



Current Perspective

Decision-making in early breast cancer: guidelines and decision tools

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Abstract

The meta-analysis of trials of adjuvant systemic therapy for early breast cancer provides robust information on the impact of both cytotoxic chemotherapy and tamoxifen on relapse-free and overall survival to 15 years from diagnosis. These data are described in terms of relative risk reduction and are not meant to be viewed as a prescription for therapy. To translate relative risk reductions into absolute benefits for the individual patient and then trade off the gains against the long-term and short-term side-effects and toxicities is a highly complex process for the clinician, and current guidelines are formatted in such a way that they fail to use current information in a way that allows a quantitative assessment of the benefits and risks of adjuvant therapy. This review article explores current guidelines and describes some aids that may be used to help inform women about their treatment options for early breast cancer. © 2002 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Medical decision-making was a complex problem in the days before evidence-based medicine. Paradoxically with the dawning of this golden age, with data beginning to replace prejudice, the process is if anything more complex. If the randomised controlled trial is considered the ‘gold standard’ for decision-making in evidence-based medicine, then a meta-analysis or overview of many such trials has come to be regarded as the ‘platinum standard’, to coin a new phrase. Yet it is only the most naïve of clinicians or most foolhardy statistician who can truly believe that a statistical overview provides a prescription for treatment. Nowhere is this truer than in the management of early breast cancer. For over 30 years, this enigmatic disease has been the subject of large scale randomised controlled trials investigating every aspect of its treatment. Furthermore, these randomised controlled trials have been the subject of formal overview analysis at 5-yearly intervals from 1985 to the year 2000 [1–4]. These overviews allow the

clinician to be confident that certain subsets of breast cancer patients benefit from some systemic adjuvant therapy options, but do not give a quantitative value as to what the benefit will be for an individual patient with early breast cancer.

Within the last year, three influential groups have published consensus guidelines for the systemic adjuvant therapy of breast cancer. These guidelines reach somewhat different conclusions as to therapy for Stage 1 node-negative breast cancer. It is thus of interest to compare the published guidelines and to reflect on the relative strengths and weaknesses of using current guideline recommendations for treatment planning, and for using currently formatted guidelines in general. Fig. 1 graphically compares the guideline recommendations.

The simplest of the guidelines about the adjuvant use of chemotherapy are those that were reached by the November 2000 National Cancer Institute (NCI) Consensus panel [5]. The guideline statement text states, “On the basis of available data, it is accepted practice to offer cytotoxic chemotherapy to most women with lymph node metastases or with primary breast cancers larger than 1 cm in diameter (both node-negative and node-positive). For women with node-negative cancers less than 1 cm in diameter, the decision to consider chemotherapy should be individualised.” The guidelines

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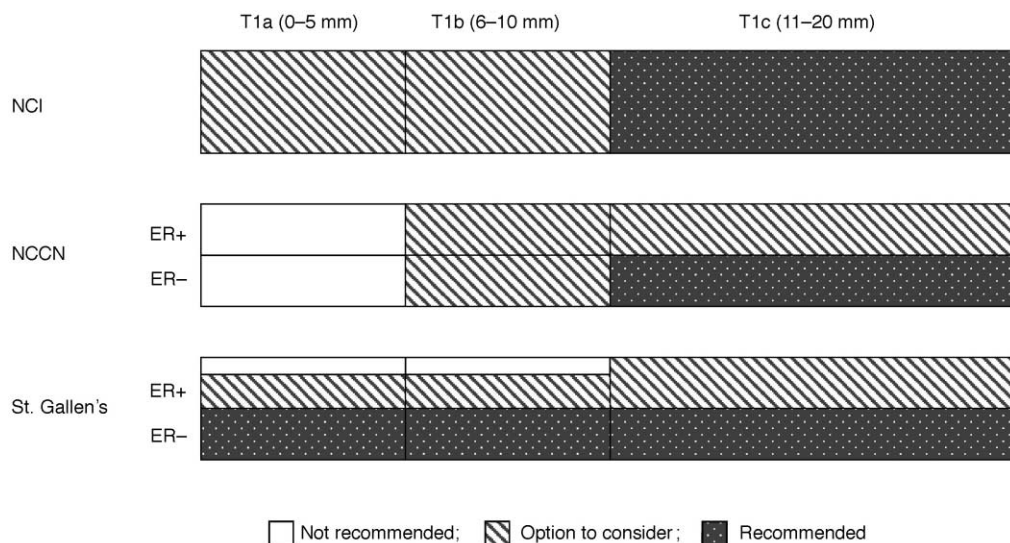


Fig. 1. Contrasting recommendations about chemotherapy from the different guidelines. NCI, National Cancer Institute; ER–, oestrogen receptor-negative; ER+, oestrogen receptor-positive; NCCN, National Comprehensive Cancer Network.

do not provide guidance as to which low-risk node-negative patients might not be considered candidates for adjuvant chemotherapy beyond those patients with favourable histological subtypes, such as patients with small tubular and mucinous cancers. Following these guidelines, virtually all node-negative patients would have chemotherapy therapy considered as an option.

