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Evidence-based Series 1-8 EDUCATION AND INFORMATION 2010

Adjuvant Systemic Therapy for Node-negative Breast Cancer

Members of the Breast Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

A review conducted in 2010 put Evidence-based Series (EBS) 1-8 in the Education and Information Section. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardize process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Evidence-based Series (EBS) 1-8 EDUCATION AND INFORMATION 2011, the resulting review report, consists of the following 4 parts:

1. **Guideline Overview**
2. **Summary**
3. **Full Report**
4. **Document Assessment and Review Tool**

and is available on the CCO website (http://www.cancercare.on.ca)
PEBC Breast Cancer Disease Site Group page at:
http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-ebs/.

Release Date: September 15, 2011

For information about the PEBC and the most current version of all reports, please visit the CCO **website** at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

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Evidence-based Series 1-8 EDUCATION AND INFORMATION 2010

Adjuvant Systemic Therapy for Node-negative Breast Cancer

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version Nov 1998	1980 to 1998	Full Report	Web publication	Not Applicable
Updated May 2003	1998 to 2002	New data added to original Full Report	Updated Web publication	Most recent search done in May 2003
Reviewed Version Jun 2010	Document Assessment and Review Tool		Updated Web publication	Guideline Archived

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Evidence-based Series 1-8 ARCHIVED 2010

Adjuvant Systemic Therapy for Node-negative Breast Cancer

Guideline Review Summary

Review Date: June 11, 2010

The 2003 guideline recommendations are

ARCHIVED

This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

OVERVIEW

Evidence-based Series History

This guidance document was originally released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO) in 1998 and the first update released in February 2002. In June 2010, the PEBC guideline update strategy was applied and the recommendations were archived. The Summary and the Full Report in this review are the same as in the May 2003 version.

Update Strategy

The PEBC update strategy includes an updated search of the literature, the review and interpretation of new eligible evidence by the clinical experts from the authoring panel, and consideration of the guideline and its recommendations based on the new available evidence. See the Document Assessment and Review Tool.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

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

Literature Search and New Evidence

A search for new literature with respect to this question was not conducted as it was determined that the recommendations regarding this question are no longer relevant. The guideline and its recommendations have been ARCHIVED.

Impact on Guidelines and Its Recommendations

The Breast Cancer DSG **ARCHIVED** the 2002 recommendations. Therefore this guideline will no longer be maintained.

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Adjuvant Systemic Therapy for Node-negative Breast Cancer
Practice Guideline Report #1-8

Members of the Breast Cancer Disease Site Group

Please see the EBS 1-8 Archived 2011 Guideline Review Summary and the Document Assessment and Review Tool. for the summary of updated evidence published between 2002 and 2010

Report Date: May 1, 2003

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 or four cycles of doxorubicin/cyclophosphamide.

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

Entries to MEDLINE (1980-April 2003), the Cochrane Library (Issue 1, 2003) and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology were searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by members of the Practice Guideline Initiative's Breast Cancer Disease Site Group. This practice guideline has been reviewed and approved by the Breast Cancer Disease Site Group, which is comprised of surgeons, medical oncologists, epidemiologists, a pathologist, a medical sociologist, and a community representative.

External review of the original practice guideline report by Ontario practitioners was obtained through a mailed survey. Final approval of the original guideline was obtained from the Practice Guidelines Coordinating Committee.

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

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.

For further information about this practice guideline report, please contact:
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The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.
Visit http://www.cancercare.on.ca for all additional Practice Guidelines Initiative reports.

PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) 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 PGI 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 (PGCC), 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:

[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

For the most current versions of the guideline reports and information about the PEBC, please visit the CCO Web site at:
http://www.cancercare.on.ca
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Adjuvant Systemic Therapy for Node-negative Breast Cancer
Practice Guideline Report #1-8

Please see the EBS 1-8 Archived 2011 Guideline Review Summary and the Document Assessment and Review Tool. for the summary of updated evidence published between 2002 and 2010.

Report Date: May 1, 2003

FULL REPORT

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 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 (NCI) issued a "clinical alert" based on the early results of several randomized trials evaluating systemic therapy in node-negative breast cancer patients (2). The NCI 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 the routine clinical treatment of both node-positive and node-negative disease (1).

