Cancer Care Ontario Practice Guidelines Initiative
Sponsored By:
Cancer Care Ontario & the Ministry of Health and Long-term Care

Adjuvant Systemic Therapy for Node-negative Breast Cancer

Practice Guideline Report #1-8

ORIGINAL GUIDELINE: November 12, 1998
UPDATE: February 2002

The Breast Cancer Disease Site Group is rewriting this practice guideline report. The revised guideline report will incorporate all new evidence that has become available since the guideline was completed in 1998. The new evidence under review is noted below (labelled NEW), and is identified in the update sections of the full report. The current guideline recommendations remain in effect.

SUMMARY

Guideline Question
What is the role of systemic adjuvant therapy for women with node-negative breast cancer?

Target Population
These recommendations apply to adult patients with node-negative breast cancer.

Recommendations
Choice of Therapy

- **Pre- and postmenopausal** women at **minimal or low risk of recurrence** (<2 cm, well-differentiated and all other factors favourable or <1 cm, intermediate grade and all other factors favourable) should receive no adjuvant systemic treatment. They should however be made aware that systemic therapy is offered to women at higher risk of recurrence.

- **Premenopausal** women (age <50 years) at **moderate risk of recurrence** (1-3 cm and intermediate grade, or 2-3 cm and well-differentiated) and with estrogen-receptor-positive tumours should be offered tamoxifen. Chemotherapy added to tamoxifen may provide a modest incremental benefit over tamoxifen alone. This is an ideal situation for a decision aid.

- **Premenopausal** women (age <50 years) at **high risk of recurrence** (>3 cm, irrespective of any other factors, or >1 cm with either estrogen-receptor-negative, high grade or lymphatic/vascular invasion) should be offered chemotherapy. There are insufficient data at the present time to recommend the addition of tamoxifen to chemotherapy in this subgroup. If the patient refuses chemotherapy and the tumour is estrogen-receptor-positive, tamoxifen may be considered. There is insufficient data to determine the risk category of a tumour <1 cm in diameter associated with a poor prognostic factor (e.g., grade III, estrogen-receptor-negative, lymphatic/vascular invasion).
Postmenopausal women (age >50 years) at high risk of recurrence (>3 cm, or >1 cm with high grade or lymphatic/vascular invasion) and with estrogen-receptor-positive tumours should be offered tamoxifen plus chemotherapy. The benefits and risks of additional chemotherapy should be discussed with the patient. If the patient refuses chemotherapy, then tamoxifen alone should be considered. Postmenopausal women at high risk of recurrence and with estrogen-receptor-negative tumours should be offered chemotherapy.

Postmenopausal women (age >50 years) at moderate risk of recurrence (1-3 cm and intermediate grade, or 2-3 cm and well-differentiated) and with estrogen-receptor-positive tumours should be offered tamoxifen. Chemotherapy added to tamoxifen may provide a modest incremental benefit over tamoxifen alone. This is an ideal situation for the use of a decision aid.

**Duration of Tamoxifen**
Hormonal therapy should consist of oral tamoxifen 20 mg daily for five years.

**Chemotherapy Regimen**
Polychemotherapy should reasonably comprise six cycles of cyclophosphamide (oral), methotrexate, fluorouracil (CMF) or four cycles of doxorubicin /cyclophosphamide (AC).

**Process of Decision-making**
A patient with node-negative breast cancer should be informed of the availability of adjuvant systemic therapy and should be offered the opportunity of discussing such therapy with an expert clinician. She should be provided with detailed information concerning her risk of recurrence if untreated, the potential efficacy of adjuvant therapy in terms of recurrence and mortality, and the potential side effects of therapy.

**Methods**
A systematic search for practice guidelines, meta-analyses and randomized trials was carried out through September 1996 using MEDLINE (from 1980) and CANCERLIT (from 1983). The search was updated in November 1997 and August 1998 using the MeSH heading breast neoplasms/dt, the text words “node” and “negative”, and “random:” as part of a text word, MeSH heading or publication type. Use was also made of review articles, textbooks and abstracts from major breast cancer meetings up to May 1998.

Evidence was selected and reviewed by two members of the Cancer Care Ontario Practice Guidelines Initiative’s (CCOPGI) Breast Cancer Disease Site Group and methodologists. This practice guideline has been reviewed and approved by the Breast Cancer Disease Site Group, which comprises surgeons, medical oncologists, radiation oncologists, epidemiologists, a pathologist, a medical pathologist and a community representative.

External Review by Ontario practitioners was obtained through a mailed survey. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee. The CCOPGI has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature, and where appropriate, integration of this literature with the original guideline information.

**NEW**
Entries to MEDLINE (to January 2002), the Cochrane Library (Issue 1, 2002) and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (1999-2001) have been searched for evidence relevant to this practice guideline. The most recent literature search was performed in February 2002.
Key Evidence

- Two individual-patient-data meta-analyses were updated in August 2001. One analyzed data from 17,723 women involved in 47 randomized trials of long-term polychemotherapy versus no chemotherapy. The other was based on data from 55 randomized trials of tamoxifen versus no tamoxifen with a total of 37,099 participants.

- Adjuvant chemotherapy reduced the rate of disease recurrence (24% relative reduction in the annual hazard of recurrence compared with no chemotherapy) and improved survival (relative reduction in the annual hazard of death was 15%) in women with breast cancer. Relative reductions in recurrence and death rates were similar for patients with node-negative and node-positive disease.

- Adjuvant tamoxifen reduced the rate of disease recurrence (26% relative reduction in the annual hazard of recurrence compared with no tamoxifen) and improved survival (relative reduction in the annual odds of death was 15%) in women with breast cancer. Relative reductions in recurrence and death rates were similar for patients with node-negative and node-positive disease, but did vary by length of tamoxifen treatment. Relative reductions in recurrence rates were 18% with one year of tamoxifen, 25% with two years and 42% with five years; relative reductions in death rates were 10% with one year of tamoxifen, 15% with two years and 22% with five years.

- Chemotherapy can be associated with a variety of adverse effects such as alopecia, nausea and vomiting, and infection. There are relatively few adverse effects associated with tamoxifen but very rarely tamoxifen can cause venous thromboembolism or endometrial cancer.

Prepared by the Breast Cancer Disease Site Group

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PREAMBLE: About Our Practice Guideline Reports

The Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the CCOPGI using the methodology of the Practice Guidelines Development Cycle.¹ The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, community representatives and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

For the most current versions of the guideline reports and information about the CCOPGI and the Program, please visit our Internet site at: http://www.cancercare.on.ca/ccopgi/
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FULL REPORT

Original guideline information and new information that has emerged from review and updating activities is labelled ORIGINAL and UPDATE, respectively.

I. QUESTION
What is the role of systemic adjuvant therapy for women with node-negative breast cancer?

II. CHOICE OF TOPIC AND RATIONALE
Although adjuvant systemic therapy was already commonly used in women with node-positive breast cancer in the early 1980s, it was not routinely used in women with node-negative disease (1). In 1988, the US National Cancer Institute issued a "Clinical Alert" based on the early results of several randomized trials evaluating systemic therapy in node-negative breast cancer patients (2). They suggested that adjuvant hormonal therapy or chemotherapy might have a meaningful impact on the natural history of node-negative breast cancer. Following the alert, adjuvant systemic therapy began to be used more commonly in routine clinical practice (1).

