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PRACTICE GUIDELINE

Optimal systemic therapy for early breast cancer in women: a clinical practice guideline

A. Eisen MD, G.G. Fletcher MSc,† S. Gandhi MSc MD,* M. Mates MD,‡ O.C. Freedman MD,§ S.F. Dent MD,|| M.E. Trudeau MD,* and members of the Early Breast Cancer Systemic Therapy Consensus Panel#*

ABSTRACT

The Breast Cancer Disease Site Group of Cancer Care Ontario identified the need for new guidelines for the adjuvant systemic therapy of early-stage breast cancer. The specific question to be addressed was "What is the optimal adjuvant systemic therapy for female patients with early-stage operable breast cancer, when patient and disease factors are considered?"

A systematic review was prepared based on literature searches conducted using the MEDLINE and EMBASE databases for the period January 2008 to March 5, 2012, and updated to May 12, 2014. Guidelines were located from that search, from the Standards and Guidelines Evidence directory of cancer guidelines, and from the Web sites of major guideline organizations. The literature located was subdivided into the broad categories of chemotherapy, hormonal therapy, and therapy targeted to HER2 (human epidermal growth factor receptor 2). Although several of the systemic therapies discussed in this guideline can be considered in the neoadjuvant setting, the review focused on trials with rates of disease-free and overall survival as endpoints and thus excluded several trials that used pathologic complete response as a primary endpoint.

Based on the systematic review, the working group drafted recommendations on the use of chemotherapy, hormonal therapy, and targeted therapy; based on their professional experience, they also drafted recommendations on patient and disease characteristics and recurrence risk. The literature review and draft recommendations were circulated to a consensus panel of medical oncologists who had expertise in breast cancer and who represented the regions of Ontario. Items without initial consensus were discussed at an in-person consensus meeting held in Toronto, November 23, 2012. The final recommendations are those for which consensus was reached before or at the meeting. Some of the key evidence was revised after the updated literature search. Evidence reviews for systemic chemotherapy, endocrine therapy, and targeted therapy for HER2-positive disease are reported in separate articles in this supplement. The full three-part 1-21 evidence-based series, including complete details of the development and consensus processes, can be found on the Cancer Care Ontario Web site at https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-ebs.

KEY WORDS

Treatment guidelines, consensus process, early breast cancer, adjuvant systemic treatment, chemotherapy, endocrine therapy, HER2-targeted therapy

1. INTRODUCTION

The survival of women diagnosed with early-stage breast cancer in Canada has improved significantly since the early 1980s. The age-standardized mortality rate fell 43% between 1986 and 2014, an improvement that has been attributed both to the increased use of mammographic screening and to advances in the use of systemic adjuvant therapy[1]. And yet a recent review of chemotherapy utilization in Ontario revealed substantial regional variation in the utilization of chemotherapy regimens[2].

The Program in Evidence-Based Care (PEBC) of Cancer Care Ontario (CCO) was formed to produce evidence-based guidance for oncology practitioners in the form of practice guidelines or evidence summaries. The PEBC Breast Cancer Disease Site Group has produced multiple guidance documents for individual drugs used in systemic adjuvant therapy; those documents are available at the CCO Web site (https://www.cancercare.on.ca/toolbox/qualityguidelines/). In 2012, the group decided that

The complete version of this guideline is posted on the Cancer Care Ontario Web site at https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-ebs/.

therapeutic advances warranted the development, from an Ontario perspective, of updated, comprehensive recommendations for systemic therapy in early-stage breast cancer.

The target population for the present guideline is female patients who are being considered for, or who are receiving, systemic therapy for early-stage invasive breast cancer (see the Methods section). For the purposes of this guideline, early breast cancer was defined largely as invasive cancer stages I–IIA (T1N0–1, T2N0). However, some studies that described breast cancer simply as "operable" or that included operable stage IIB–IIIA cancers were included if stage IIA patients formed part of the population and if patients staged I–IIB constituted at least half the population.

The intended users of this guideline are oncology practitioners, typically medical oncologists in Ontario who prescribe adjuvant systemic therapy to women with early-stage breast cancer. Other users can include health care practitioners in training, hospital administrators, and patients. The stakeholders who constituted the consensus panel and who participated in the guideline development process included medical oncologists who treat breast cancer across the province. To ensure input from practices throughout Ontario, breast cancer experts from cancer centres in each of the province's fourteen local health integration networks were contacted. Medical oncologists from hospitals not affiliated with a cancer centre, who were known provincially to have an interest in breast cancer, were also asked to participate.

2. METHODS

2.1 Question

The guideline addresses this question:

- What is the optimal adjuvant systemic therapy for female patients with early-stage operable breast cancer, when patient and disease factors are considered?

2.2 Systematic Review

In developing evidence-based guidelines, CCO's PEBC uses the methods of the practice guidelines development cycle[3,4]. For the present project, the core methodology used to develop the evidentiary base was the systematic review. The evidence thus obtained forms the basis of the recommendations developed by the Early Breast Cancer Systemic Therapy Consensus Panel. The topic areas of patient and disease characteristics and recurrence risk were not directly covered by the systematic review; recommendations 1–7 are based on consensus reached by the panel members.

The systematic review was based on literature searches conducted using the MEDLINE and EMBASE databases for the period January 2008 to March 5, 2012, and updated to May 12, 2014. The systematic reviews of chemotherapy, hormonal therapy, and biologic or targeted therapy for HER2 (human epidermal growth factor receptor 2)–positive cancer are published separately in this supplement and in the three-part evidence-based series at the CCO Web site[5]. The full search strategy and the inclusion and exclusion criteria are presented in the latter documents.

2.3 Development of Recommendations

A working group of content experts from the Breast Cancer Disease Site Group summarized the evidence and drafted 34 clinical recommendations that were then circulated to all consensus panel members as a survey. Panel members were asked to rate their agreement with the recommendations. Consensus was defined as the attainment of a minimum 80% agreement ("agree" or "strongly agree"), with no "strongly disagree" votes. Recommendations that lacked consensus or that achieved consensus with some disagreement were presented at a consensus meeting on November 23, 2012, with a vote being taken after discussion. Before the meeting, 10 statements had not attained consensus and required debate. Of those 10 statements, participants were able to reach consensus for 9. An additional 8 statements had attained consensus with some disagreement. Those 8 statements were further reviewed to identify the reasons for disagreement and were subsequently accepted. The 16 statements that had attained consensus during the survey did not require review. As a result of the literature review update after the consensus meeting, 2 statements (recommendations 18 and 23) were modified to allow for up to 10 years of tamoxifen (instead of 5 years), and the consensus panel was asked to approve the change.