Concern was expressed, however, because 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 treated with adjuvant systemic therapy, many might be subjected to unnecessary therapy and the associated adverse side effects. Two proposals developed to meet this concern. First, systemic therapy should be reserved for node-negative patients at increased risk of recurrence based on certain intrinsic characteristics of the tumour (3)--this proposal led to much research attempting to identify prognostic factors for recurrence. Second, 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 refers to treatment with various cytotoxic drug combinations. Hormonal therapy refers to treatment with the antiestrogen tamoxifen.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (4). Evidence was selected and reviewed by two members of the Breast Cancer Disease Site Group (DSG) and methodologists.

The practice guideline report 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. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The PGI 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.

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

Literature Search Strategy

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

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 April 2003), the Cochrane Library (Issue 1, 2003), the Physician Data Query (PDQ) database and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (1999-2002). The literature search was not restricted by language of publication.

Inclusion Criteria

Articles were selected if they were:

1. 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.
2. Evidence-based practice guidelines addressing the guideline questions were also included.

Both abstract and full reports were eligible.

IV. RESULTS

Chemotherapy

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. A brief review of these later trials follows the description of a meta-analysis, published originally in 1988 and updated in 1992 (5) and 1995 (6). 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.

Table 1. Early breast cancer trialists' overview for node-negative breast cancer, 1992 (5).

	Reduction in Annual Odds of Recurrence* (SD)	Reduction in Annual Odds of Death* (SD)
Chemotherapy	26% (7)	18% (8)
Tamoxifen	26% (4)	17% (5)

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

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

Study (Reference number)	Treatment	# Patients	Disease-free Survival Rate (follow-up)		p-value
Milan (7,8)	CMF x 9 months No adjuvant treatment	45 45	5% 42%	(7 years)	0.0001
Ludwig (9)	CMF x 1 month No adjuvant treatment	848 427	74% 68%	(5 years)	0.02
NSABP B13 (10,11)	MTX 5 FU X 12 months No adjuvant treatment	339 340	74% 59%	(8 years)	<0.001
Intergroup (12,13)	CMFP x 6 months No adjuvant treatment	196 210	83% 61%	(5 years)	<0.0001

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

The Early Breast Cancer Trialists conducted a meta-analysis of 31 trials evaluating adjuvant polychemotherapy in 11,000 women with early-stage breast cancer (5). 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 <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 <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 >70 years of age, but the number 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) (6). 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 (ER-negative) tumours were randomized to nine months of CMF or to no treatment (7). There was a statistically significant improvement in both DFS (85% in the CMF group compared with 42% (8) 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 (8). 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%, respectively. However, the fact that control patients did so poorly has raised concerns about the results of this trial.

In the trial conducted by the Ludwig group, 1,275 women with node-negative breast cancer were randomized to one month of adjuvant CMF or to no treatment (9). The five-year DFS rate was significantly improved with chemotherapy (74% alive and disease-free compared with 68% in the control group; hazard ratio [HR], 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 (HR, 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 ER-negative tumours were randomized to sequential methotrexate and fluorouracil or to no treatment (10). 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) (11).

In the Intergroup trial, 406 women with either ER-negative tumours or tumours ≥3 cm in diameter were randomized to CMF/prednisone (CMFP) or to no treatment (12,13). 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 being 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. Amenorrhea occurs in approximately 50% of patients and venous thromboembolism in approximately 2% of patients. Hospitalization for febrile neutropenia occurs in approximately 1% 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 also 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 1562 patients who received standard-dose doxorubicin/cyclophosphamide (AC) (15).

Update

The Early Breast Cancer Trialists' Collaboration meta-analysis (5) 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 CMF. Patients with node-negative breast cancer were included, but the number of women in this subgroup was 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 >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 an 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.

The Breast Cancer DSG also reviewed the following additional evidence:

1. 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 (13);
2. Fluorouracil, epirubicin and cyclophosphamide (FEC) versus no chemotherapy:
   - published results of a clinical trial of adjuvant 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);
3. 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/fluouracil (CEF) in premenopausal women with node-negative breast cancer (11u),
- an ASCO abstract reporting results of a randomized trial of CMF versus fluorouracil/doxorubicin/cyclophosphamide (FAC) in women with node-negative breast cancer (12u);

4. 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 chemotherapy 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

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 (5) and 1995 (16). 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.