The concern was raised, however, that many patients with node-negative breast cancer have a very low risk of relapse following initial surgery alone. If all patients with node-negative disease were to be treated, many patients might be subjected to unnecessary therapy with associated adverse effects. Two concepts then evolved. Firstly, that systemic therapy should be reserved for those node-negative patients at increased risk of recurrence based on certain intrinsic characteristics of the tumour (3). This led to much research attempting to identify prognostic factors predictive for recurrence. Secondly, the type of systemic therapy used should be based on factors predicting treatment response. These factors identify patient subpopulations that have a larger or smaller probability of response to a given systemic therapy.

Two main forms of adjuvant systemic therapy have been used: chemotherapy and hormonal therapy. Chemotherapy consists of the use of various cytotoxic drug combinations. Hormonal therapy refers to treatment with the antiestrogen tamoxifen.

III. METHODS
Guideline Development
This guideline report was developed by the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI), using the methodology of the Practice Guidelines Development Cycle1. Evidence was selected and reviewed by two members of the CCOPGI's Breast Cancer Disease Site Group (Breast Cancer DSG) and methodologists. The guideline is a convenient and up-to-date source of the best available evidence on the role of systemic adjuvant therapy for women with node-negative breast cancer, developed through systematic reviews, evidence synthesis and input from practitioners in Ontario. It is intended to enable evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

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The CCOPGI has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature, and where appropriate, integration of this literature with the original guideline information.

Guideline History
This practice guideline report was originally completed on November 12, 1998 and published in *Current Oncology* 1999;6(2):78-89. The guideline was reviewed monthly in 1999, and quarterly beginning in 2000 with the most recent update being February 2002. Original guideline information and new information that has emerged from review and updating activities is labelled ORIGINAL and UPDATE, respectively, in this report.

Literature Search Strategy

**Original: November 1998**
A systematic search for practice guidelines, meta-analyses and randomized trials was carried out through September 1996 using MEDLINE (from 1980) and CANCERLIT (from 1983). The search was updated in November 1997 and August 1998 using the MeSH heading breast neoplasms/dt, the text words “node” and “negative”, and “A\random:” as part of a text word, MeSH heading or publication type. Use was also made of review articles, textbooks and abstracts from major breast cancer meetings up to May 1998.

**Update: February 2002**
The literature search was revised to combine disease-specific text words and subject headings (breast, mammary, cancer, carcinoma, neoplasm[s], node[-]negative), treatment-specific terms (antineoplastic agents, chemotherapy, tamoxifen, hormonal therapy, antiestrogen, adjuvant, systemic therapy), and design-specific terms (meta-analysis, randomized controlled trial[s]). The literature search has been updated with the revised search terms using MEDLINE (through January 2002), the Cochrane Library (Issue 1, 2002), the Physician Data Query (PDQ) database, and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (1999-2001). The literature search was not restricted by language of publication.

Inclusion Criteria

**Original: February 1996**
The original guideline did not explicitly define inclusion criteria.

**Update: February 2002**
Articles were selected if they were meta-analyses or randomized controlled trials comparing systemic adjuvant therapies in the treatment of women with node-negative breast cancer. Outcomes of interest included overall or disease-free survival, local recurrence, distant recurrence, or quality of life.

Evidence-based practice guidelines addressing the guideline questions were also included. Both abstract and full reports were eligible.

IV. RESULTS

Chemotherapy

**Original: November 1998**
Several randomized trials have been conducted evaluating different chemotherapy regimens in women with node-negative breast cancer. In the early trials, node-negative patients were a subgroup of a larger study population, while in the more recent trials, chemotherapy was evaluated specifically in node-negative patients. These later trials will be briefly reviewed after describing a meta-analysis, published originally in 1988, and updated in 1992 (4) and 1995 (5). The most important summary of the evidence related to chemotherapy comes from this large meta-analysis which was based on individual patient data (Table 1). The four trials (Table 2) described were all
included in the meta-analysis and results from these trials were consistent with the results of the meta-analysis.

The Early Breast Cancer Trialists conducted a meta-analysis of 31 trials evaluating adjuvant polychemotherapy in 11,000 women with early stage breast cancer (4). Although different chemotherapy regimens were used in the trials, cyclophosphamide, methotrexate, fluorouracil (CMF) was one of the more common regimens. In 2,710 patients with node-negative breast cancer, the relative reduction in the risk (annual odds) of recurrence was 26% (standard deviation [SD], 7; p<0.0001) and the relative reduction in mortality was 18% (SD, 8; p=0.03) when chemotherapy was compared with control. The five- and ten-year disease-free survival (DFS) rates for patients who received chemotherapy were 75.0% and 61.5%, respectively. The corresponding values for the control patients were 67.0% and 54.5%. The survival rates at ten years were 67.2% with chemotherapy and 63.2% with control. Chemotherapy was associated with reductions in the risk of recurrence and death in all age groups, although the effect size was greatest in women less than 50 years of age. The risk reduction for recurrence or death for node-negative and node-positive patients combined was 36% (SD, 5) for women less than 50 years, 29% (SD, 5) for women 50 to 59, and 20% (SD, 5) for women 60 to 69 years. No effect was observed in women over 70 years of age, but the numbers of patients in this group was relatively small.

In the 1995 update of the meta-analysis, the recurrence-free survival at ten years for node-negative patients < 50 years of age who received chemotherapy was 68.3% compared with 58.0% for control patients (p<0.00001) (5). The corresponding data for survival at ten years were 77.6% and 71.9% respectively (p=0.02). For node-negative women who were 50-60 years of age, the ten-year recurrence free survival was 65.6% for women who received chemotherapy compared with 59.9% in the control group (p=0.0007). The corresponding data for survival were 71.2% and 64.8% respectively (p=0.005).

In the Milan trial, 90 node-negative patients with estrogen-receptor-negative tumours were randomized to nine months of CMF or no treatment (6). There was a statistically significant improvement in both DFS (85% in the CMF group compared with 42% (7) in the control group; log-rank p=0.0001) and overall survival (86% in the CMF group compared with 58% in the control group; log-rank p=0.006) seven years after surgery in the women who received chemotherapy. The separation between the survival curves for both disease-free (p=0.008) and overall (p=0.03) survival was maintained over an extended period of follow-up (7). Nine to 12 years after surgery, DFS rates were 71% for the CMF group and 43% for the control group; overall survival rates were 80% and 50%. However, concern has been raised with the results of this trial because the control patients did so poorly.

In the trial conducted by the Ludwig group, 1275 women with node-negative breast cancer were randomized to one month of adjuvant CMF or no treatment (8). The five-year DFS rate was significantly improved with chemotherapy (74% alive and disease-free compared with 68% in the control group; hazard ratio, 0.78; 95% confidence interval (CI), 0.63 to 0.96; p=0.02). Five years after mastectomy, 88% of the treated group and 85% of the control group were alive (hazard ratio, 0.85; 95%CI, 0.62 to 1.16; p=0.31).

In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-13 trial, 679 node-negative patients with estrogen-receptor-negative tumours were randomized to sequential methotrexate and fluorouracil or no treatment (9). The four-year DFS rate was improved from 71% to 80% with chemotherapy (log rank p=0.003). Survival rates were similar after four years of follow-up (87% in the chemotherapy group compared with 86% in the control group, log rank p=0.8). A subsequent report on long-term follow-up described eight-year DFS rates of 74% with chemotherapy and 59% for control (p<0.001). At eight years, 82% of treated patients and 77% of control patients were alive (p=0.06) (10).