2.4 Internal and External Review Process

Before submission of the draft report for external review, the systematic review and practice guideline were reviewed by the PEBC Report Approval Panel, which consists of the PEBC director and two other individuals with expertise in clinical and methodology issues. The PEBC Report Approval Panel reviewed the draft systematic review and practice guideline and provided feedback, which was incorporated into the guideline.

The draft document was then distributed for external review. External review included both a targeted peer review (intended to obtain direct feedback from a small number of content experts) and a professional consultation (intended to facilitate dissemination of the guideline to Ontario practitioners and to provide opportunity for additional feedback). Results of those two sources of feedback can be found in the full guideline report on the CCO Web site[5].

3. RESULTS

After removal of duplicate citations, the searches in MEDLINE and EMBASE located 14,444 publications (11,435 RCTs and 3009 systematic reviews, guidelines, or meta-analyses). After screening based on the inclusion and exclusion criteria and the addition of publications from other sources (reference lists, targeted searches for publications of studies initially found only as abstracts), 516 publications of trials remained, of which 221 were relevant to chemotherapy, 232 to hormonal therapy, and 60 to targeted therapy. Approximately 50 trials (chemotherapy, hormonal therapy, and targeted therapy) had not been cited in major guidelines or systematic reviews. Details of the included trials can be found in the systematic reviews published in this supplement and in the evidence-based series on the CCO Web site[5].

4. RECOMMENDATIONS AND KEY EVIDENCE

All recommendations are made assuming that patient preference is considered and that the chosen treatment is determined in consultation between the patient and the doctor. That assumption is mentioned more explicitly in several recommendations in which the balance between risk and benefit is less clear overall or for certain patient groups. Key evidence and qualifying statements follow the recommendations; the full systematic review should be consulted for details concerning recommendations 8–34.

4.1 Patient and Disease Characteristics and Recurrence Risk

Recommendations for adjuvant systemic therapy in breast cancer are guided mostly by patient and disease characteristics. Those factors help to stratify patients into low-, intermediate-, and high-risk categories[6–8]. The recommendations for risk stratification were created by

- extraction of information from clinical practice guidelines found during the systematic review.
- assessment of patient and disease factors evaluated or addressed in clinical trials included in the systematic review.
- initial expert consensus on additional relevant factors that might not have been specifically addressed in the reviewed guidelines and clinical trials.

4.1.1 Recommendation 1

In making a decision about adjuvant systemic therapies for breast cancer, these disease characteristics (histopathologic parameters) are considered relevant (either prognostic or predictive):

- Lymph node status
- T Stage
- Estrogen receptor (ER) status
- Progesterone receptor (PR) status
- HER2 status
- Tumour grade
- Presence of tumour lymphovascular invasion

Qualifying Statements: *PR Status:* The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis[9] found that PR status was not an important independent factor for determining response to endocrine therapy with tamoxifen. The consensus panel members cautioned that PR status in the studies used for the EBCTCG meta-analysis might have been analyzed using older pathology methods and, compared with ER analysis, might not be as well standardized. Disease that is ER-negative and PR-positive is very rare, such that a pathology result with that profile usually requires retesting and confirmation. The method used to ascertain ER and PR status is important, and positivity should be determined according to guidelines from CCO, the American Society of Clinical Oncology (ASCO), and the College of American Pathologists (CAP)[10–13]. The EBCTCG meta-analysis did not address disease response to endocrine agents other than tamoxifen in patients with ER-negative, PR-positive cancer. Nonetheless, PR status might still have prognostic value even if it is not deemed useful in determining tamoxifen response.

Lymphovascular Invasion: Lymphovascular invasion predicted worse outcome in some studies[14,15] and might therefore be useful as a prognostic factor. According to the St. Gallen Consensus Conference[8,16], it is not sufficient to decide chemotherapy. The panel wondered whether lymphovascular invasion results are reproducible from one laboratory to another.

Other Characteristics Without Consensus: Ki-67: Measurement of Ki-67 is currently considered more clinically useful in other cancers, such as lymphoma. Analytic reproducibility of Ki-67 in breast cancer is generally poor from one centre to another because testing methods are not standardized, and no clear cut-off values have been defined. Some studies show a prognostic role for Ki-67, and Ki-67 has been incorporated into some molecular gene signatures, such as Oncotype DX (Genomic Health, Redwood City, CA, U.S.A.). Finally, Ki-67 has not been prospectively validated. It is premature to recommend its use as a standard parameter for patient risk stratification, although it could be evaluated in clinical trials.

Intrinsic Subtype: Intrinsic breast cancer subtypes that correlate with prognosis (luminal A, luminal B, HER2-enriched, basal, and normal) have been established. Several retrospective analyses describe response by those subtypes to various systemic treatments. However, the utility of the subtypes (beyond measurement of ER, PR, HER2, and grade) is not clear.

At the time of writing, the use of the subtypes in clinical decision-making outside of a clinical trial is not recommended.

4.1.2 Recommendation 2

The following risk stratification tools can be used in determining the utility of certain systemic therapies in patients with early-stage breast cancer:

- Oncotype DX score (for hormone receptor–positive; N0, $N1_{mic}$, or isolated tumour cell; and HER2-negative cancers)
- Adjuvant! Online (http://www.adjuvantonline.com)

Qualifying Statements: The Oncotype DX assay uses real-time reverse-transcription polymerase chain reaction to analyze expression of a panel of 21 genes. In a report from CCO's Molecular Oncology Advisory Committee[17], the assay was compared with other molecular tests. Oncotype DX includes 5 reference genes and 16 genes found to correlate with distant relapse in hormone receptor–positive breast cancer. The test was initially validated in the patient cohorts of three independent trials.

Tumours tested using Oncotype DX are stratified as having a low, intermediate, or high recurrence score, and each individual score is associated with a distinct 10-year distant relapse rate, assuming 5 years of endocrine therapy with tamoxifen. The additional benefit of chemotherapy varies by recurrence score, whereby patients with low scores experience little to no benefit, and those with high scores experience the most benefit[18]. The utility of chemotherapy in the intermediate recurrence score zone is currently less clear, although a phase III clinical trial (TAILORX), once reported, might help to address that question. The test is most useful in patients with hormone receptor–positive, HER2-negative, lymph node–negative cancer. Studies have retrospectively evaluated the use of Oncotype DX in patients with lymph node–positive cancer, but those studies are not entirely robust from a statistical standpoint[19,20].