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

Study (Reference number)	Treatment	# Patients	Disease-free Survival Rate (follow-up)		p-value
NATO (17)	Tamoxifen No treatment	300 305	73% 65%	(median follow-up = 66 months)	0.0001
Scottish (18)	Tamoxifen No treatment	374 373	79% 65%	(5 years)	0.0001
NSABP B14 (19,20)	Tamoxifen Placebo	1418 1426	82% 72%	(5 years)	<0.000005

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 (5). 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%, respectively. 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 ER-negative tumours. In women <50 years of age with estrogen-receptor-positive (ER-positive) tumours, the risk reduction was 19% (SD, 6)

for recurrence and 13% (SD, 8) for mortality. In women <50 with ER-negative tumours, the risk reduction for recurrence was 3% (SD, 8); tamoxifen had no effect on mortality.

These results have been updated using data collected up to 1995 (16). Tamoxifen had little effect on ER-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 (17). 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 (18). There was a statistically significant difference in DFS in favour of adjuvant tamoxifen compared with control (HR, 0.62; 95% CI, 0.49 to 0.79; p=0.0001) and a trend toward improved survival with adjuvant tamoxifen (HR, 0.77; 95% CI, 0.58 to 1.02; p=0.07).

In the NSABP B-14 trial, 2,844 node-negative women with ER-positive tumours were randomized to tamoxifen or placebo for five years (19,20). 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 (21,22).

Update

The Breast Cancer DSG is reviewing evidence from the following:

1. 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).
2. ii) duration of tamoxifen:
   - updated results of the NSABP B-14 trial of five versus >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

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 ER-positive, node-negative breast cancer were randomized to tamoxifen alone (T) or tamoxifen plus methotrexate/fluorouracil chemotherapy (MFT) or tamoxifen plus CMF chemotherapy (CMFT) (23). There was an improvement in the five-year DFS 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

The Breast Cancer DSG is reviewing evidence from:

- 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),
- a randomized trial of tamoxifen versus CMF followed by tamoxifen in postmenopausal women with node-negative breast cancer (20u).

Definition of Risk Category

Tumour size, histologic differentiation (grade), and hormone-receptor status are factors that have traditionally been employed in trying to predict the likelihood of recurrence of breast cancer in node-negative patients (3). Data supporting the prognostic utility of these factors come from descriptive series (e.g., the Surveillance, Epidemiology, and End Results [SEER] Program and San Antonio databases) and from cohorts of patients enrolled in randomized trials (24-37). In addition, the presence of lymphatic and vascular invasion has been found to be associated with an increased risk of recurrence (37-40).

The influence of tumour size on prognosis appears to be a continuum, with tumours <1 cm in diameter having a very low risk of recurrence (32,33). No precise size that 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 semiquantitative grading system is 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), ER-positive status and well-differentiated histology are considered good prognostic characteristics, whereas larger tumour size (i.e., >3 cm), ER-negative status, poorly differentiated histology, and the presence of lymphatic/vascular invasion are considered to be predictors of increased risk of breast cancer recurrence.

Other factors being evaluated for their prognostic ability 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/or 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 cribriform 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%.

Table 4. Risk category.

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

* 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 that are <1 cm and high grade or <1 cm with lymphatic/vascular invasion.

Update
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
Since the Ontario guideline was completed by the PGI, 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 PGI 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 the 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 CMF ii) 4 cycles of AC. More intensive combinations such as CEF 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

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).

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

Patient Group	Risk		
(Responsiveness)	**Minimal/Low**	**Moderate**	**High**
Premenopausal (< 50 years)			
Estrogen-receptor-positive	no treatment	tamoxifen*	chemotherapy**
Estrogen-receptor-negative	-	-	chemotherapy
Postmenopausal (≥50 years)			
Estrogen-receptor-positive	no treatment	tamoxifen*	tamoxifen plus chemotherapy
Estrogen-receptor-negative	-	-	chemotherapy

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

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

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 (5) and that five years is superior to two years (16). The two relatively large trials involving node-negative patients (NSABP, Scottish) used five years of tamoxifen (18,20). Results of two recent randomized trials failed to detect an improvement with ten years of tamoxifen compared with five years (43,44). A recent Scandinavian trial and a recent British trial have demonstrated the superiority of five years of tamoxifen compared with two years (45,46), a finding supported by data from the most recent update of the Early Breast Cancer Trialists' meta-analysis (16).