In the Intergroup trial, 406 women with either estrogen-receptor-negative tumours or tumours ≥3 cm in diameter were randomized to cyclophosphamide / methotrexate / fluorouracil / /prednisone (CMFP) or no treatment (11,12). There was a significant increase in the three-year
DFS rate with chemotherapy (84%) compared with observation (69%) (log rank p=0.0001). This benefit was maintained at the five-year follow-up when DFS rates were 83% with chemotherapy and 61% with observation (log rank p<0.0001). The five-year survival rates were 86% for the treated group and 80% for the control group (log rank p=0.31).

Adjuvant chemotherapy can be associated with adverse effects. The type of adverse effect and its frequency is dependent on the chemotherapy regimen. Nausea and vomiting are generally well controlled with antiemetics. Alopecia (reversible) occurs in approximately 40% of patients receiving CMF-type chemotherapy. Hospitalization for febrile neutropenia occurs in approximately 1% of patients. Amenorrhea occurs in approximately 50% of patients and venous thromboembolism in approximately 2% of patients. Anthracycline-containing chemotherapy is associated with more acute nausea and vomiting than CMF, and with complete alopecia. There is the theoretical risk of cardiac injury with anthracycline-based chemotherapy but it is likely to be very rare with conventional doses. Chemotherapy can theoretically be leukemogenic. In a review of a series of trials of CMF-containing adjuvant therapy conducted in Milan, three cases of leukemia were observed in 2,465 patients (cumulative risk at 15 years equals 0.23%) (13). The NSABP has reported two cases of leukemia in 1,562 patients who received standard-dose doxorubicin/cyclophosphamide (AC) (14).

Update: February 2002
The Early Breast Cancer Trialists' meta-analysis (4) was updated in 1997 (1u) and 2001 (2u). The latest analysis includes data from 47 randomized trials of prolonged adjuvant polychemotherapy versus no chemotherapy in 17,723 women with early stage breast cancer (1u). Nineteen trials evaluated cyclophosphamide, methotrexate and fluorouracil (CMF). Patients with node-negative breast cancer were included but the number of women in this subgroup is not reported. The authors of the meta-analysis state that there were no significant differences in relative risk reductions for mortality or recurrence between node-positive and node-negative disease. Overall, the relative reduction in the risk (annual hazard) of recurrence was 23.5% (SD, 2.1; p<0.00001) and the relative reduction in mortality was 15.3% (SD, 2.4; p<0.00001) when chemotherapy was compared with no chemotherapy. The five-year survival rates for node-negative patients <50 years of age were 86.5% with chemotherapy and 83.5% without. The ten-year survival rates for node-negative patients <50 years of age were 77.6% with chemotherapy and 71.9% without. Corresponding survival rates in the 50-69 year-old group were: 85.3% with chemotherapy and 81.4% without at five years, and 71.2% and 64.8% at ten years. Chemotherapy was also associated with reductions in the risk of recurrence. Few data from randomized trials were available for women over 70 years of age.

The Early Breast Cancer Trialists' also pooled individual-patient data from 11 randomized trials of anthracycline-containing regimens versus CMF (1u,2u). They detected a 12% relative reduction in recurrence rate (p=0.006) and a 11% relative reduction in mortality (p=0.02) with anthracycline-based chemotherapy compared to CMF. Estimated five-year survival rates were 71.5% with anthracycline-based chemotherapy and 68.8% with CMF.

Other evidence that the Breast Cancer DSG is reviewing includes:

i) CMF versus no chemotherapy:
- preliminary results from a randomized trial of adjuvant CMF versus observation in women with node-negative breast cancer and elevated urokinase-type plasminogen activator (uPA) or plasminogen activator inhibitor type 1 (PAI-1) levels (3u),
- published results of a clinical trial of adjuvant CMF versus observation in women with rapidly proliferating node-negative breast cancer (4u),
- an ASCO abstract reporting ten-year follow-up data from a randomized trial of adjuvant CMF versus observation for node-negative breast cancer (5u),
- updated results (6u) from the Intergroup trial of adjuvant CMFP versus observation described in the original guideline report (12);
ii) FEC versus no chemotherapy:
- published results of a clinical trial of adjuvant fluorouracil, epirubicin and cyclophosphamide (FEC) versus observation in women with rapidly proliferating node-negative breast cancer (7u),
- an ASCO abstract reporting results from the subgroup of node-negative patients with poor prognostic factors in a randomized trial of adjuvant FEC versus observation (8u);

iii) CMF versus other multi-agent chemotherapy:
- a published report of the NSABP B-23 randomized trial of CMF versus AC (± tamoxifen) in women with node-negative ER-negative breast cancer (9u),
- an ASCO abstract reporting preliminary results of an Intergroup randomized trial of CMF versus cyclophosphamide/doxorubicin/5-fluorouracil (CAF) (± tamoxifen) in women with high-risk node-negative breast cancer (10u),
- an ASCO abstract reporting preliminary results of an Intergroup randomized trial of CMF versus cyclophosphamide, epirubicin, fluorouracil (CEF) in premenopausal women with node-negative breast cancer (11u),
- an ASCO abstract reporting results of a randomized trial of CMF versus fluorouracil, doxorubicin and cyclophosphamide (FAC) in women with node-negative breast cancer (12u);

iv) quality of life:
- a pooled analysis of quality-adjusted time without symptoms and toxicity, based on data from 16,892 women enrolled in randomized trials that compared with no chemotherapy (13u),
- an evaluation of long-term quality of life among premenopausal women with node-negative breast cancer who participated in a randomized trial of CMF versus observation (14u).

Tamoxifen

Original: November 1998

There have been a number of trials evaluating tamoxifen in women with node-negative breast cancer. In some of these trials, the node-negative women were a subgroup of a larger study population. Three of the larger studies, described below, were included in a meta-analysis published in 1988, and updated in 1992 (4) and 1995 (15). The most important summary of the evidence related to tamoxifen comes from this large meta-analysis which was based on individual patient data (Table 1). Results from the three trials (Table 3) described are consistent with the results of the meta-analysis.

The meta-analysis conducted by the Early Breast Cancer Trialists included data on 30,000 women enrolled in 40 clinical trials of tamoxifen versus control (4). In 12,910 node-negative patients, the relative reduction in the risk (annual odds) of recurrence was 26% (SD, 4; p<0.00001) and the relative reduction in mortality was 17% (SD, 5; p=0.0002) (Table 1). Tamoxifen-treated patients had a five-year DFS rate of 83.5% and a ten-year DFS rate of 68.1%. The corresponding values for the control patients were 77.3% and 63.1%. The survival rate at ten years was 74.5% for tamoxifen patients versus 71.0% for control. Tamoxifen was associated with a reduction in the risk of both recurrence and death in all categories of women except young women with estrogen-receptor-negative tumours. In women less than 50 years of age with estrogen-receptor-positive tumours, the risk reduction was 19% (SD, 6) for recurrence and 13% (SD, 8) for mortality. In women under 50 with estrogen-receptor-negative tumours, the risk reduction for recurrence was 3% (SD, 8); there was no effect of tamoxifen on mortality.

These results have been updated using data collected up to 1995 (15). Tamoxifen had little effect in estrogen-receptor-negative tumours. In node-negative women, five years of tamoxifen was associated with a 49% (SD, 4) relative reduction in the risk of recurrence and a 25% (SD, 5) relative reduction in mortality. These data correspond to recurrence-free survival rates at ten years of 79.2% for tamoxifen patients and 64.3% for control patients, and to ten-year survival rates of 78.9% and 73.3% respectively.
In the randomized trial by the Nolvadex Adjuvant Trial Organization (NATO), 300 node-negative women received tamoxifen for two years and 305 received no treatment (16). There were 80 recurrences (27%) and 55 deaths (18%) in the treated group, and 107 recurrences (35%) and 77 deaths (25%) in the control group at the time of follow-up (median = 66 months). The authors stated that the results observed in this subgroup were not different from those for the entire study population, where there was a statistically significant difference between tamoxifen and control.