Oncotype DX is not consistently funded by health authorities across Canada. The consensus panel agreed the test is useful in selecting patients either with hormone receptor (ER or PR)–positive, HER2-negative, lymph node–negative cancer or with lymph node micrometastasis in whom the additional benefit of chemotherapy compared with endocrine therapy alone is unclear.

Prognostic information from the U.S. Surveillance, Epidemiology and End Results cancer information database forms the core of Adjuvant! Online, which was validated by Olivotto *et al.*[21]. Correlations generated by Adjuvant! Online are good overall, with some exceptions. In the U.K. validation[22], patients did worse than predicted, a result that might relate to differences in the U.S. and U.K. health systems. Adjuvant! Online and Oncotype DX produce correlations that are good in patients with mid-risk of recurrence, but poor at the high and low ends.

Several consensus panel participants considered Adjuvant! Online a good tool to help explain risk and treatment options to patients, but said that they do not use it for decision-making because it does not include other factors that have to be considered, such as HER2 status. Risks depend on the comorbidities entered into the system.

4.1.3 Recommendation 3

These patient factors should be considered in making adjuvant systemic therapy decisions:

- Age
- Menopausal status
- Medical comorbidities (including validated tools used to measure health status)

Qualifying Statements: The consensus panel agreed that age should not be the sole factor used in selecting patients for chemotherapy. In the absence of other medical comorbidities, advanced age should not be used as an independent criterion to not recommend chemotherapy. Younger age can more often be correlated with aggressive tumour biology or subtypes, and can also predict response to certain treatments, but it should not be an independent factor in determining candidacy for chemotherapy. A desire to spare fertility in younger patients and a desire to avoid certain adverse effects in older patients might affect selection of treatment. Age has been used as a surrogate for menopausal status in some clinical studies (see recommendations 15–25 with respect to endocrine therapy).

4.1.4 Recommendation 4

In patients who would likely tolerate and accept chemotherapy, adjuvant chemotherapy should be considered for patients with these tumour characteristics (in no particular order):

- Node-positive [one or more lymph nodes having a macrometastatic deposit (>2 mm)]
- ER-negative, with a tumour more than 5 mm in size
- HER2-positive
- High-risk, lymph node–negative, with a tumour more than 5 mm in size and another high-risk feature (see recommendation 5)
- Adjuvant! Online 10-year risk of death from breast cancer greater than 10%

Qualifying Statements: Consideration of disease factors in the selection of patients to receive chemotherapy was based on review of existing guidelines and models of risk stratification as outlined in the Introduction. The Adjuvant! Online 10-year risk of death was considered by the panel at two cut-offs: 10% and 15%. The consensus for 15% was strong; the consensus for 10% was less robust. Therefore, a

10-year risk of death judged to be either 10% or 15% using the Adjuvant! Online model is a reasonable threshold for considering chemotherapy.

4.1.5 Recommendation 5

When considering lymph node–negative tumours greater than 5 mm in size, these features should be considered high-risk (with the patients therefore considered candidates for chemotherapy):

- Grade 3
- Triple-negative (ER-, PR-, and HER2-negative)
- Positive for lymphovascular invasion
- Oncotype DX recurrence score associated with an estimated 15% or greater risk of distant relapse at 10 years
- HER2-positive

Qualifying Statements: The panel reached consensus for considering all the specified features to be high risk; patients with tumours having these characteristics should therefore be considered for adjuvant chemotherapy. As noted earlier, these features were derived from review of existing guidelines and models of risk stratification.

4.1.6 Recommendation 6

Patients with the following disease characteristics might not benefit from adjuvant chemotherapy:

- A tumour less than 5 mm in size, lymph node–negative disease, and no other high-risk features (see recommendation 5)

4.1.7 Recommendation 7

Adjuvant chemotherapy might not be required in patients with HER2-negative, strongly ER-positive, PR-positive breast cancer with any of these additional characteristics:

- Lymph node–positive with micrometastasis (<2 mm) only
  OR
- Tumour less than 5 mm in size
  OR
- Oncotype DX recurrence score with an estimated distant relapse risk of less than 15% at 10 years

Qualifying Statements (recommendations 6 and 7): Cut-offs for the degree of ER expression do not formally exist. The generally accepted degree of strong ER positivity is more than 90%, and that level was used for the consensus question. Refer to local pathology policy with respect to the degree of ER expression.

Few RCTs have addressed the role of systemic chemotherapy in female patients with early-stage breast cancer having a good prognosis. In addition, available data concerning the benefit of systemic therapy in patients with lymph node–positive micrometastatic disease (≤2 mm) are limited. The International Breast Cancer Study Group 23-01 trial concluded that axillary dissection could be avoided in patients with early breast cancer and limited sentinel node involvement (micrometastasis only), thus eliminating the complications of axillary surgery with no adverse effect on survival rates[23]. In the 23-01 trial, more than 60% of patients received adjuvant endocrine treatment alone, with excellent 5-year disease-free survival (DFS) and overall survival (OS).

Sentinel node micrometastases have been associated with an adverse prognosis in some long-term follow-up studies. Retrospective data have shown some benefit of systemic therapy in patients with micrometastatic disease. Until the results of prospective RCTs are available, the potential role of systemic therapy should be discussed with each patient[24].

Prognostic tools such as Adjuvant! Online and Oncotype DX can be used to assist health care providers in determining the potential benefit of chemotherapy.

The potential benefit of adjuvant systemic therapy is modest for patients with small (<1 cm) node-negative breast cancer that is endocrine-sensitive and HER2-negative. Such patients can be considered for endocrine therapy alone (see the guideline from the U.S. National Comprehensive Cancer Network[7]).

Although most of the consensus group agreed that patients with lymph node–positive breast cancer with micrometastasis only (<2 mm) and no other high-risk features might not need adjuvant chemotherapy, 25% disagreed or were undecided, and consensus was not reached. However, consensus was reached about potentially omitting chemotherapy when patients are found to have lower-risk (see recommendation 7) strongly ER-positive or PR-positive disease. There was disagreement about whether lymph node micrometastasis alone is a high- or low-risk factor. Lymph node positivity with micrometastasis alone is therefore not included in the recommendation.