Chemotherapy Regimen

Few studies of / involving node-negative breast cancer patients have used "standard CMF" as the treatment arm. Nonetheless, extrapolation from studies of 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 (47). In the NSABP B-20 trial, there has been no difference detected yet between CMF plus tamoxifen and MF plus tamoxifen (23).

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., AC or CAF, in node-negative patients. AC, which is often used in patients with node-positive disease (48), is shorter in duration and has a different toxicity profile than CMF. However, potential cardiomyopathy and leukemia with AC are serious concerns. 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 receiving anthracycline-containing chemotherapy.

The National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) compared CEF with CMF in node-positive women with breast cancer (48). CEF was superior to CMF for both disease-free survival and overall survival, but was associated with increased toxicity, including leukemia.

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

VI. ONGOING TRIALS

A number of ongoing randomized trials of adjuvant systemic therapy include women with node-negative or node-positive breast cancer. The following two trials are restricted to women with node-negative disease:

CLB-40101: Phase III randomized study of adjuvant cyclophosphamide and doxorubicin versus paclitaxel in women with high-risk, node-negative breast cancer.

FRE-FNCLCC-PACS-05/0106: Phase III randomized study of 4 versus 6 courses of adjuvant FEC in women with stage I or II breast cancer.

VII. DISEASE SITE GROUP CONSENSUS PROCESS

A draft of the practice guideline report was discussed at the Breast Cancer 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, on condition that minor refinements in the wording of the treatment recommendations be made.

At the Breast Cancer DSG 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 (6,16) and were discussed and incorporated into the guideline report.

Some members of the DSG felt that the results of the MA.5 trial that established the superiority of CEF over CMF in premenopausal, node-positive patients could be extrapolated to node-negative women (49).

The use of combined chemotherapy and tamoxifen was discussed at length. The results of the NSABP B-20 trial were reviewed (22), and their demonstration of the superiority of chemotherapy plus tamoxifen versus tamoxifen alone was found to be consistent with other trials. In the recently reported Intergroup study comparing tamoxifen with tamoxifen plus CAF in postmenopausal node-positive women, the DFS 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 (6). 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 the inclusion of 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 ER-negative, node-negative patients were randomized to MF for six months versus CMF for six months (47). The five-year DFS 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 (23). Of importance is the fact 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 the toxicity of oral cyclophosphamide resulted in lower drug absorption and consequently, reduced effect from the inclusion of 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 DFS (48).

The DSG addressed the question of whether chemotherapy should be added for tamoxifen-responsive patients, and if so, whether for all subgroups. The agreement was 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.

The addition of chemotherapy to tamoxifen for high risk (> 3 cm, or grade III) estrogen-receptor-positive postmenopausal women was also agreed upon. (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 a 40% occurrence in CMF patients. MF was not favoured because of its observed inferiority in the NSABP B-19 trial.

The DSG agreed that in high risk (> 3 cm, or grade III) ER-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 National Cancer Institute of Canada Clinical Trials Group 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

This section describes the external review activities undertaken for the original guideline report.

Draft Practice Guideline

Based on the evidence contained in the original guideline 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 in the original guideline report and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods
In 1998, 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 (post card) and four weeks (complete package mailed again). The results of the survey were reviewed by the Breast Cancer DSG.

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 completed the survey. Eighty-five percent agreed or strongly agreed with the methods and data synthesis, 78% endorsed the practice guideline report, and 80% endorsed the 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 draft recommendations were 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 CMF cyclophosphamide (oral)/methotrexate/fluorouracil or four cycles of doxorubicin/cyclophosphamide.

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.

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 or four cycles of doxorubicin /cyclophosphamide.

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

- The Cancer Care Ontario Practice Guidelines Initiative Breast Cancer Disease Site Group. The role of adjuvant systemic therapy in node-negative breast cancer. Curr Oncol.1999:6(2):78-89.

XI. ACKNOWLEDGEMENTS

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For a full list of members of the Breast Cancer Disease Site Group, please visit the CCO Web pages at http://www.cancercare.on.ca/.

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Appendix 1. 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

EBS 1-8 Document Assessment & Review Form.