The Scottish Cancer Trials Office conducted a study in which 747 women with node-negative breast cancer were randomized to adjuvant treatment with tamoxifen for five years or to tamoxifen at first relapse (17). There was a statistically significant difference in DFS in favour of adjuvant tamoxifen compared with control (hazard ratio, 0.62; 95% CI, 0.49 to 0.79; p=0.0001) and a trend toward improved survival with adjuvant tamoxifen (hazard ratio, 0.77; 95% CI, 0.58 to 1.02; p=0.07).

In the NSABP B-14 trial, 2,844 node-negative women with estrogen-receptor-positive tumours were randomized to tamoxifen or placebo for five years (18,19). After five years of follow-up, the DFS rate with tamoxifen was 82% compared with 72% in the placebo group (log rank p<0.000005). Survival curves were similar for the two treatment groups. After five years of follow-up, 94% of the tamoxifen patients and 93% of the placebo patients were alive (log rank p = 0.2).

Tamoxifen is associated with relatively few adverse effects. Up to 50% of women on tamoxifen experience hot flashes. Very rarely, tamoxifen can cause depression and venous thromboembolism. Recent studies have reported an approximate risk of endometrial cancer of one in 500 (20,21).

**Update: February 2002**

The Breast Cancer DSG is reviewing evidence from the following:

i) tamoxifen versus no tamoxifen:
- an analysis of 10-year survival data from a subgroup of participants in the Stockholm trial of tamoxifen versus no tamoxifen, who had been treated with breast-conserving surgery plus radiotherapy as primary therapy for node-negative breast cancer (15u),
- an abstract report from the 2001 San Antonio Breast Cancer Symposium of a randomized trial of tamoxifen versus no tamoxifen (± radiotherapy) as adjuvant therapy for node-negative grade I tumours ≤2 cm in size (16u);
- an abstract of preliminary results from the NSABP B-21 trial of radiotherapy plus tamoxifen versus radiotherapy plus placebo after lumpectomy in women with node-negative breast cancer ≤1.0 cm (17u).

ii) duration of tamoxifen:
- updated results of the NSABP B-14 trial of five versus more than five years of tamoxifen (18u),
- preliminary results from a randomized trial of three years of tamoxifen versus long-term tamoxifen use (19u).

**Chemotherapy plus tamoxifen**

*Original: November 1998*

Published results were found for only one randomized trial evaluating chemotherapy plus tamoxifen although several trials are ongoing. Fisher et al. recently reported results from the NSABP B-20 trial in which 2,363 women with estrogen-receptor-positive, node-negative breast cancer were randomized to tamoxifen alone (T) or tamoxifen plus methotrexate, fluorouracil chemotherapy (MFT) or tamoxifen plus CMF chemotherapy (CMFT) (22). There was an improvement in the five-year disease-free survival rate in favour of chemotherapy plus tamoxifen (MFT 90% versus T 85%, p=0.01; CMFT 89% versus T 85%, p=0.001). Five-year survival rates were 97% for MFT, 96% for CMFT, and 94% for tamoxifen alone (MFT versus T, p=0.05; CMFT versus T, p=0.03). The rate of deep vein thrombosis or pulmonary embolism was 4.5% in the
CMFT group and 4.2% in the MFT group, compared with 1.2% in the patients who received tamoxifen alone.

Update: February 2002
The Breast Cancer DSG is reviewing evidence from:
- published results of the NSABP B-23 trial of four types of adjuvant therapy (CMF plus placebo, AC plus placebo, CMF plus tamoxifen, AC plus tamoxifen) in women with node-negative ER-negative breast cancer (9u),
- an ASCO abstract reporting preliminary results of a randomized trial of tamoxifen versus CMF followed by tamoxifen in postmenopausal women with node-negative breast cancer (20u).

Definition of Risk Category
Original: November 1998
Tumour size, histologic differentiation (grade) and hormone receptor status are factors that have traditionally been employed in trying to predict the likelihood of recurrent breast cancer in node-negative patients (3). Data supporting the prognostic utility of these factors come from descriptive series (e.g., the SEER and San Antonio databases) and from cohorts of patients enrolled in randomized trials (23-36). In addition, the presence of lymphatic and vascular invasion have been found to be associated with an increased risk of recurrence (36-39).

The influence of tumour size on prognosis appears to be a continuum, with tumours less than 1 cm in diameter having a very low risk of recurrence (31,32). No precise size which differentiates high risk from low risk has been determined, but a number of studies have used 2 cm as a cut-off to differentiate high risk from low risk (19,40).

Several different histologic grading systems have been reported, but in Canada most pathologists use Elston’s modification of the Bloom Richardson grading system (41). This is a semiquantitative grading system based on the degree of nuclear pleomorphism (mild, score 1; moderate, score 2; marked, score 3), tubule formation (>75%, score 1; 10-75%, score 2; <10%, score 3) and mitotic index (0-9 per 10 Hpf, score 1; 10-20 per 10 Hpf, score 2; >20 per 10 Hpf, score 3). Each score is added to give a combined score from 3 to 9 (3 to 5 points, grade I or well differentiated; 6 or 7 points, grade II or moderately differentiated; 8 or 9 points, grade III or poorly differentiated). The prognosis of grade I tumours is considered good, while that of grade III tumours is considered poor. It is unclear whether grade II tumours have an intermediate prognosis or should be grouped with grade I or grade III tumours.

Small tumour size (i.e., <1 cm), estrogen-receptor-positive (ER-positive) status and well-differentiated histology are considered good prognostic characteristics; whereas larger tumour size (i.e., >3 cm), estrogen-receptor-negative (ER-negative) status, poorly differentiated histology and the presence of lymphatic/vascular invasion are considered to be predictors of increased risk of recurrent breast cancer.

Many other factors are being evaluated for their prognostic ability. These include ploidy, S-phase fraction, cathepsin D, heat shock proteins, Her-2 neu oncogene overexpression and p53 mutations. As of yet, none of these factors has been demonstrated to add prognostic information to tumour size, receptor status and histologic grade (34).

Patients with node-negative breast cancer can be classified into three prognostic groups (35) (Table 4):
1. Patients in the minimal- to low-risk group for recurrence have tumours less than 1 cm in size with all other prognostic factors favourable (grade I, ER-positive, no lymphatic/vascular invasion). There are insufficient data to determine the risk category of a tumour <1 cm in diameter associated with a poor prognostic factor (e.g., grade III). It is possible that such tumours should be classified into the intermediate risk group. Some clinicians will also include well-differentiated (grade I) tumours <2 cm in size with all other factors favourable in the low-
risk group. Low-risk patients have a less than 10% risk of recurrence within five years. The corresponding absolute reduction in recurrence at five years is between 1 and 3%, assuming a 30% relative risk reduction with systemic adjuvant therapy. (There are some "special" type histologies: e.g., pure tubular, pure mucinous and invasive cribiform carcinomas, which in some reports have been associated with a good prognosis. Some clinicians will include tumours of special histology and 1 to 3 cm in size in the low-risk group.)

2. Patients at moderate risk for recurrence have tumours that are between 1 and 3 cm in size and grade II or 2 to 3 cm in size and well-differentiated (grade I). Moderate risk patients have a 10 to 20% probability of recurrence within five years, and systemic adjuvant therapy is associated with an absolute benefit of between 3 and 6% at five years.