4.2 Selection of Optimal Adjuvant Chemotherapy Regimens

4.2.1 Recommendation 8

In patients who can tolerate it, use of a regimen containing anthracycline–taxane is considered the optimal strategy for adjuvant chemotherapy, particularly for patients deemed to be at high risk.

Key Evidence: Aggregate data from several phase III clinical studies and from meta-analyses have established the superiority of many anthracycline–taxane-based regimens compared with other chemotherapy (see Tables 2 and 3 in the evidence-based series[5]).

The 2012 EBCTCG meta-analysis[25] highlighted the superiority of anthracycline–taxane regimens that do not alter the number of anthracycline cycles [for example, doxorubicin–cyclophosphamide (AC) × 4 → docetaxel (T) × 4] over anthracycline alone

(for example, AC × 4). Although the EBCTCG found no significant differences in outcome if, compared with simply increasing the number of anthracycline treatments [5-fluorouracil–epirubicin–cyclophosphamide (FEC) × 6], the anthracycline treatments were truncated and a taxane was added instead [for example, FEC × 3 → T × 3], longer-term follow-up of the included studies (see Table 3 in the evidence-based series[5]) suggested the presence of a benefit for taxane. The PACS 01 trial, which compared FEC × 3 → T × 3 with FEC × 6, found improved survival rates for the anthracycline–taxane combination at 8 years[26].

Truncating the number of anthracycline cycles when adding a taxane can mitigate certain important adverse effects such as cardiotoxicity and leukemia, which occur more frequently with more cycles of anthracycline (for example, PACS 01[27], review by Trudeau *et al.*[28], and a recent meta-analysis[29]). Data from individual trials support these regimens:

- FEC × 3 → T × 3 (superior to FEC × 6) (from PACS 01[26,27,30–32])
- AC × 4 → T ×4 (superior to AC × 4) [from National Surgical Adjuvant Breast and Bowel Project (NSABP) B27[33]]
- Docetaxel–doxorubicin–cyclophosphamide × 6 [superior to 5-fluorouracil–doxorubicin–cyclophosphamide × 6] [from the Breast Cancer International Research Group (BCIRG) 001 trial[34–36]]
- AC × 4 → paclitaxel (P) × 4 administered every 3 weeks is an option in selected cases, but was found to be inferior to AC × 4 → P administered weekly (from the Eastern Cooperative Oncology Group 1199 trial[37]), to cyclophosphamide–epirubicin–5-fluorouracil, and to dose-intense epirubicin–cyclophosphamide → P (from MA.21[38]).

4.2.2 Recommendation 9

For patients in whom a taxane is contraindicated, an optimal-dose anthracycline regimen (doxorubicin ≥ 240 mg/m^2 or epirubicin ≥ 360 mg/m^2) is recommended.

Key Evidence: Anthracyclines have been established to be superior to some non-anthracycline chemotherapy regimens (see Table 2 in the evidence-based series[5]).

Studies included in the 2012 EBCTCG meta-analysis[25] indicate that, in general, anthracycline-based regimens are superior to non-anthracycline non-taxane regimens, provided that an optimal anthracycline cumulative dosage is achieved (defined as a total epirubicin dose exceeding 360 mg/m^2 or doxorubicin dose exceeding 240 mg/m^2).

4.2.3 Recommendation 10

The addition of gemcitabine or capecitabine to an anthracycline–taxane regimen is not recommended for adjuvant chemotherapy.

Key Evidence: The addition of gemcitabine or capecitabine to an anthracycline–taxane regimen does not improve rates of DFS or OS and is more toxic[39,40] (see Table 3 in the evidence-based series[5]).

4.2.4 Recommendation 11

In patients more than 65 years of age, capecitabine is not recommended as an adjuvant chemotherapy option in lieu of adjuvant AC or cyclophosphamide–methotrexate–5-fluorouracil [CMF (oral cyclophosphamide)].

Key Evidence: In patients more than 65 years of age, adjuvant capecitabine was found to be inferior to CMF (oral cyclophosphamide) × 6 and AC × 4[41] (see Table 1 in the evidence-based series[5]).

4.2.5 Recommendation 12

For patients in whom anthracycline–taxane is contraindicated, CMF (with oral cyclophosphamide) is an acceptable chemotherapy regimen.

Key Evidence: In the adjuvant setting, CMF chemotherapy has been found to be better than no chemotherapy[42] (see Table 1 in the evidence-based series[5]), and CMF × 6 (with oral cyclophosphamide) has been found to be no worse than AC × 4[41].

4.2.6 Recommendation 13

These adjuvant chemotherapy regimens can be used for patients with early-stage breast cancer (see also recommendation 14 for non-anthracycline regimens):

- FEC × 3 → T × 3 (superior to FEC × 6)
- AC × 4 → T × 4 (superior to AC × 4)
- Docetaxel–doxorubicin–cyclophosphamide × 6 (superior to 5-fluorouracil–doxorubicin–cyclophosphamide × 6)
- AC × 4 → P administered weekly
- Dose-dense, dose-intense epirubicin–cyclophosphamide → P
- Dose-dense AC → P (every 2 weeks)

Key Evidence and Qualifying Statements: Phase III clinical studies have shown improved outcomes with use of the adjuvant anthracycline- and anthracycline–taxane-based regimens listed in recommendation 13 (see Tables 2 and 3 in the evidence-based series[5]).

The initial consensus questionnaire omitted FEC followed by weekly P. That regimen was discussed at the meeting, and participants were asked to add it to the answer sheet for the second round of voting. Of the 16 participants, 4 did not answer the question at that round; consensus was therefore not reached. Of participants who voted, 11 agreed, and 1 was undecided.

Consensus was not reached on the use of cyclophosphamide–epirubicin–5-fluorouracil (5 of 16 disagreed or were undecided). That regimen might have a role in a subgroup of patients with very high risk of recurrence and good health who can tolerate

it, although regimens with similar efficacy and a lower risk of adverse effects are probably available.

4.2.7 Recommendation 14

Docetaxel–cyclophosphamide (TC) is an adjuvant regimen that can be used when an anthracycline is not preferred.

Key Evidence and Qualifying Statements: The U.S. Oncology Research 9735 study found superiority for TC × 4 compared with AC × 4[43] (see Table 3 in the evidence-based series[5]). How a taxane regimen such as TC compares with an anthracycline–taxane regimen is unclear. The ongoing and interrelated NSABP B46, U.S. Oncology Research 06-090, and NSABP B49 trials are currently comparing TC with docetaxel–doxorubicin–cyclophosphamide (visit http://clinicaltrials.gov/ct2/show/NCT01547741 and http://clinicaltrials.gov/ct2/show/NCT00887536).

