from 1948 to 1985 and including more than 75,000 patients is a landmark event [1]. It showed reductions in relative risk with use of adjuvant therapy of up to 30%. The expanded use of adjuvant therapy outside the clinical trial setting was assumed or implied to be cost effective. In addition, the National Surgical Adjuvant Breast and Bowel Project (NSABP) has conducted multiple clinical trials addressing the primary surgical management of early breast cancer as well as adjuvant treatments.

Guidelines for treatment exist for all strata of nodal and hormone-receptor status. The most widely recognized recommendations are from the 1990 NIH Consensus Conference and the 1992 and 1995 St. Gallen conferences [2,3]. The general conclusion of these conferences is that almost all patients with clinical and pathologic stage I or II breast cancer, regardless of age or menopausal, nodal, or receptor status, should be offered some form of adjuvant therapy in hopes of improving disease-free and overall survival. The primary remaining questions are not whether to use adjuvant therapy, but which form to use and how to identify patients who are unlikely to experience a meaningful increase in these outcomes.

In this commentary, we wish to discuss the difference between efficacy and effectiveness of a treatment, provide some information related to the discordance between recommendations and guidelines and the actual use of adjuvant therapies in clinical care, review some highlights of the cost-effectiveness assessments that our team has done on adjuvant therapies, and make recommendations on the future design of economic assessments in clinical trials and general practice. The reader is encouraged to see other articles in this supplement (Smith and Hillner; Weeks) for further discussion on decision analysis and quality of life studies.

Efficacy vs Effectiveness

Efficacy refers to a treatment that does more good than harm among those who receive it. Efficacy is
established in the controlled setting of a clinical trial. This reflects, as near as possible, ideal conditions with selected patients.

In contrast, a treatment's effectiveness is determined by whether it does more good than harm in those to whom it is offered. This specifically refers to general populations that may have less selected patients with more variations in comorbidity, clinician involvement, patient compliance, follow-up costs, etc. Effectiveness refers to the generalizability of an intervention, while efficacy refers to internal validity.

As discussed earlier, the findings of the efficacy of adjuvant treatments reported in the metaanalysis were obtained from randomized clinical trials. However, previous population-based studies from the late 1980s have either not found a benefit in survival or could not separate a benefit due to lead-time bias (increased survival due to early detection). Therefore, until recently, there has been some uncertainty about whether adjuvant therapy in general populations leads to benefits equal to those found in clinical trials.

For this reason, the study by Olivotto and colleagues from British Columbia is particularly important [4]. These investigators took advantage of how cancer care is recommended and delivered in their province to address the impact of adjuvant therapy for breast cancer. In British Columbia, there is a single centralized cancer agency that keeps a population-based registry. In addition, an ongoing consensus process makes province-wide recommendations for cancer treatments. Since medical care is an entitlement program, ability to pay is not a barrier to the use of adjuvant therapy as may occur in the United States. During the years studied, the use of screening mammography was not common, and the incidence of new breast cancer cases was stable. Therefore, the chance of a substantial lead-time bias is unlikely.

As shown in Table 1, the investigators studied three cohorts of patients and assessed their disease-free and overall survival before and after the adoption of adjuvant therapy recommendations for these groups. The cohorts were followed for 7 to 16 years with less than 2% being lost to follow-up. The findings of a 32% reduction in the chance of dying of breast cancer in premenopausal and 20% in postmenopausal women between 1974 and 1984 is similar to the findings from the metaanalysis. Therefore, if widely used, these therapies do produce benefits similar to those found in randomized trials.

We have explored the use of adjuvant therapies in a different population. Our study links the clinical data reported to the Virginia Cancer Registry with Medicare claims in elderly Virginia women [5]. We have currently completed analyses related to the use of adjuvant therapies from 1985 to 1989. In stage II (node-positive) breast cancer, the use of adjuvant therapies in these years was substantially lower than that observed in British Columbia. We found that about 45% of all women with node-positive cancer received an adjuvant therapy (see Figure 1). In addition, we observed a substantial age variation in the use of adjuvant therapies, with hormonal therapy being constant at 30% to 35% in all age groups, while chemotherapy declined from about 20% in the 65- to 69-year-old group to less than 3% in those over age 80.

This analysis was limited by the lack of estrogen-receptor data. Other workers have found that in about 80% of elderly women, breast cancer is hormone-receptor positive. However, in our study, only 9% of node-negative and 33% of node-positive elderly women received hormonal therapy.

**Estimating Cost Effectiveness of Adjuvant Therapies Using Decision Analysis**

Metaanalysis, decision analysis, and cost-effectiveness analysis are conceptually related quantitative methods used to combine information to arrive at a summary conclusion [6]. The historical impetus for the development of each of these three methods grew out of the need to resolve uncertainty: for metaanalysis, uncertainty about conflicting results in the medical literature; for decision analysis, uncertainty about management of clinical problems; and for cost-effectiveness analysis, uncertainty about how to best allocate finite resources.