3. A patient with a tumour >3 cm in size, irrespective of any other factors, should be considered at high risk. In addition, a patient with a tumour which is >1 cm in size associated with any of the following unfavourable prognostic features should also be considered at high risk: grade III, ER-negative or lymphatic/vascular invasion. These patients have a 20 to 50% probability of recurrence within five years and systemic adjuvant therapy is associated with an absolute benefit of between 4 and 15%.

Update: February 2002
The Breast Cancer DSG is reviewing evidence from two papers and one abstract on prognostic factors for recurrence and survival in women with node-negative breast cancer (21u-23u).

Practice Guidelines
Update: February 2002
Since the Ontario guideline was completed by the CCOPGI, three other evidence-based clinical practice guidelines on adjuvant systemic therapy for node-negative breast cancer have become available (24u-26u). The recommendations related to the use of chemotherapy and tamoxifen in all three were based on the meta-analyses published by the Early Breast Cancer Trialists' Collaboration (4,5,15,1u). These guidelines also reviewed the evidence on ovarian ablation (27u), which had not been included in the original CCOPGI guideline.

The Australian National Health and Medical Research Council (NHMRC) National Breast Cancer Centre completed practice guidelines for the management of early-stage breast cancer in 1995 and revised them in July 2000 (24u). Guidelines were issued by the Scottish Intercollegiate Guidelines Network in October 1998 (25u). In both cases, the recommendations on the use of chemotherapy and tamoxifen in women with early breast cancer did not differentiate between those with node-negative and node-positive disease.

In January 2001, the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer issued an updated Canadian guideline on adjuvant systemic therapy (26u). Based on evidence available in November 2000, they recommended that:

- Pre- and postmenopausal women who are at low risk of recurrence can be advised not to have adjuvant systemic treatment. Women who are at low risk, if seeking treatment, may consider tamoxifen.
- Women at high risk should be advised to have adjuvant systemic therapy. Chemotherapy should be recommended for all premenopausal women (less than 50 years of age) and for postmenopausal women (50 years of age or older) with ER-negative tumours. Tamoxifen should be recommended as first choice for postmenopausal women with ER-positive tumours. For this last group of patients, further benefit is obtained from the addition of chemotherapy to tamoxifen, but the expected incremental toxicity must also be considered. Whether tamoxifen following chemotherapy should be routinely recommended for premenopausal women with ER-positive tumours is unclear.
For women at intermediate risk with ER-positive tumours, tamoxifen should normally be the first choice. For those who decline tamoxifen, chemotherapy may be considered.

For most patients over 70 years of age who are at high risk, tamoxifen is recommended for ER-positive tumours. For those with ER-negative disease who are in robust good health, chemotherapy is a valid option.

There are two recommended chemotherapy regimens: i) 6 cycles of cyclophosphamide, methotrexate and 5-fluorouracil (CMF); ii) 4 cycles of Adriamycin and cyclophosphamide (AC). More intensive combinations such as CEF (cyclophosphamide, epirubicin and 5-fluorouracil) and AC-Taxol have not yet been evaluated in node-negative disease.

Tamoxifen should normally be administered at a dose of 20 mg daily for 5 years.

Two new pieces of evidence, published after the Ontario guideline was completed, were reviewed by the national guideline developers:
- an abstract reporting preliminary results of the NSABP B-23 trial of chemotherapy with or without tamoxifen (28u),
- an abstract reporting preliminary results of an Intergroup trial of CMF versus CAF with or without tamoxifen (10u).

V. INTERPRETIVE SUMMARY

Original: November 1998

Choice of Therapy
Risk of recurrence is categorized as high, medium or low according to the size of the tumour, histologic grade, estrogen receptor status and lymphatic/vascular invasion (Table 4). The probability of response to therapy (responsiveness) is based on the patient's age and the estrogen receptor status of the tumour. The choice of therapy should be based on the patient's risk of recurrence and factors which predict responsiveness to therapy (Table 5).

Duration of Tamoxifen
In the original trials evaluating tamoxifen in node-negative breast cancer, the duration of treatment with tamoxifen was either one, two or five years. Indirect analyses from the Early Breast Cancer Trialists' meta-analysis suggest that two years or more of tamoxifen is superior to one year of tamoxifen (4) and that five years is superior to two years (15). The two relatively large trials in node-negative patients (NSABP, Scottish) used five years of tamoxifen (17,19). Results of two recent randomized trials failed to detect an improvement with ten years of tamoxifen compared with five years (42,43). A recent Scandinavian trial and a recent British trial have demonstrated the superiority of five years of tamoxifen compared with two years (44,45). This is supported by data from the most recent update of the Early Breast Cancer Trialists' meta-analysis (15).

Chemotherapy Regimen
Few studies in node-negative breast cancer patients have used "standard CMF" as the treatment arm. Nonetheless, extrapolation from studies in node-positive patients has resulted in oral CMF being the treatment of choice in many centres. There is wide experience with CMF and its toxicity profile is well known. In the NSABP B-19 trial conducted in node-negative women, CMF was superior to methotrexate, fluorouracil (MF) but was associated with increased toxicity (46). In the NSABP B-20 trial, there has been no difference detected yet between CMF plus tamoxifen and MF plus tamoxifen (22).

The use of an anthracycline regimen in node-negative patients is not straightforward. There are no clinical trials evaluating commonly used anthracycline-containing regimens, e.g., doxorubicin/cyclophosphamide (AC) or cyclophosphamide/doxorubicin/5-fluorouracil (CAF), in node-negative patients. AC is often used in patients with node-positive disease (47). It is shorter in duration and
has a different toxicity profile than CMF. There is the concern, however, of potential cardiomyopathy and leukemia with AC. On the other hand, some patients with high-risk node-negative disease have a recurrence rate similar to that of patients with node-positive disease in which anthracycline-containing chemotherapy is offered. The National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) compared cyclophosphamide, epirubicin, fluorouracil (CEF) with CMF in node-positive women with breast cancer (48). CEF was superior to CMF in terms of both disease-free survival and overall survival. CEF was associated with increased toxicity including leukemia.

Please see Appendix I for suggested doses and schedules for chemotherapy.

VI. ONGOING TRIALS
The following randomized trials include women with node-negative breast cancer, and stratify allocation by nodal status:

Chemotherapy
CAN-NCIC-MA21: Phase III randomized study of adjuvant cyclophosphamide, epirubicin and fluorouracil versus cyclophosphamide, epirubicin, filgrastim (G-CSF), and epoetin alfa followed by paclitaxel versus cyclophosphamide and doxorubicin followed by paclitaxel in premenopausal or early postmenopausal women with previously resected node positive or high-risk node negative stage I-IIIA breast cancer.

CRC-TU-NEAT, EU-98041: Phase III randomized study of adjuvant cyclophosphamide, methotrexate, and fluorouracil with or without epirubicin in women with early stage breast cancer.

UCLA-010200601, NCI-G01-1978, BCIRG-006, AVENTIS-TAX-GMA-302: Phase III randomized study of adjuvant doxorubicin, cyclophosphamide, and docetaxel with or without trastuzumab (Herceptin) versus trastuzumab, docetaxel, and either carboplatin or cisplatin in women with HER2-neu-expressing node-positive or high-risk node-negative operable breast cancer.

LB-49906, SWOG-E1199, E-1199, NCCTG-E1199: Phase III randomized study of doxorubicin and cyclophosphamide followed by paclitaxel or docetaxel in women with node-positive or high-risk node-negative stage II or IIIA breast cancer.