A more comprehensive statement about the adjuvant therapy of early breast cancer has been published by the National Comprehensive Cancer Network (NCCN) [6]. In this set of guidelines, the only set of Stage 1 patients for whom chemotherapy is considered mandatory are patients with oestrogen receptor-negative tumours >10 mm in size. For patients with tumours >5 mm in size adjuvant chemotherapy is an option, to be favoured if the patient's tumour had unfavourable features such as angiolymphatic invasion, high mitotic rate, or poor histological or nuclear grade. For patients with T1a tumours or for patients with favourable histological subtypes (tubular, mucinous, medullary), adjuvant chemotherapy was not recommended.

The most detailed set of guidelines was produced by the St Gallen's Consensus Panel [7]. In this set of guidelines, adjuvant chemotherapy is the preferred option for all stage 1 oestrogen receptor-negative patients, irrespective of tumour size. Adjuvant chemotherapy is an option to be considered for all oestrogen receptor-positive patients, except for the very small subset of patients who have tumours ≤10 mm in size who have Grade 1 tumours and are older than 35 years of age.

What is striking about these three sets of guidelines is how little agreement there is between them. The only points that they agree on is that patients with oestrogen receptor-negative tumours with tumours >10 mm should receive adjuvant chemotherapy, and that for

patients with oestrogen receptor-positive T1b tumours chemotherapy might be considered as an option. In many common clinical scenarios, patients would be given radically different therapies. For example, a 50-year-old woman with a stage 1 oestrogen receptor-negative moderately differentiated 4 mm tumour would be told that systemic adjuvant therapy was mandated, not indicated, or possibly to be considered, by doctors following the St Gallen's, NCCN or NCI guidelines, respectively.

How is such a wide divergence of opinions possible, given that all of the guidelines are derived from evidence-based reviews? We would suggest guidelines are widely divergent because they lack quantitative underpinnings. Specifically, in the guidelines mentioned here, there are no quantitative estimates for what might be expected to be gained in terms of probability of survival and avoidance of relapse, and also no quantitative estimates of what the costs might be in terms of short-term and long-term risks of side-effects, and simple expenditure of money. A crucially important point is that although it is clear that many patients will accept very low degrees of benefit, women differ in the amount of benefit that is felt to be worthwhile in order to make taking adjuvant systemic chemotherapy therapy worthwhile [8]. Thus, it is going to be impossible to draw up guidelines of who should and who should not be offered adjuvant therapy that would make sense for all breast cancer patients.

There are more quantitative alternative evidence-based approaches to guidelines that might be used in adjuvant therapy decision-making. Three of the most highly developed are the Q-TWiST method, the use of Decision Boards, and computer programs aimed at shared decision-making.

2. Q-TWiST

The first of these is the Q-TWiST method developed by Richard Gelber and his colleagues [9]. This method estimates Quality adjusted Time Without Symptoms or Treatment. The basic methodology depends on giving weighted values to different health states. These values can range from 1.0 (good health with no symptoms due to therapy or cancer), to 0.0 at time of death, intermediate values reflecting lesser health states due to toxicity of therapy or symptoms of cancer. The state of the average patient getting different treatment options is integrated over time and an estimate of quality adjusted time can be derived.

This methodology can be applied to real clinical trial data, and estimates can be derived from different subsets of patients who have participated in clinical trials [10]. The results of the meta analysis of the trials of adjuvant chemotherapy analysed according to Q-TWiST have recently been published in the *Lancet* [11]. The authors concluded that overall chemotherapy-treated younger women gained an average of 10.3 months of relapse-free survival and 5.4 months of overall survival within 10 years compared with the no-chemotherapy group. After adjustment for toxicity and the utility for surviving with relapse, the estimate of TWiST was a more modest 4.3 months, with the interpretation of whether patients were gaining Q-TWiST highly dependent on the estimates of the value of the time spent undergoing chemotherapy and the value of time after relapse (see figures 2 and 3 and table 1 of Ref. [11]).

The Q-TWiST method is powerful, but it is one that is difficult to apply in a practical sense to individual patients. Specifically, it is highly dependent on the value placed on different health states. It is also not represented in a format where a clinician can ask a simple question such as, “How much benefit (in terms of Q-TWiST) might a 60 year old woman with a Stage 1 oestrogen receptor-negative cancer expect given a specific type of chemotherapy?” It is in theory possible to develop such a tool but, in a practical sense, none exists at this time.