4.3 Adjuvant Endocrine Therapy

4.3.1 Recommendation 15

For the purpose of selecting adjuvant endocrine therapy, the most reliable definitions of menopause are

- bilateral oophorectomy or
- at least 12 months of amenorrhea before initiation of chemotherapy or tamoxifen.

In female patients 60 years of age or younger who experience amenorrhea secondary to chemotherapy or tamoxifen, defining menopause is difficult; care must be taken when initiating an aromatase inhibitor (AI).

Key Evidence and Qualifying Statements: Caution is essential when defining menopause in patients who have previously undergone hysterectomy with ovaries left in place. In such patients, levels of luteinizing hormone and follicle-stimulating hormone measured before receipt of chemotherapy or tamoxifen can be useful in determining menopausal status.

The definition of menopause varies from study to study, with most using an age cut-off of 50 or 60 years.

Accurate identification of postmenopausal status is crucial if AI therapy is used, because AIs cause a reflex increase in gonadotropin secretion in premenopausal patients[44].

The incidence of chemotherapy-induced amenorrhea depends on the regimen used and the age of the patient[45,46].

Cessation of menses does not necessarily denote the absence of ovarian function, and premenopausal estradiol levels can be found in patients with chemotherapy-induced amenorrhea[47]. In addition, hormone levels and the absence of menses are unreliable indicators of menopause during treatment with tamoxifen[48].

4.3.2 Recommendation 16

Adjuvant endocrine therapy should be considered in all patients with ER-positive cancer, defined by the ASCO and CAP guidelines as ER immunohistochemistry (IHC) staining of 1% or greater, taking into consideration overall disease risk, patient preference, and potential adverse effects.

Key Evidence and Qualifying Statements: The evidence is summarized in Section 2, Subsection 4.3 of the evidence-based series[5]. The recommendation follows the ASCO and CAP guidelines[10–13]. Discussion at the consensus meeting acknowledged that the benefit of hormone-targeted therapy was greater in patients with higher ER levels.

4.3.3 Recommendation 17

Consensus was not reached about whether to administer adjuvant endocrine therapy in patients with ER-negative but PR-positive tumours.

4.3.4 Recommendation 18

Tamoxifen for 5 years has been the standard of care, but tamoxifen for up to 10 years is a reasonable option for premenopausal patients with ER-positive tumours, regardless of chemotherapy use.

Key Evidence and Qualifying Statements: Evidence for tamoxifen use is summarized in Subsection 4.3.1 of the evidence-based series[5]. Tamoxifen for 5 years improves rates of DFS and OS in the adjuvant setting in both pre- and postmenopausal patients. Monotherapy with tamoxifen for 5 years is superior to therapy for 2–3 years.

The ATLAS[49] and ATTOM[50] trials found that extending the duration of tamoxifen to 10 years in ER-positive patients further reduced the risk of breast cancer recurrence, breast cancer mortality, and overall mortality. The incidences of pulmonary embolus and endometrial cancer were increased, but were not associated with a significant difference in mortality from those causes.

4.3.5 Recommendation 19

Ovarian ablation or suppression (OA/S) is a reasonable treatment option for premenopausal patients with ER-positive tumours who refuse or who are not candidates for any other systemic therapy.

Key Evidence and Qualifying Statements: See Table 12 in the evidence-based series[5].

Ovarian ablation can be achieved using surgery or radiation, and ovarian suppression can be achieved using luteinizing hormone–releasing hormone agonists.

4.3.6 Recommendation 20

In premenopausal patients with ER-positive tumours (treated with or without chemotherapy), the addition of OA/S to tamoxifen is not the standard of care.

Some consensus panel participants disagreed with the recommendation because it did not make allowance for subgroups and could be misinterpreted to mean that OA/S plus tamoxifen should not be used. Because those participants did not vote "strongly

disagree," the recommendation passed the consensus rules, and rewording was not considered.

Subsequent to submission of this guideline for publication, additional results from the SOFT trial became available, indicating that, for women who remain premenopausal after chemotherapy (as demonstrated by estradiol levels), suppression of ovarian function in addition to tamoxifen reduces the risk of breast cancer recurrence, with a further reduction when exemestane rather than tamoxifen is used[51].

Key Evidence and Qualifying Statements: In early breast cancer, OA/S plus tamoxifen is not currently the standard of care for all premenopausal patients with ER-positive cancer. Some of the authors consider this combination appropriate in certain subgroups—for example, patients who are younger or at a higher risk of recurrence. Use of an AI is addressed in recommendation 21.

Results from the SOFT and TEXT trials (see recommendation 21 and Table 8 in the evidence-based series[5]) suggest that ovarian suppression plus exemestane is better than ovarian suppression plus tamoxifen. Those trials also found that patients deemed by their physicians not to require chemotherapy experienced DFS rates of 96% with exemestane plus ovarian suppression and 93% with tamoxifen plus ovarian suppression, suggesting that some patients who are at low risk of recurrence might not require chemotherapy if they receive appropriate endocrine therapy.

Additional results comparing tamoxifen plus ovarian suppression with tamoxifen alone were reported after this guideline was completed[51,52]. A benefit for the addition of ovarian suppression to tamoxifen was observed (DFS: 86.6% vs. 84.7%; $p = 0.10$ before adjustment, $p = 0.03$ after adjustment for prognostic factors). Most recurrences—and thus greater benefit—were found in those who received chemotherapy; no difference in DFS (93.4% vs. 93.3%) or OS (99.2% vs. 99.8%) was observed in the subgroup of patients who had not received prior chemotherapy. The benefit of ovarian function suppression in addition to exemestane was especially seen in the group of patients less than 35 years of age.

The combination of ovarian function suppression and exemestane was associated with more toxicity and more adverse effects on quality of life. The latter effects have to be considered when choosing between tamoxifen, tamoxifen plus ovarian suppression, and exemestane plus ovarian suppression[52–54].

4.3.7 Recommendation 21

In premenopausal patients with ER-positive tumours, treated with or without chemotherapy, OA/S plus 5 years of an AI is not the standard of care.