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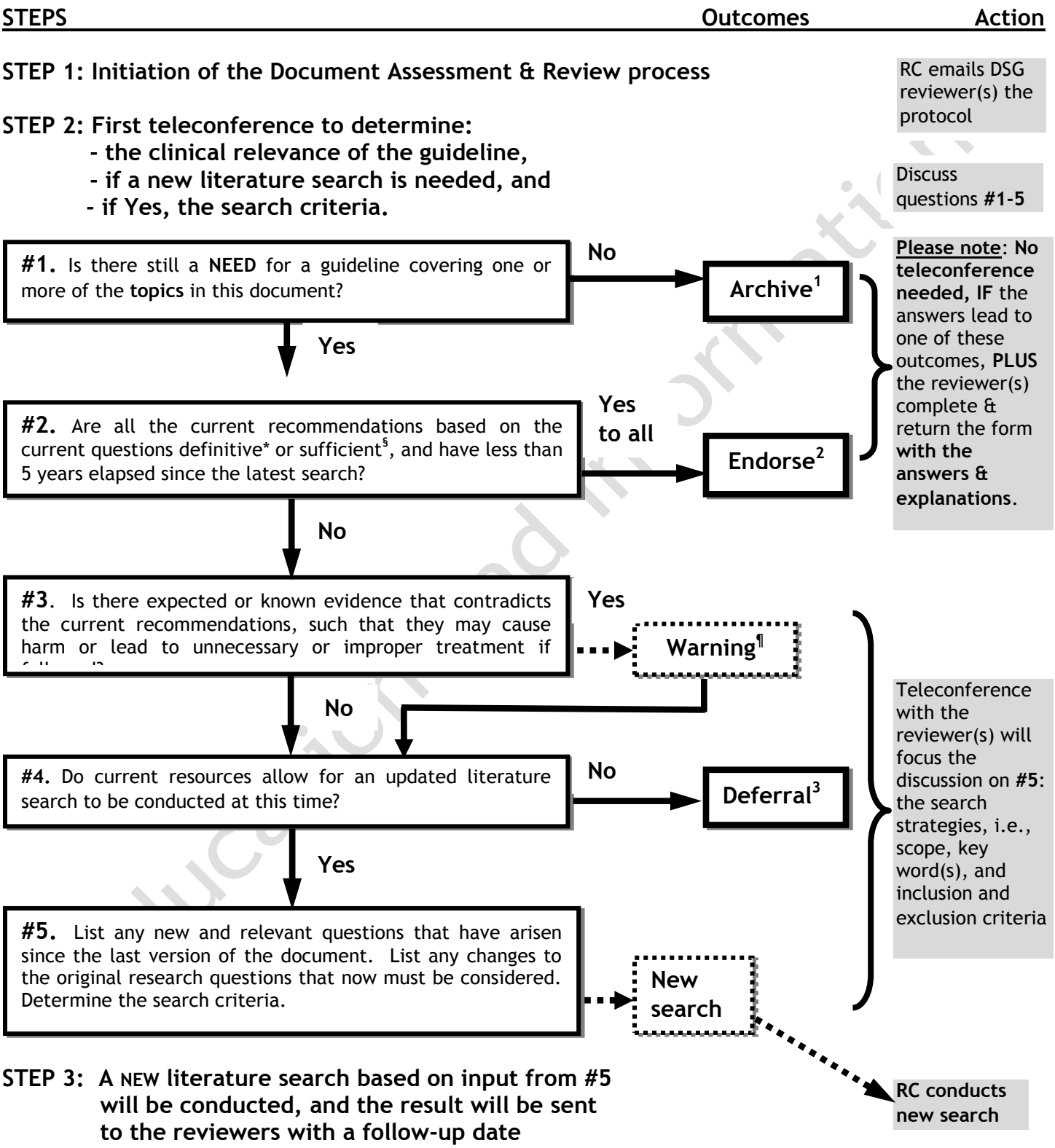
DOCUMENT ASSESSMENT AND REVIEW TOOL