3. Decision Boards

Another approach is a Canadian effort that produces ‘Decision Boards’ [12–14]. On the Decision Boards, preprinted segments can be arranged to show to the patient the consequences in terms of reduction of the risk of relapse or death (shown as pie charts). In addition, information about the risk of treatment-related toxicity is presented. This method is well accepted by physicians and their patients. These Decision Boards are produced for a set of scenarios (different stages of disease and different treatment options).

This method has the power that it presents to the patient in understandable terms the trade-offs between risk and benefit that might be expected by the patient for different treatment options.

4. Shared decision-making computer programs

A third approach is that of the development of computer programs that are designed to be used to help adjuvant therapy decision-making. An example of this approach is the computer program, Adjuvant! [15]. This program produces printout sheets that are shared between the doctor and the patient for discussion of the possible benefit of different treatment options, and also the risk of toxicity and side-effects. This method is more flexible in that it recalculates its estimates of risk of relapse and death, and estimates of the benefit of adjuvant therapy on the basis of information entered about individual patients.

Fig. 2 shows the main screen for Adjuvant!. Examination of its elements makes it immediately apparent how difficult it is to write a simple set guidelines for adjuvant therapy. Guidelines need to take into account measures of competing mortality (patient age and comorbidity); measures of the risk of tumour-related mortality (tumour size, nodal involvement and additional prognostic information such as histological grade); and finally the effectiveness of the adjuvant therapy options being considered (which are affected by age, oestrogen receptor status and the type of adjuvant therapy).

The program draws on information from major databases and meta-analyses to make estimates of cancer-related and non-cancer-related mortality, and for the estimates of the effectiveness of adjuvant therapy options. An example, using this tool for making estimates of the impact of survival of the most common presentation for an individual breast cancer patient today, is shown in Fig. 2. The median age of breast cancer patients is 65 years. The average patient is not in perfect health, but has some minor comorbidity. The most common presentation is as a patient with a Stage 1, node-negative, T1c, tumour of moderate histological grade and a positive oestrogen receptor status.

In the next 10 years, Adjuvant! projects that this woman without adjuvant therapy would be expected to have a 9% chance of dying of breast cancer and a 12% chance of dying of other causes. How much would system adjuvant therapy improve her outcome? Tamoxifen would be expected to confer a 28% proportional risk reduction. This translates at 10 years into a 2% survival advantage. What about adding systemic adjuvant chemotherapy therapy? For example, using a regimen with an efficacy of cyclophosphamide, methotrexate, 5-fluorouracil (CMF). The overview gives an estimate of

Fig. 2. Main screen of the decision aid, Adjuvant!

<10% for the proportional risk reduction afforded by adjuvant CMF-like therapies in oestrogen receptor-positive, postmenopausal women [3]. Adjuvant! uses an estimate of 8%. This translates into a net benefit of only approximately ~1% (0.6%). Adjuvant! supplies general information about the risks associated with adjuvant CMF and age-specific information about the risks of 5 years of tamoxifen [16].

Such a woman would be making the choice between no adjuvant therapy, hormonal therapy alone (with a 2% improvement) or combined chemo-hormonal therapy with perhaps an additional 1% benefit. Interestingly, the NCI guidelines would suggest the standard of care would include adjuvant chemotherapy for such a patient, the NCCN and St Gallen's guidelines would suggest that chemotherapy be considered as an option. None of these guidelines would have made apparent what the magnitude of benefit for adjuvant chemotherapy would be.

5. Other decision points during the treatment of early breast cancer

There are a number of other decisions that are made during the treatment of early breast cancer. For women with invasive breast cancers, these include: (1) choice of surgical options (mastectomy, mastectomy plus reconstruction, versus breast-conserving therapy plus radiation), (2) decision as to where to have the post-

mastectomy chest wall radiation, and (3) whether tamoxifen should be considered as an adjuvant therapy for the prevention of contralateral second primaries. For women with *in situ* cancers, there are similar questions regarding surgery, radiation and endocrine therapies. For a number of these issues, there are 'Guidelines' but, in most instances, there are few quantitative tools that allow an individual to make an informed choice. An example of a useful tool is the Gale Model breast cancer risk assessment tool [17], which allows the risk of developing a primary breast cancer to be estimated by individuals but, unfortunately, it does not allow assessment of the risk of side-effects of tamoxifen to be assessed (the strong age dependency of these effects are not generally appreciated, and patients are generally given inaccurate average values) [16].

6. Summary

A wealth of quantitative information about outcome is being obtained from randomised clinical trials. From these results, evidence-based guidelines are being derived. Unfortunately, these guidelines often give little or no quantitative information about the magnitude of benefit that might be expected or given up by following them. Although derived from the same information, different guidelines often give different recommendations,

in part because of differing underlying assumptions, one of which is the clinician's view of what amount of benefit would be considered worthwhile. In this time of more informed patients who have an expectation of participation in the decision-making process, non-quantitative guidelines are often less than satisfying and decision tools may have some special advantages.

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