Subsequent to submission of this guideline for publication, additional results from the SOFT trial became available, indicating that, for women who remain premenopausal after chemotherapy (as demonstrated by estradiol levels), suppression of ovarian function in addition to tamoxifen reduces risk of breast cancer recurrence, with a further reduction when exemestane rather than tamoxifen is used[51].

Key Evidence and Qualifying Statements: The standard of practice in Canada and the United States is to use tamoxifen in premenopausal patients; European clinicians tend to favour an AI plus OA[55].

In postmenopausal patients, AIs have been found to be superior to tamoxifen (see recommendations 22 and 24). It has been proposed that AIs would be better than tamoxifen in premenopausal patients, but their use would require OA/S to lower estrogen levels to postmenopausal levels.

The SOFT and TEXT trials (see Table 8 in the evidence-based series[5]) found that, compared with tamoxifen plus OA/S, exemestane plus OA/S was associated with improved DFS (91.1% vs. 87.3%; hazard ratio: 0.72; $p = 0.0002$). Those trials also found that patients deemed by their physicians not to require chemotherapy experienced survival rates of 96% with exemestane plus OA/S and 93% with tamoxifen plus OA/S, suggesting that some patients who are at low risk of recurrence might not require chemotherapy if they receive appropriate endocrine therapy.

Additional results comparing tamoxifen plus ovarian suppression with tamoxifen alone were reported after this guideline was completed[51,52]. A benefit for the addition of ovarian suppression to tamoxifen was observed (DFS: 86.6% vs. 84.7%; $p = 0.10$ before adjustment, $p = 0.03$ after adjustment for prognostic factors). Most recurrences—and thus greater benefit—were found in those who received chemotherapy; no difference in DFS (93.4% vs. 93.3%) or OS (99.2% vs. 99.8%) was observed in the subgroup of patients who had not received prior chemotherapy. The benefit of ovarian function suppression in addition to exemestane was especially seen in the group of patients less than 35 years of age.

The combination of ovarian function suppression and exemestane was associated with more toxicity and more adverse effects on quality of life. The latter effects have to be considered when choosing between tamoxifen, tamoxifen plus ovarian suppression, and exemestane plus ovarian suppression[52–54].

4.3.8 Recommendation 22

The optimal[a] adjuvant endocrine therapy for postmenopausal patients with ER-positive tumours should include an AI.

Key Evidence and Qualifying Statements: The evidence is summarized in Tables 6–9 in the evidence-based series[5]. Studies consistently demonstrate that,

[a] Some consensus panel participants felt that the word "optimal" might not apply to all patients. The risk–benefit ratio of using tamoxifen rather than AI must be taken into account, recognizing the different side effect profiles of those medications.

compared with the use of tamoxifen alone, use of an AI either alone or sequentially after tamoxifen therapy is associated with a reduced risk of recurrence and an improved DFS rate[56]. The absolute gain in breast cancer endpoints is greater for patients with a poorer prognosis.

4.3.9 Recommendation 23

Tamoxifen for up to 10 years is an acceptable treatment for postmenopausal patients with ER-positive tumours treated with or without chemotherapy.

Key Evidence and Qualifying Statements: Evidence on tamoxifen use is summarized in Subsection 4.3.1 of the evidence-based series[5].

Although the result of incorporating an AI into treatment is an improved DFS rate and reduced recurrence, tamoxifen alone might be appropriate in some patients. The risk–benefit ratio of using tamoxifen and AI must be taken into account, recognizing the different adverse effect profiles of those medications. Extended tamoxifen (beyond 5 years) is supported by the ATLAS[49] and ATTom trials[50] (see recommendation 18).

4.3.10 Recommendation 24

For postmenopausal patients with ER-positive breast cancer (treated with or without chemotherapy) the acceptable strategies for the use of AIs are

- upfront therapy for 5 years (instead of tamoxifen).
- switch to an AI after 2–3 years of tamoxifen (for a total of 5 years of endocrine therapy).
- extended adjuvant therapy for 5 years after completion of 5 years of tamoxifen.

Key Evidence and Qualifying Statements: Tables 6–8 in the evidence-based series[5] summarize the phase III clinical studies that evaluated the role of AIs in postmenopausal patients with ER-positive breast cancer. All the included studies detected a small benefit in the absolute DFS rate and indicated that AIs can be administered using any of several strategies: upfront, as a switch after 2–3 years of tamoxifen, or as extended adjuvant therapy after 5 years of tamoxifen.

All consensus participants either disagreed with (12 of 16) or were undecided about (4 of 16) giving AIs as extended adjuvant therapy longer than 5 years after completion of 5 years of tamoxifen.

Some studies suggest that the relative benefits of tamoxifen and various AIs might depend on patient characteristics (for example, nodal status, hormone receptor status), although such dependence has to be verified in future studies.

4.3.11 Recommendation 25

In patients with ER-positive tumours who do not receive adjuvant endocrine therapy immediately after surgery or chemotherapy, delayed endocrine therapy is still clinically beneficial.

Key Evidence and Qualifying Statements: The evidence-based series[5] contains evidence for the delayed initiation of both tamoxifen and AIs (Section 2, Subsection 4.3).

The relevant trials initiated endocrine therapy at a mean of 2 years from diagnosis. The benefits of tamoxifen with respect to DFS and OS rates remained even when tamoxifen was initiated more than 2 years after definitive surgery or adjuvant chemotherapy[57,58]; patients should therefore be offered tamoxifen even when a delay occurs after surgery or adjuvant chemotherapy.

4.4 Adjuvant Targeted Therapy (HER2-Positive Cancers)

4.4.1 Recommendation 26

Only patients with HER2-positive breast cancer [IHC 3+, *in situ* hybridization (ISH) ratio ≥ 2, or 6+ HER2 gene copies per cell nucleus] should be offered adjuvant trastuzumab.

Key Evidence and Qualifying Statements: For HER2-positive early-stage breast cancer, trastuzumab is the targeted therapy that has been most fully evaluated in completed RCTs[59–63].

The ASCO and CAP[64,65] definitions of a positive HER2 result is IHC staining of 3+ (uniform, intense membrane staining of >10% of invasive tumour cells), an ISH (fluorescence, silver, or chromogenic) ratio (HER2 gene signals to chromosome 17 signals) of 2.0 of more, or HER2 gene polysomy of 6.0 or more HER2 gene copies per nucleus. Equivocal results—defined as IHC staining of 2+; an average HER2 copy number of 4.0 or more and fewer than 6.0 signals per cell by single-probe ISH; or a HER2/CEP17 ratio of less than 2.0, with an average HER2 copy number of 4.0 or more and fewer than 6.0 signals per cell by dual-probe ISH—should be reported as equivocal and reassessed using a reflex test (same specimen, alternative test) or a new test (new specimen if available, same or alternative test).