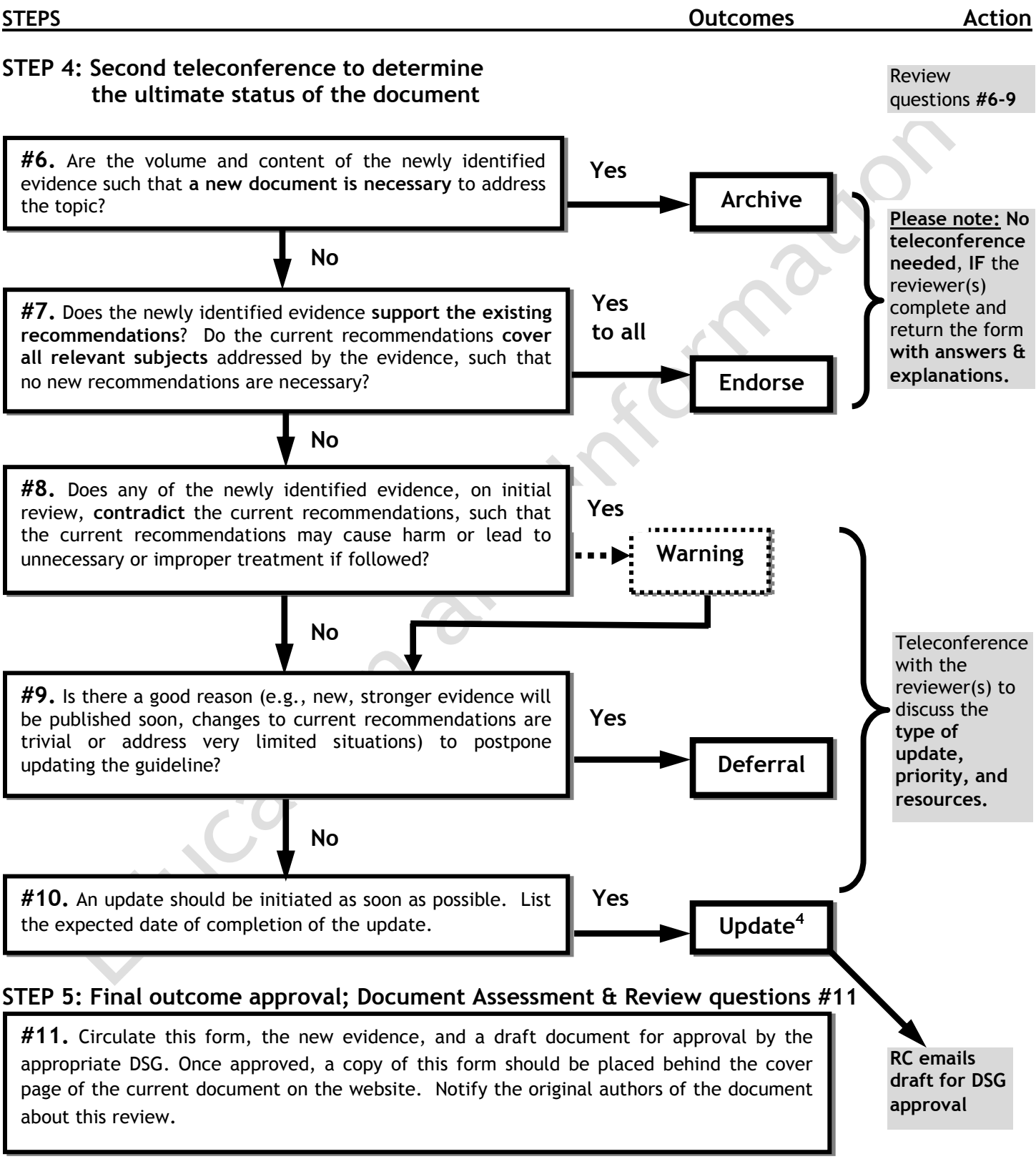
Number and title of document under review	UPG #1-8 Adjuvant Systemic Therapy for Node-Negative Breast Cancer
Date of current version	May 1, 2003
Clinical reviewer	Dr. Maureen Trudeau Dr. Andrea Eisen
Research coordinator	Rovena Tey
Date initiated	June 2010
Date and final results / outcomes	**June 11, 2010 (ARCHIVED)**
Instructions. Beginning at question 1, below, answer the questions in sequential order, following the instructions in the black boxes as you go.	
1. Is there still a need for a guideline covering one or more of the topics in this document **as is**? Answer Yes or No, and explain if necessary:	1. NO • Guideline 1-8 should be **ARCHIVED**. If No, then the document should be **ARCHIVED**[1] with no further action; **go to 11**. If Yes, then **go to 2**.
2. Are all the current recommendations based on the current questions **definitive**[*] or **sufficient**[§], and have less than **5 years elapsed** since the latest search? Answer Yes or No, and explain if necessary:	2. If Yes, the document can be **ENDORSED**[2] with no further action; **go to 11**. If No, **go to 3**.
3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, providing references of known evidence:	3. If Yes, the document should be taken off the website as soon as possible. A **WARNING**[¶] should be put in its place informing a user that the document is only available by email, with a brief explanation of the reasons. If No, g**o to 4**.
4. Do current resources allow for an updated literature search to be conducted at this time? Answer Yes or No, and explain as necessary. Provide an expected date of completion of the updated search, if applicable:	4. If No, a **DEFERRAL**[3] should be placed on the document indicating it cannot be updated at this time, but will be reviewed again on a yearly basis. If Yes, go **to 5**.
5a. **Guideline Research Questions.** Please review the original guideline research questions below and if applicable, list any MINOR changes to the questions that now must be considered. If a question is no longer relevant, it can be deleted. The Document Assessment & Review process evaluates the guideline **as is** and CANNOT accommodate significant changes to the questions or the addition of new questions introducing new patient populations or new agents/interventions because if this what is required in order to make this guideline relevant, then a brand new document should be produced and this guideline as is should be ARCHIVED (i.e., go back to Q1 of this form and answer NO).	