Although each of these methods appears superficially simple, their proper conduct can be complex and may rely on multifaceted methodology. The skills required to perform these type of analyses include extensive knowledge of research study design, practical skills and knowledge of the limitations and data collection, statistics, and critical appraisal of the published literature. These skills are also used in other areas of outcomes research and are the cornerstone of practice guidelines development.

Decision analysis is a quantitative approach that assesses the relative value of different decisions or decision options. In a medical setting, these typically are physician actions such as testing or
treatments [7]. The information from a decision analysis is derived from a hypothetical cohort of patients and is used to recommend management for an individual patient or to formulate policy recommendations for a group of similar patients. As outlined in an earlier article in the symposium (Smith and Hillner), decision analysis begins by systematically breaking a problem down into its component parts and creating a decision tree to represent the components and decision options. The uncertainties in the various components (trees) are identified. The medical literature or expert opinion is used as a source to estimate probabilities and define the range of uncertainties around these probabilities. The values for each outcome, such as survival or quality-adjusted survival, are measured or inferred.

**Node-Negative Disease and Other Questions** - The previously described metaanalysis was originally reported in 1988 [11] and subsequently updated in 1992 [1]. In 1988, the National Cancer Institute issued a Clinical Alert to all physicians recommending that all node-negative breast cancer patients be considered for treatment with adjuvant chemotherapy [12]. The question of whether to recommend chemotherapy for these patients has focused on the difference in the relative and absolute benefits of chemotherapy, since women with node-negative disease have a relatively low risk of subsequent systemic recurrence. All women with breast cancer experience anxiety about their potential future survival, but if adjuvant chemotherapy is given to all node-negative patients, all would experience the adverse effects of chemotherapy and incur the costs of treatment, while the majority might not experience an increase in survival.

For this and subsequent questions, we developed a decision analysis model based on the conceptual framework outlined in Table 2 [8-10]. The model addresses the question from a societal perspective using hypothetical cohorts of women who did or did not undergo chemotherapy and who are subsequently followed using a mathematical Markov process to assess their lifetime survival and risk of recurrence. The model describes nine different health states possible after diagnosis, from wellness to death.

The initial study of node-negative patients used a relative risk reduction of 30%, based on reports from randomized clinical trials, and this was subsequently confirmed by the 1992 metaanalysis. The model considered only direct health care costs based on a retrospective cost analysis of individuals at one academic health center and published cost estimates for treating disease recurrence. The model was done with and without quality of life adjustments based on the use of a linear analog scale of surrogates. Since this was a hypothetical cohort, no specific comorbidities were considered or patients excluded.

The model showed that the benefit of adjuvant chemotherapy was highly dependent on the likelihood of disease recurrence, which varied with patient age and biologic features of the tumor. As shown in Figure 2, an average 45-year-old woman with an estimated annual recurrence risk of 4% would have survival benefit of an increase in quality-adjusted life expectancy of about 5 months. However, for older women with smaller cancers with an annual recurrence rate of 1%, the benefit would decrease to less than 1 month. In contrast, in women with an 8% annual probability of recurrence, such as those with a large estrogen-receptor negative tumor, the treatment would increase quality-adjusted survival by approximately 8 months.

The model, by translating the results of the metaanalysis into units that are more intuitively accessible to patients, physicians, and policymakers, has been used to tailor recommendations to individual patients and guide policy development. The relative cost effectiveness of adjuvant chemotherapy for those women who are at average (4% to 5%) or high risk of recurrence (6% to 8%) is within commonly accepted ranges of less than $30,000 per quality-adjusted life year (QALY).

**Cost Comparisons** - We have done similar assessments exploring the use of adjuvant chemotherapy in the elderly and the use of combination chemotherapy and tamoxifen (Nolvadex) in premenopausal women. For each of these settings, it was found that the absolute benefit of therapy dominated the cost-effectiveness determinations. Given the relatively modest cost of chemotherapy, if it is effective in a community setting, then it is anticipated to have an acceptable incremental cost-effectiveness ratio based on comparisons with other commonly performed medical interventions such as hemodialysis or treatment of hypertension.

As stressed by others in this symposium, there is no defined threshold of an acceptable or unacceptable incremental cost-effectiveness ratio. Hemodialysis is a reference value commonly used by default, since it is paid for as a societal entitlement. Expanded discussions of the role of cost effectiveness in the evaluation and adoption of new technologies are available [13-15].

**Limitations of Decision Analysis Models** - The primary limitations of these models were in the precision of the cost data and the relative crudeness in the quality of life assessments. The monitoring of the costs of the delivery of adjuvant therapy and the subsequent management of...
patients with breast cancer has been relatively little explored outside older assessments of Medicare-eligible elderly patients. Large prepaid health plans in the United States have expressed interest in further assessing this question, but, to date, their work has been primarily for internal purposes and has not been published.