4.4.2 Recommendation 27

Trastuzumab plus chemotherapy is recommended for all patients with HER2-positive, node-positive breast cancer and for patients with HER2-positive, node-negative breast cancer greater than 1 cm in size.

Key Evidence and Qualifying Statements: Phase III clinical studies have demonstrated improved DFS and OS with the addition of trastuzumab to chemotherapy (compared with chemotherapy alone) in HER2-positive early breast cancer (see Table 14 in the evidence-based series[5]).

The benefit of adjuvant trastuzumab in the absence of cytotoxic chemotherapy is unknown because it has not been evaluated in clinical trials. Trastuzumab monotherapy is being evaluated against

trastuzumab plus chemotherapy in elderly patients in the N-SAS BC07 (RESPECT) study[66].

4.4.3 Recommendation 28

Trastuzumab therapy can be considered in small tumours (≤1 cm) as part of clinical studies or evidence-building programs (such as the one currently available in Ontario).

Key Evidence and Qualifying Statements: Evidence for trastuzumab use is included in Section 2, Subsection 4.4, of the evidence-based series[5].

Because most of the major phase III trials that confirmed the benefit of adjuvant trastuzumab did not include small (≤1 cm diameter) node-negative breast cancers, evidence from RCTs evaluating the effect of trastuzumab in tumours 1 cm or smaller in size is sparse.

Although no confirmatory trial has been conducted, there is no reason to think that patients with high-risk pT1a/bN0M0 breast cancer cannot benefit from trastuzumab in the same way that patients with more advanced stages of the disease do. No threshold according to tumour size appears to exist, and size alone should not be the deciding factor in deciding whether to administer trastuzumab to patients with tumours 1 cm or less in size. In Ontario, tumours 1 cm or less in size can be treated under the CCO Evidence-Building Program.

4.4.4 Recommendation 29

Trastuzumab can be administered with any acceptable adjuvant chemotherapy regimen.

Key Evidence and Qualifying Statements: Table 14 in the evidence-based series[5] provides evidence concerning the use of trastuzumab with chemotherapy. Most of the existing evidence pertains to anthracycline–taxane-based regimens.

Three large RCTs (>1000 patients) administered anthracycline–taxane combinations (AC → P in NSABP B31[67] and NCCTG N9831[59,60,67–70], AC → T in BCIRG 006[61,62]). The BCIRG 006 trial also included a non-anthracycline-containing arm [docetaxel–carboplatin–trastuzumab (TCH)]. Trastuzumab use was associated with a significant benefit in survival rate in all those trials.

The HERA trial[71] gave trastuzumab to any patient who had received prior chemotherapy (neoadjuvant, adjuvant, or both). The type of chemotherapy given was not randomized: 68% received anthracycline, 26% anthracycline–taxane, and 6% no anthracycline. When results were censored to account for crossover to trastuzumab after unblinding, the DFS and OS rate benefits persisted. The trial suggests a benefit for trastuzumab in combination with any chemotherapy, but the issue of which chemotherapy is optimal was not addressed.

The PEBC 1-17 guideline[72] recommended that trastuzumab be used with an anthracycline instead of CMF.

Because anthracyclines are known to be cardiotoxic, and anthracyclines plus trastuzumab even more cardiotoxic, non-anthracycline regimens could be more appropriate in some patients. The BCIRG 006 trial[61,62] compared both AC → docetaxel–trastuzumab (TH) and TCH (a non-anthracycline regimen) to the AC → T control. The TCH and AC → TH regimens were both superior to AC → T. No significant differences in OS or DFS rates were observed with the various trastuzumab regimens, although AC → TH seemed to have a stronger effect in some subgroups. The incidences of cardiotoxicity and leukemia were much lower with TCH. Whether TCH is equivalent to AC → TH was not established, because the trial was not designed to test for noninferiority between the two trastuzumab-containing regimens.

4.4.5 Recommendation 30

The administration of trastuzumab concurrently with the anthracycline component of a chemotherapy regimen is generally not recommended because of the potential for increased cardiotoxicity.

Key Evidence and Qualifying Statements: Anthracyclines are known to be cardiotoxic, and anthracycline followed by trastuzumab even more cardiotoxic. Anthracyclines administered concurrently with trastuzumab in patients with metastatic breast cancer resulted in a high rate (25%) of congestive heart failure. Concurrent use of trastuzumab with anthracycline has been explored in several small trials in the neoadjuvant setting without significant cardiotoxicity. Long-term results of those trials have yet to be reported. That approach should therefore not be considered outside the context of a clinical trial.

4.4.6 Recommendation 31

Adjuvant trastuzumab can be initiated either concurrently or sequentially with the taxane portion of a chemotherapy regimen.

Key Evidence and Qualifying Statements: The evidence is summarized in Section 2, Subsection 4.4.2, of the evidence-based series[5].

There appear to be no significant differences in survival outcomes when taxane and trastuzumab are given either concurrently or sequentially; however, initiating trastuzumab concurrently with the taxane is still generally preferred.

4.4.7 Recommendation 32

Less cardiotoxicity is seen with TCH than with AC → TH, and TCH is recommended for patients at higher risk for cardiotoxicity.

Key Evidence and Qualifying Statements: Evidence for TCH has been reported, and the TCH regimen was found to be similar to AC → TH (see Table 14 in the evidence-based series[5]). The BCIRG 006 trial[61,62] compared both

AC → TH and TCH (a non-anthracycline regimen) with the AC → T control. The TCH and AC → TH regimens were both superior to AC → T. No significant differences in the rates of OS or DFS were observed between the trastuzumab regimens, although AC → TH seemed to have a stronger effect in some subgroups. Much lower incidences of cardiotoxicity and leukemia were reported with TCH. Whether TCH is equivalent to AC → TH was not established, because the trial was not designed to determine noninferiority between the two trastuzumab-containing arms.

4.4.8 Recommendation 33

No phase III evidence exists for the addition of trastuzumab to some chemotherapy regimens, such as TC. However, those regimens might be in use and are reasonable options, particularly to mitigate cardiotoxicity in certain patients.

