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PRACTICE GUIDELINE

Locoregional therapy of locally advanced breast cancer: a clinical practice guideline

M. Brackstone MD, G.G. Fletcher MSc,† I.S. Dayes MD MSc,‡ Y. Madarnas MD,§ S.K. SenGupta MD,|| S. Verma MD,# and Members of the Breast Cancer Disease Site Group***

ABSTRACT

Questions

1. In female patients with locally advanced breast cancer (LABC) and good response to neoadjuvant chemotherapy (NACT), including endocrine therapy, what is the role of breast-conserving surgery (BCS) compared with mastectomy?
2. In female patients with LABC,
   a. is radiotherapy (RT) indicated for those who have undergone mastectomy?
   b. does locoregional RT, compared with breast or chest wall RT alone, result in a higher survival rate and lower recurrence rates?
   c. is RT indicated for those achieving a pathologic complete response (pCR) to NACT?
3. In female patients with LABC who receive NACT, is the most appropriate axillary staging procedure sentinel lymph node biopsy (SLNB) or axillary dissection? Is SLNB indicated before NACT rather than at the time of surgery?
4. How should female patients with LABC that does not respond to initial NACT be treated?

Methods

This guideline was developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) and the Breast Cancer Disease Site Group (DSG). A systematic review was prepared based on literature searches conducted using the MEDLINE and EMBASE databases for the period 1996 to December 11, 2013. Guidelines were located from that search and from the Web sites of major guideline organizations. The working group drafted recommendations based on the systemic review. The systematic review and recommendations were then circulated to the Breast Cancer DSG and the PEBC Report Approval Panel for internal review; the revised document underwent external review. The full three-part evidence series can be found on the Cancer Care Ontario Web site.

Recommendations

- For most patients with LABC, modified radical mastectomy should be considered the standard of care. For some patients with noninflammatory LABC, BCS can be considered on a case-by-case basis when the surgeon deems that the disease can be fully resected and the patient expresses a strong preference for breast preservation.
- For patients with LABC, RT after mastectomy is recommended.
- It is recommended that, after BCS or mastectomy, patients with LABC receive locoregional RT encompassing the breast or chest wall and local node-bearing areas.
- It is recommended that postoperative RT remain the standard of care for patients with LABC who achieve pCR to NACT.
- It is recommended that axillary dissection remain the standard of care for axillary staging in LABC, with the judicious use of SLNB in patients who are advised of the limitations of the current data.
- Although SLNB either before or after NACT is technically feasible, the data are insufficient to make any recommendation about the optimal timing of SLNB with respect to NACT. Limited data suggest higher sentinel lymph node identification rates and lower false negative identification rates when SLNB is conducted before NACT; however, those data must be balanced against the requirement for two operations if SLNB is not performed at the time of resection of the main tumour.
- It is recommended that patients receiving neoadjuvant anthracycline–taxane-based therapy (or other sequential regimens) whose tumours do not respond to the initial agent or agents, or who experience disease progression, be expedited to the next agent or agents of the regimen.

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/.

- For patients who, in the opinion of the treating physician, fail to respond or progress on first-line NACT, several therapeutic options can be considered, including second-line chemotherapy, hormonal therapy (if appropriate), RT, or immediate surgery (if technically feasible). Treatment should be individualized through discussion at a multidisciplinary case conference, considering tumour characteristics, patient factors and preferences, and risk of adverse effects.
- It is recommended that prospective randomized clinical trials be designed for patients with LABC who fail to respond to NACT so that more definitive treatment recommendations can be developed.

KEY WORDS

Locally advanced breast cancer, LABC, locoregional disease, radiotherapy, SLNB, mastectomy, neoadjuvant chemotherapy, pathologic complete response

1. INTRODUCTION

The guideline presented here addresses several questions related to locally advanced breast cancer (LABC) as defined in the Methods section. In early breast cancer, breast-conserving surgery (BCS) with adjuvant radiotherapy (RT) has been found, in patients meeting BCS selection criteria, to be equivalent to mastectomy for long-term outcomes; and BCS is preferred by many patients for cosmetic and psychological reasons. The applicability of BCS to LABC and the use and extent of RT after mastectomy is still a matter of debate.