Current and Future Approaches to Determining Cost Effectiveness in Early Breast Cancer

**Retrospective vs Prospective**-The previously described decision analysis models are based on hypothetical cohorts of patients. The previously described study from British Columbia is one of only a few retrospective cohorts reporting community effectiveness of therapy. Since in most states cancer is a reportable disease, further assessments using registry data should be pursued. However, retrospective assessments are limited by well-known flaws and plagued by incompleteness. The future of cost and outcomes assessments is in the prospective assessment of cohorts in a randomized trial setting (efficacy) and/or cohorts within an integrated delivery system (effectiveness).

The advantages of prospective assessment of economic and quality of life analyses of medical interventions are outlined in Table 3 and are discussed elsewhere in detail in this symposium (Bennett and Westerman). We are unaware of any prospective economic assessments within integrated health plans. In the randomized trial settings, doing an economic analysis within the clinical trial is being increasingly considered and occasionally incorporated into the primary data collected within the trial. This topic was recently addressed at a conference sponsored by the National Cancer Institute [16].

**When Are Quality of Life and Economic Assessments Warranted?**-Table 4 lists factors supporting an economic analysis of a clinical trial. For breast cancer, most of these factors apply, given that any new form of therapy is likely to supersede and rapidly supplant other interventions. Whether the alternative strategies differ substantially in cost and/or quality of life is more difficult to ascertain.

Table 5 shows our assessment of whether different categories of clinical questions currently being investigated in early breast cancer warrant quality of life and/or economic companions. The scoring on a 0 to 4 point scale is solely the opinion of the authors.

The use of neoadjuvant chemotherapy before surgical management vs traditional approaches is unlikely to have major economic differences; rather, quality of life associated with breast preservation vs mastectomy is the primary question. Studies assessing dose sequencing are primarily an issue of pure treatment efficacy with subsequent quality of life and economic factors related only to recurrences.

Studies involving high-dose or dose-intensive therapy with stem cell support and growth factors are obvious candidates for this type of companion assessment. This is particularly true if the relative efficacy compared to the standard approach is relatively modest. The finding from other treatment settings where quality of life directly relates to treatment response is more difficult to show in the adjuvant setting where there is minimal disease-specific morbidity. Therefore, quality of life assessments are likely to provide useful insights.

A major finding of the 1992 metaanalysis was the size of the efficacy of ovarian ablation, compared with other antiestrogen approaches. There are several ongoing trials in which single vs multimodal endocrine therapy for premenopausal women is being studied. Quality of life determination of multimodal endocrine therapy, specifically including ovarian ablation, is a totally unexplored area. Economic considerations are unlikely to be a major factor unless the size of the relative benefits of the superior, presumably more intensive and expensive therapy, are modest.

The 1992 metaanalysis found that chemotherapy plus tamoxifen appears superior to tamoxifen alone in estrogen-receptor-rich women. However, the number of patients was relatively small, and this comparison was an indirect one. Direct comparisons of chemotherapy plus tamoxifen compared with tamoxifen alone within the assessment had confidence intervals that included no additional benefit. If the survival benefit in subsequent studies is confirmed to be this large (eg, relative risk reduction of 20% or more), then quality of life and economic factors will be clearly dominated by the superior efficacy of combination therapy. However, if the benefit is unfortunately small (eg, relative risk of less than 10%), these factors will play a role in the formulation of guidelines for use of adjuvant chemotherapy in this population.

About 35% of new breast cancers occur in elderly women (age greater than 70), but these patients have been generally excluded from prior randomized assessments. Two major questions, involving
the need for axillary node dissection and the use of radiotherapy after breast-conserving surgery, have clear quality of life and economic implications for these women. Whether an axillary node dissection is necessary when adjuvant tamoxifen is used after primary surgical control has been actively debated [17]. Axillary node dissection has a clearly defined risk of morbidity due to lymphedema and has modest economic consequences due to either a prolonged hospital stay or a longer surgical procedure. However, axillary node dissection may reduce axillary recurrence.

Studies have shown that 30% to 50% of elderly women treated with breast-conserving surgery do not receive local radiation therapy [5,18]. This withholding of radiation therapy after breast-conserving surgery probably reflects the influences of patient preference and physician practices, and may reflect an implicit effectiveness or cost-effectiveness judgment by the physician. Whether this is appropriate depends on the local risk of recurrence, especially if adjuvant tamoxifen is given. Therefore, the International Breast Collaborative Trial 10-93 addressing this question is critical and should have a retrospective economic assessment.

**Conclusion**

The evaluation in randomized clinical trials of adjuvant treatments in early breast cancer is the richest of any area of oncology. Our prior work has shown that if an adjuvant therapy is effective, it will generally have an incremental cost-effectiveness ratio that is less than most commonly performed interventions. Future cost-effectiveness assessments should expand from retrospective studies of hypothetical cohorts to prospective evaluations within clinical trials or integrated health delivery systems.

**References:**


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