5b. **Inclusion and Exclusion criteria.** List below any changes to the selection criteria in the original version made necessary by new questions, changes to existing questions, or changes in available evidence (e.g., limit a search to randomized trials that originally included non-randomized evidence).	
5c. Conduct an updated literature search based on that done for the current version and modified by 5a and 5b above. Report the results below.	
Go to 6.	
6. Is the volume and content of the new evidence so extensive such that a simple update will be difficult?	6. If Yes, then the document should be **ARCHIVED** with no further action; **go to 11**. If No, **go to 7**.
7. On initial review, does the newly identified evidence support the **existing recommendations**? Do the current recommendations **cover all relevant subjects** addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No, and explain if necessary:	7. If Yes, the document can be **ENDORSED**. If No, **go to 8**.
8. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:	8. If Yes, a **WARNING** note will be placed on the web site. If No, **go to 9**.
9. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	9. If Yes, the document update will be **DEFERRED**, indicating that the document can be used for decision making and the update will be deferred until the expected evidence becomes available. If No, **go to 10.**
10. An update should be initiated as soon as possible. List the expected date of completion of the update:	10. An **UPDATE**[4] will be posted on the website, indicating an update is in progress.
11. Circulate this form to the appropriate Disease Site Group for their approval. Once approved, a copy of this form should be placed behind the cover page of the current document on the website. Notify the original authors of the document about this review.	
DSG Approval Date:	**June 11, 2010**

DOCUMENT ASSESSMENT & REVIEW 5-STEP FLOW CHART



FLOW CHART (cont.)



DOCUMENT ASSESSMENT AND REVIEW DEFINITIONS

Document Assessment and Review Terms

*DEFINITIVE RECOMMENDATIONS – Definitive means that the current recommendations address the relevant subject area so fully that it would be very surprising to identify any contradictory or clarifying evidence.

§ SUFFICIENT RECOMMENDATIONS – Sufficient means that the current recommendations are based on consensus, opinion and/or limited evidence, and the likelihood of finding any further evidence of any variety is very small (e.g., in rare or poorly studied disease).

¶ WARNING – A warning indicates that, although the topic is still relevant, there may be, or is, new evidence that may contradict the guideline recommendations or otherwise make the document suspect as a guide to clinical decision making. The document is removed from the website, and a warning is put in its place. A new literature search may be needed, depending on the clinical priority and resources.

Document Assessment and Review Outcomes

1. **ARCHIVED** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and **each page is watermarked** with the phrase "ARCHIVED".

2. **ENDORSED** – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DEFERRAL** – A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action for a number of reasons. The reasons for the deferral are in the Document Assessment and Review Tool in the document.

4. **UPDATE –** An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.