Tamoxifen
CRC-TU-ATTOM, EU-98042: Phase III randomized adjuvant study of tamoxifen in women with early breast cancer. Compares the disease-free and overall survival of women with early breast cancer who are randomized to stop adjuvant tamoxifen with those randomized to continue for at least five extra years.

Letrozole
EORTC-10983, SWOG-JMA17, CLB-49805, CAN-NCIC-MA17, NCCTG-JMA.17: Phase III randomized study of letrozole versus placebo in women with primary breast cancer who have completed at least five years of adjuvant tamoxifen.

VII. DISEASE SITE GROUP CONSENSUS PROCESS
Original: November 1998
A draft of the practice guideline report was discussed at the Breast Cancer Disease Site Group (DSG) meeting in April 1997. Feedback, particularly in two areas (i.e., definition of histologic grade and inclusion of lymphatic/vascular invasion as a poor prognostic factor) led to changes in the report. The report was discussed again at a DSG meeting in November 1997 and approved, conditional on minor refinements in the wording of the treatment recommendations.
At the Breast Cancer Disease Site Group meeting of April 1998, the results of the practitioner feedback survey were discussed and addressed in the practice guideline report. The results of the 1995 Early Breast Cancer Trialists' meta-analysis had become available (5,15). These were discussed and incorporated into the guideline report.

Some members of the Site Group felt that the results of the MA.5 trial which established the superiority of CEF over CMF in premenopausal node-positive patients could be extrapolated to node-negative women (48).

The use of the combination of chemotherapy and tamoxifen was discussed at length. The results of the NSABP B-20 trial were reviewed (21). The results of this trial, demonstrating the superiority of chemotherapy plus tamoxifen versus tamoxifen alone, are consistent with other trials. In the recently reported Intergroup study comparing tamoxifen with tamoxifen plus CAF, in postmenopausal node-positive women the disease-free survival was 72% in the tamoxifen patients versus 79% in the CAFT patients (p=0.01) (49). No difference was detected in survival. In the 1995 Early Breast Cancer Trialists' meta-analysis, the relative reduction in recurrence in the chemotherapy plus tamoxifen arm compared with tamoxifen alone was 19% (SD, 3) and for mortality 11% (SD, 4) for women > 50 years of age (5). The data for women < 50 years of age were 21% (SD, 13) and 25% (SD, 14), respectively. In summary, the evidence from the NSABP B-20 trial is consistent with the results of other studies comparing chemotherapy plus tamoxifen versus tamoxifen alone in patients with node-positive breast cancer.

The 1995 Early Breast Cancer Trialists' meta-analysis detected a relative reduction in recurrence of 54% (SD, 8) in women > 50 years of age who received chemotherapy plus tamoxifen compared with chemotherapy alone and a reduction in mortality of 49% (SD, 10) in this age group (15). The relative reductions for women < 50 years were 40% (SD, 19) for recurrence and 39% (SD, 22) for mortality. (Note: The number of women in this subgroup was relatively small.)

If one accepts that chemotherapy provides an additional benefit to tamoxifen alone, then the question is which chemotherapy to use? In the NSABP B-19 trial, pre- and postmenopausal estrogen-receptor-negative, node-negative patients were randomized to MF for six months versus CMF for six months (46). The five-year disease-free survival rate was 73% for the MF patients versus 82% for the CMF patients (p<0.001). The five-year survival rate was 85% in the former group compared with 88% in the latter group (p=0.06). There was increased toxicity in patients who received CMF. It is interesting to note that in the B-19 trial CMF was superior to MF. In the B-20, trial there has been no difference detected yet between CMFT patients and MFT patients (22). It is important to note that there were mostly premenopausal women in the B-19 trial whereas the B-20 trial included many postmenopausal women. It is conceivable that in the older women, because of the toxicity of oral cyclophosphamide, there was less absorption of this drug and hence there was little effect of the addition of the cyclophosphamide in this regimen. In the NSABP B-15 trial, CMF was compared with AC in node-positive patients and no difference was detected in disease-free survival (47).

The DSG addressed the question of whether chemotherapy should be added for tamoxifen-responsive patients, and if so, whether to all subgroups. It was agreed that there was still a low-risk group for whom no adjuvant therapy should be recommended (e.g., < 2 cm, all prognostic factors favourable). However, these women should be made aware that systemic therapy is offered to women at higher risk of recurrence.

It was also agreed that for high risk (> 3 cm, or grade III) estrogen-receptor-positive postmenopausal women, chemotherapy should be added to tamoxifen. (Note: tamoxifen is considered standard therapy in this situation based on a large body of evidence in node-negative and node-positive disease from the Early Breast Cancer Trialists' meta-analysis.) Reasonable chemotherapy regimens in this situation are CMF or AC. Although AC was found to be equivalent to CMF in node-positive patients, its use in node-negative disease is by extrapolation. These two regimens have different toxicity profiles; for example, AC is associated with complete alopecia in all
patients versus 40% of the time in CMF patients. MF was not favoured because of its observed inferiority in the NSABP B-19 trial.

It was agreed that in high risk (> 3 cm, or grade III) estrogen-receptor-positive premenopausal women, chemotherapy would remain as the systemic adjuvant therapy of choice. There are insufficient data at the present time to recommend the addition of tamoxifen to chemotherapy in this subgroup. (The evidence from the Early Breast Cancer Trialists’ meta-analysis is based on small numbers of patients and the results for survival are not statistically significant.) In addition, there is an ongoing clinical trial being conducted by the NCIC-CTG examining the additional benefit of tamoxifen after adjuvant chemotherapy in this subgroup of patients.

The DSG was less clear on what should be done with patients at moderate risk of recurrence. There was less enthusiasm for adding chemotherapy to tamoxifen for this group of patients compared to the high risk group. The moderate-risk group would be an ideal group in which to evaluate a decision aid. If a decision board cannot be used, then tamoxifen should be recommended. However, these women should be made aware that chemotherapy plus tamoxifen is offered to women at higher risk of recurrence.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Original: November 1998

This section describes the external review activities undertaken for the original guideline report. For a description of external review activities of the new information presented in the updated sections of this report, please refer to Update below.

Draft Practice Guideline

Based on the evidence contained under the Original subtitles throughout this report, the Breast Cancer DSG drafted the following recommendations:

Target population

These recommendations apply to adult patients with node-negative breast cancer.

Draft recommendations

Choice of therapy

- Pre- and postmenopausal women with minimal or low risk of recurrence (<2 cm, well-differentiated and all other factors favourable) should receive no adjuvant systemic treatment. They should however be made aware that systemic therapy is offered to women at higher risk of recurrence.
- Premenopausal women (age <50 years) with estrogen-receptor-positive tumours that are 1-3 cm in size and intermediate grade, or 2-3 cm and well differentiated should be offered tamoxifen. If the patient refuses tamoxifen, chemotherapy may be considered.
- Premenopausal women (age <50 years) with tumours which are >3 cm irrespective of any other factors, or are >1 cm and are either estrogen-receptor negative, high grade or have lymphatic/vascular invasion should be offered chemotherapy. If the patient refuses chemotherapy and the tumour is estrogen-receptor-positive, tamoxifen may be considered. There is insufficient data to determine the risk category of a tumour <1 cm in diameter associated with a poor prognostic factor (e.g., grade III, estrogen-receptor negative, lymphatic/vascular invasion).
- Postmenopausal women (age >50 years) at moderate risk of recurrence (1-3 cm and intermediate grade, or 2-3 cm and well differentiated), or high risk of recurrence (>3 cm, or > 1 cm with high grade or lymphatic/vascular invasion) and with estrogen-receptor-positive tumours should be offered tamoxifen. If the patient refuses tamoxifen, chemotherapy may be considered.
• Postmenopausal women (age >50 years) at high risk of recurrence (>3 cm or >1 cm with either high grade or lymphatic/vascular invasion) and with estrogen-receptor-negative tumours should be offered chemotherapy. If a patient refuses chemotherapy or is over 70 years, tamoxifen may be considered.