Key Evidence and Qualifying Statements: The HERA trial[63,71,73,74], a large phase III international RCT, randomized patients with HER2-positive early breast cancer to 1 or 2 years or no years of trastuzumab after completion of adjuvant systemic therapy (investigator choice). Regardless of the chemotherapy backbone, patients experienced a significant clinical benefit with the addition of trastuzumab to chemotherapy. The TC regimen has not been formally evaluated with trastuzumab in the context of a RCT; however, given the results of the HERA trial (systemic therapy per investigator choice), TC could be considered a reasonable systemic option in combination with trastuzumab, particularly in patients for whom there is concern with respect to cardiotoxicity.

4.4.9 Recommendation 34

Patients should be offered 1 year total of adjuvant trastuzumab, with regular assessments of cardiac function during that period.

Key Evidence and Qualifying Statements: The recent HERA update[63] on the 1- and 2-year trastuzumab subgroups found no DFS or OS rate benefit for the longer treatment duration, but did find increased cardiotoxicity (based on the secondary cardiac endpoint).

The PHARE trial is a phase III RCT comparing 6 with 12 months of adjuvant trastuzumab. Results presented at the European Society for Medical Oncology 2012 meeting[75,76] were inconclusive with respect to whether 6 months of trastuzumab is noninferior to 12 months (a nonsignificant trend favoured 12 months). Further results after 3.5 years of follow-up[77] also concluded that 6 months of trastuzumab had failed to show noninferiority compared with 12 months trastuzumab, although significantly more cardiac events occurred in the 12-month group (5.7% vs. 1.9%).

Two small trials (FINHER, 9 weeks of trastuzumab[78,79]; and E-2198, 12 vs. 52 weeks trastuzumab[80]) suggest that trastuzumab might be beneficial—and result in less cardiotoxicity than longer treatment does—when administered for shorter durations. Results have to be confirmed in larger trials that are ongoing. The short-HER and SOLD studies are looking at 1 year compared with 9 weeks of trastuzumab, and the Hellenic Group and PERSEPHONE trials are looking at 1 year compared with 6 months of trastuzumab. Based on the completed trials, plus the neoadjuvant trials (which found that, compared with chemotherapy alone, trastuzumab plus chemotherapy increased the pathologic complete response rate), some authors have suggested that shorter trastuzumab therapy (even if not optimal for preventing recurrence) might be acceptable, particularly for patients who cannot tolerate trastuzumab for 1 year.

5. IMPLEMENTATION

The systematic review and its companion recommendations are intended to promote evidence-based practice in Ontario; issues specific to other jurisdictions (including low- or middle-income countries) were not considered. The recommendations found in this guideline are most applicable to the Ontario (and likely the North American) oncology practice setting. Although approval of drugs is managed by Health Canada, funding for particular systemic therapy agents is handled provincially in Canada and affects public reimbursement for certain therapeutic agents in each province. Some treatments recommended in this guideline are fairly resource-intensive (for example, taxane chemotherapy and trastuzumab). As such, those treatments might be sustainable only in higher-income nations. The local practice setting, including resource constraints, has to be heeded when considering implementation of systemic therapy recommendations. Guidelines by groups such as the Breast Health Global Initiative[81–83] could help users of this guideline to better choose the most resource-appropriate systemic therapies for their unique practice setting.

6. REVIEW AND UPDATE

Practice guidelines and literature reviews developed by the PEBC are regularly reviewed and updated. For the full 1-21 evidence-based series and subsequent updates, please visit the CCO Web site at https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-ebs/.

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8. CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: MET had responsibility as Head of Medical Oncology for donations from Roche and Amgen to the cancer program and fellowship funding from Eisai, Roche, Novartis, and Amgen. MET has received grants or research support from Astellas, Medivation, and Novartis. SFD is a principal investigator for the APHINITY trial and has received speaking honoraria from Hoffman–La Roche, Amgen, and Novartis; travel support from Celgene and Roche; and unrestricted educational grants from Roche, Pfizer, GlaxoSmithKline, and Amgen. AE received a grant from Genomic Health and was a NCIC principal investigator for the olympiA trial. SG has received consulting fees as an advisory board participant and speaker at education rounds for Novartis. The other authors declared that they had no conflicts.

Other members of the Early Breast Cancer Consensus Panel declared the following conflicts in accordance with the PEBC conflict of interest policy: One was principal investigator and received grants for clinical trials from GlaxoSmithKline, Roche, Novartis, and Bristol–Myers Squibb. Another was the local principal investigator for a trial of foretinib and NCIC co-chair for the MAC.15 study of Oncotype DX, and received a travel grant from Novartis. A third was principal investigator and received grants for the Marianne trials (MA17R). A fourth received a grant from Roche for case-based educational module development and was principal investigator at her institution for several multicentre trials.

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Correspondence to: Andrea Eisen, Division of Medical Oncology, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, T2038, Toronto, Ontario M4N 3M5.
E-mail: andrea.eisen@sunnybrook.ca

* Sunnybrook Health Science Centre, Toronto, ON.
† Program in Evidence-Based Care, Cancer Care Ontario; and Department of Oncology, McMaster University, Hamilton, ON.
‡ Cancer Centre of Southeastern Ontario, Kinston General Hospital; and Queen's University, Kingston, ON.
§ Durham Regional Cancer Centre, Oshawa, ON.
‖ The Ottawa Hospital Cancer Centre and University of Ottawa, Ottawa, ON.
P. Bedard, Princess Margaret Hospital, Toronto, ON; N. Califaretti, Grand River Regional Cancer Centre, Kitchener, ON; B. Dhesy, Juravinski Hospital and Cancer Centre, Hamilton, ON; D.A. Dueck, Northwestern Ontario Regional Cancer Centre, Thunder Bay, ON; K. Enright, Peel Regional Cancer Centre, Mississauga, ON; V. Glenns, North York, ON; C. Hamm, Windsor Regional Cancer Centre, Windsor, ON; Y. Madarnas, Department of Oncology, Queen's University, Kingston, ON; Y. Rahim, Southlake Regional Cancer Centre, Newmarket, ON; S. Rask, Royal Victoria Hospital, Barrie, ON; A. Robinson, Kingston General Hospital, Kingston, ON [formerly Health Sciences North, Sudbury, ON]; S. Spadafora, Algoma District Cancer Program, Sault Area Hospital, Sault Ste. Marie, ON; S. Verma, The Ottawa Hospital Regional Cancer Centre, Ottawa, ON; J. Younus, London Regional Cancer Program, London, ON.