**Duration of tamoxifen**
Hormonal therapy should consist of oral tamoxifen 20 mg daily for five years.

**Chemotherapy regimen**
Polychemotherapy should reasonably comprise six cycles of CMF (oral) or four cycles of AC.

**Process of decision-making**
Patients with node-negative breast cancer should be informed of the availability of adjuvant systemic therapy and should be offered the opportunity of discussing such therapy with an expert clinician. She should be provided with detailed information concerning her risk of recurrence if untreated, the potential efficacy of adjuvant therapy in terms of recurrence and mortality, and the potential side effects of therapy.

**Practitioner Feedback**
Based on the evidence contained under the Original subtitles in this report and the draft recommendations presented above, feedback was sought from Ontario clinicians.

**Methods**
Practitioner feedback was obtained through a mailed survey of 159 practitioners in Ontario. The survey consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (postcard) and four weeks (complete package mailed again). The results of the survey were reviewed by the Breast Cancer Disease Site Group.

**Results**
One hundred twenty-three (77%) surveys were returned. Ninety-six (78%) respondents indicated that the practice-guideline-in-progress report was relevant to their clinical practice and they completed the survey. Eighty-five percent agreed or strongly agreed with the methods and data synthesis, 78% endorsed the evidence-based report, and 80% endorsed the evidence-based report as a practice guideline.

Fifty-eight (47%) respondents provided written comments. The main points were:
• the results of the NSABP B-20 study comparing chemotherapy plus tamoxifen with tamoxifen, published during the practitioner feedback survey, need to be incorporated into the evidence and their impact on the recommendation assessed;
• chemotherapy regimens other than CMF and AC are used by some practitioners to treat patients with node-negative breast cancer.

**Modifications/actions**
The results of the NSABP B-20 study and a discussion of the use of CEF in node-negative patients were added to the report. The treatment recommendations were revised to suggest that moderate-risk patients be offered the use of a decision board or equivalent comparing tamoxifen with tamoxifen plus chemotherapy and that postmenopausal high-risk ER-positive women be offered tamoxifen plus chemotherapy. The revised evidence-based recommendation was approved as a practice guideline.
Approved Practice Guideline Recommendations
This practice guideline reflects the integration of the draft recommendations in the External Review process and has been approved by the Breast Cancer DSG and the Practice Guideline Coordinating Committee.

Choice of therapy
- Pre- and postmenopausal women at minimal or low risk of recurrence (<2 cm, well-differentiated and all other factors favourable or <1 cm, intermediate grade and all other factors favourable) should receive no adjuvant systemic treatment. They should however be made aware that systemic therapy is offered to women at higher risk of recurrence.
- Premenopausal women (age <50 years) at moderate risk of recurrence (1-3 cm and intermediate grade, or 2-3 cm and well-differentiated) and with estrogen-receptor-positive tumours should be offered tamoxifen. Chemotherapy added to tamoxifen may provide a modest incremental benefit over tamoxifen alone. This is an ideal situation for a decision aid.
- Premenopausal women (age <50 years) at high risk of recurrence (>3 cm, irrespective of any other factors, or >1 cm with either estrogen-receptor-negative, high grade or lymphatic/vascular invasion) should be offered chemotherapy. There are insufficient data at the present time to recommend the addition of tamoxifen to chemotherapy in this subgroup. If the patient refuses chemotherapy and the tumour is estrogen-receptor-positive, tamoxifen may be considered. There is insufficient data to determine the risk category of a tumour <1 cm in diameter associated with a poor prognostic factor (e.g., grade III, estrogen-receptor-negative, lymphatic/vascular invasion).
- Postmenopausal women (age >50 years) at high risk of recurrence (>3 cm, or >1 cm with high grade or lymphatic/vascular invasion) and with estrogen-receptor-positive tumours should be offered tamoxifen plus chemotherapy. The benefits and risks of additional chemotherapy should be discussed with the patient. If the patient refuses chemotherapy, then tamoxifen alone should be considered. Postmenopausal women at high risk of recurrence and with estrogen-receptor-negative tumours should be offered chemotherapy.
- Postmenopausal women (age >50 years) at moderate risk of recurrence (1-3 cm and intermediate grade, or 2-3 cm and well-differentiated) and with estrogen-receptor-positive tumours should be offered tamoxifen. Chemotherapy added to tamoxifen may provide a modest incremental benefit over tamoxifen alone. This is an ideal situation for the use of a decision aid.

Duration of tamoxifen
Hormonal therapy should consist of oral tamoxifen 20 mg daily for five years.

Chemotherapy regimen
Polychemotherapy should reasonably comprise six cycles of cyclophosphamide (oral), methotrexate, fluorouracil (CMF) or four cycles of doxorubicin/cyclophosphamide (AC).

Process of decision-making
A patient with node-negative breast cancer should be informed of the availability of adjuvant systemic therapy and should be offered the opportunity of discussing such therapy with an expert clinician. She should be provided with detailed information concerning her risk of recurrence if untreated, the potential efficacy of adjuvant therapy in terms of recurrence and mortality, and the potential side effects of therapy.
Update: February 2002
No further external review has taken place.

IX. PRACTICE GUIDELINE
This practice guideline reflects the evidence from the original guideline report.

Target Population
These recommendations apply to adult patients with node-negative breast cancer.

Recommendations

Choice of Therapy

- **Pre- and postmenopausal** women at **minimal or low risk of recurrence** (<2 cm, well-differentiated and all other factors favourable or <1 cm, intermediate grade and all other factors favourable) should receive no adjuvant systemic treatment. They should however be made aware that systemic therapy is offered to women at higher risk of recurrence.

- **Premenopausal** women (age <50 years) at **moderate risk of recurrence** (1-3 cm and intermediate grade, or 2-3 cm and well-differentiated) and with estrogen-receptor-positive tumours should be offered tamoxifen. Chemotherapy added to tamoxifen may provide a modest incremental benefit over tamoxifen alone. This is an ideal situation for a decision aid.

- **Premenopausal** women (age <50 years) at **high risk of recurrence** (>3 cm, irrespective of any other factors, or >1 cm with either estrogen-receptor-negative, high grade or lymphatic/vascular invasion) should be offered chemotherapy. There are insufficient data at the present time to recommend the addition of tamoxifen to chemotherapy in this subgroup. If the patient refuses chemotherapy and the tumour is estrogen-receptor-positive, tamoxifen may be considered. There is insufficient data to determine the risk category of a tumour <1 cm in diameter associated with a poor prognostic factor (e.g., grade III, estrogen-receptor-negative, lymphatic/vascular invasion).

- **Postmenopausal** women (age >50 years) at **high risk of recurrence** (>3 cm, or >1 cm with high grade or lymphatic/vascular invasion) and with estrogen-receptor-positive tumours should be offered tamoxifen plus chemotherapy. The benefits and risks of additional chemotherapy should be discussed with the patient. If the patient refuses chemotherapy, then tamoxifen alone should be considered. Postmenopausal women at high risk of recurrence and with estrogen-receptor-negative tumours should be offered chemotherapy.

- **Postmenopausal** women (age >50 years) at **moderate risk of recurrence** (1-3 cm and intermediate grade, or 2-3 cm and well-differentiated) and with estrogen-receptor-positive tumours should be offered tamoxifen. Chemotherapy added to tamoxifen may provide a modest incremental benefit over tamoxifen alone. This is an ideal situation for the use of a decision aid.

Duration of Tamoxifen
Hormonal therapy should consist of oral tamoxifen 20 mg daily for five years.

Chemotherapy Regimen
Polychemotherapy should reasonably comprise six cycles of cyclophosphamide (oral), methotrexate, fluorouracil (CMF) or four cycles of doxorubicin /cyclophosphamide (AC).

Process of Decision-making
A patient with node-negative breast cancer should be informed of the availability of adjuvant systemic therapy and should be offered the opportunity of discussing such therapy with an expert clinician. She should be provided with detailed information concerning her risk of recurrence if
untreated, the potential efficacy of adjuvant therapy in terms of recurrence and mortality, and the potential side effects of therapy.

X. JOURNAL REFERENCE

XI. ACKNOWLEDGEMENTS
The Breast Cancer Disease Site Group would like to thank Mark Levine and David Ginsburg for taking the lead in drafting and revising this practice guideline report.

The Breast Cancer Disease Site Group would like to thank Eva Tomiak and Maureen Trudeau for taking the lead in updating this practice guideline report.

For a full list of members of the Cancer Care Ontario Breast Cancer Disease Site Group please visit the website of the Program in Evidence-based Care at http://www.cancercare.on.ca/ccopgi.
Table 1: Early breast cancer trialists overview for node-negative breast cancer, 1990 (4).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Reduction in Annual Odds of Recurrence* (SD)</th>
<th>Reduction in Annual Odds of Death* (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>26% (7)</td>
<td>18% (8)</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>26% (4)</td>
<td>17% (5)</td>
</tr>
</tbody>
</table>

* Compared with control (i.e., no chemotherapy or no tamoxifen)

Table 2: Randomized trials of chemotherapy in node-negative breast cancer.

<table>
<thead>
<tr>
<th>Study (Reference number)</th>
<th>Treatment</th>
<th># Patients</th>
<th>Disease-free Survival Rate (follow-up)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milan (6,7)</td>
<td>CMF x 9 months</td>
<td>45/45</td>
<td>5% (42%)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>No adjuvant treatment</td>
<td></td>
<td>(7 years)</td>
<td></td>
</tr>
<tr>
<td>Ludwig (8)</td>
<td>CMF x 1 month</td>
<td>848/427</td>
<td>74% (68%)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>No adjuvant treatment</td>
<td></td>
<td>(5 years)</td>
<td></td>
</tr>
<tr>
<td>NSABP B13 (9,10)</td>
<td>MTX 5 FU X 12 months</td>
<td>339/340</td>
<td>74% (59%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>No adjuvant treatment</td>
<td></td>
<td>(8 years)</td>
<td></td>
</tr>
<tr>
<td>Intergroup (11,12)</td>
<td>CMFP x 6 months</td>
<td>196/210</td>
<td>83% (61%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>No adjuvant treatment</td>
<td></td>
<td>(5 years)</td>
<td></td>
</tr>
</tbody>
</table>

CMF = cyclophosphamide, methotrexate, fluorouracil
MTX 5 FU = sequential methotrexate, fluorouracil
CMFP = cyclophosphamide, methotrexate, fluorouracil, prednisone

Table 3: Randomized trials of tamoxifen in node-negative breast cancer.

<table>
<thead>
<tr>
<th>Study (Reference number)</th>
<th>Treatment</th>
<th># Patients</th>
<th>Disease-free Survival Rate (follow-up)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NATO (16)</td>
<td>Tamoxifen</td>
<td>300/305</td>
<td>73% (65%)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>No treatment</td>
<td></td>
<td>(median follow-up = 66 months)</td>
<td></td>
</tr>
<tr>
<td>Scottish (17)</td>
<td>Tamoxifen</td>
<td>374/373</td>
<td>79% (65%)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>No treatment</td>
<td></td>
<td>(5 years)</td>
<td></td>
</tr>
<tr>
<td>NSABP B14 (18,19)</td>
<td>Tamoxifen</td>
<td>1418/1426</td>
<td>82% (72%)</td>
<td>&lt;0.00005</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>(5 years)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 4: Risk category.

<table>
<thead>
<tr>
<th>Risk Category (Baseline failure rate)</th>
<th>Tumour Size (cm)</th>
<th>Differentiation (grade)</th>
<th>Estrogen receptor</th>
<th>Lymphatic/vascular invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt; 10%)</td>
<td>&lt; 1*</td>
<td>well (I), moderate (II)</td>
<td>+</td>
<td>absent</td>
</tr>
<tr>
<td></td>
<td>&lt; 2</td>
<td>well (I)</td>
<td>+</td>
<td>absent</td>
</tr>
<tr>
<td>Moderate (10-20%)</td>
<td>1-3</td>
<td>moderate (II)</td>
<td>+</td>
<td>absent</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>well (I)</td>
<td>+</td>
<td>absent</td>
</tr>
<tr>
<td>High (&gt; 20%)</td>
<td>≥ 1**</td>
<td>poorly (III)</td>
<td>-</td>
<td>present</td>
</tr>
<tr>
<td></td>
<td>&gt; 3</td>
<td>any (I, II, III)</td>
<td>-</td>
<td>any</td>
</tr>
</tbody>
</table>

* Some clinicians use 2 cm rather than 1 cm to define low risk if the tumour is well-differentiated. Others include a 1-2 cm, well-differentiated tumour in the moderate risk category.

** There are insufficient data on the natural history of tumours which are <1 cm and high grade, or <1 cm with lymphatic/vascular invasion.

### Table 5: Recommendations for adjuvant treatment for node-negative breast cancer.

<table>
<thead>
<tr>
<th>Patient Group (Responsiveness)</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal (&lt; 50 years)</td>
<td>Minimal/Low</td>
</tr>
<tr>
<td>Estrogen-receptor-positive</td>
<td>no treatment</td>
</tr>
<tr>
<td>Estrogen-receptor-negative</td>
<td>-</td>
</tr>
<tr>
<td>Postmenopausal (≥50 years)</td>
<td>no treatment</td>
</tr>
<tr>
<td>Estrogen-receptor-positive</td>
<td>-</td>
</tr>
<tr>
<td>Estrogen-receptor-negative</td>
<td>-</td>
</tr>
</tbody>
</table>

* The addition of chemotherapy to tamoxifen may provide a modest incremental benefit over tamoxifen alone. This is an ideal situation for a decision aid.

** If chemotherapy is refused, tamoxifen may be offered.
REFERENCES

Original: November 1998
This section contains all references from the original practice guideline report.


Update: February 2002
This section contains all references from the review and updating activities.


16u. Blamey RW, Chetty U, Mitchell A, on behalf of the BASO Breast Group. The BASO II trial of adjuvant radiotherapy vs. none and tamoxifen vs. none in small, node negative, grade I tumours. [abstract]. Breast Cancer Res Treat 2001;69:


Appendix I: Doses and schedules for chemotherapy for node-negative breast cancer.

1. **CMF** for six 28-day cycles: cyclophosphamide 100 mg/m² orally on days 1 to 14
   methotrexate 40 mg/m² intravenously on days 1 and 8
   5-fluorouracil 600 mg/m² intravenously on days 1 and 8

OR

2. **AC** for four 21-day cycles: Adriamycin (doxorubicin) 60 mg/m² intravenously on day 1
   cyclophosphamide 600 mg/m² intravenously on day 1