Historically, outcomes in LABC have been poor. Although neoadjuvant ("preoperative," "induction") therapy was first introduced in an attempt to improve tumour resectability and the overall survival (OS) rate with early adjuvant treatment, improved OS was not realized[1–5]. However, other clinically important outcomes were observed, including disease downstaging and the feasibility of breast conservation in selected cases, which are foundational to the continued use of neoadjuvant treatment. Furthermore, neoadjuvant chemotherapy (NACT)—here meaning any neoadjuvant systemic treatment (patients might, in some cases, receive neoadjuvant endocrine therapy or chemotherapy, or both)—can allow for an *in vivo* assessment of chemosensitivity, potentially permitting a regimen change that would not otherwise be made with traditional postoperative adjuvant treatment. Finally, NACT provides a platform for important biomarker and correlative studies to enhance understanding of the disease.

Although BCS becomes technically feasible in some patients with LABC who have a good response to NACT, there is uncertainty about whether mastectomy or BCS is most appropriate. Conversely, the optimal treatment for LABC that does not respond to initial NACT is unclear. Sentinel lymph node biopsy (SLNB) is used in early breast cancer as an alternative to full axillary lymph node dissection (ALND). The role of SLNB compared with ALND in patients with LABC receiving NACT has not been established.

Neoadjuvant chemotherapy has expanded beyond classically unresectable LABC and is now being used more frequently for some smaller tumours, especially certain clinical subtypes: for example, triple-negative and HER2-positive disease. Although the present document does not evaluate the effectiveness of NACT, expanded use of NACT means that clinical trials often cover a heterogeneous patient population (see the Target Population subsection).

2. METHODS

2.1 Guideline Development

The evidence-based guideline series developed by Cancer Care Ontario's (CCO's) Program in Evidence-Based Care (PEBC) use the methods of the practice guidelines development cycle[6,7]. The core methodology used to develop the evidentiary base for the present project was the systematic review. The resulting evidence underpins the recommendations developed by the working group and the Breast Cancer Disease Site Group (DSG). The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario. The full three-part evidence series can be found on the Cancer Care Ontario (CCO) Web site[8].

2.2 Question

1. In female patients with LABC and good response to NACT, including endocrine therapy, what is the role of BCS compared with mastectomy?
2. In female patients with LABC,
   a. is RT indicated for those who have undergone mastectomy?
   b. does locoregional RT, compared with breast or chest wall RT alone, result in a higher survival rate and lower recurrence rates?
   c. is RT indicated for those achieving a pathologic complete response (PCR) to NACT?
3. In female patients with LABC who receive NACT, is the most appropriate axillary staging procedure SLNB or ALND? Is SLNB indicated before NACT rather than at the time of surgery?
4. How should female patients with LABC that does not respond to initial NACT be treated?

2.3 Target Population

This guideline is pertinent to female patients with LABC. For purposes of the guideline, LABC includes stages IIB and IIIABC and inflammatory breast cancer, as defined in the American Joint Committee on Cancer staging manual[9].

Most studies located during the literature review included heterogeneous populations spanning stages IIB–IIIC and sometimes included inflammatory breast cancer. Few studies dealt only with stage III or specific subgroups such as patients with T3N0 cancer. Because most of the major studies did not report results separately for patients with stage IIB and III cancers, the evidence did not support recommendations based on a narrower definition of LABC or its staging subdivisions. Some clinicians do not consider stage IIB to be locally advanced, but there is an increasing trend to treat less bulky disease (stage IIB) in a manner similar to that used for LABC, including NACT. The recommendations presented here might therefore also be applicable to that group.

2.4 Literature Search

The full search strategy and inclusion criteria are presented in the systematic review[8]; only a brief summary is provided here. The literature in the MEDLINE and EMBASE databases (1996 to December 11, 2013) and the Cochrane Library was searched for relevant studies. Searches of the Web sites of Canadian and international health organizations were also conducted to identify existing clinical practice guidelines, systematic reviews, and health technology assessments relevant to the guideline questions. All studies identified through the literature search were assessed against the selection criteria by a health research methodologist from the working group (GGF), with Cindy Walker–Dilks screening results from preliminary searches. Studies of uncertain eligibility were discussed with the other authors.

2.4.1 Inclusion Criteria

The literature search was designed to retrieve systematic reviews, meta-analyses, randomized control trials (RCTS), cohort studies, and clinical practice guidelines concerning locoregional therapy for LABC. Studies had to include at least 50 patients (except for question 4), have a prospective design, and provide a statistical comparison of the interventions of interest. Systematic reviews and meta-analyses had to include a description of the review methods (literature search, study selection, data extraction).

Randomized controlled trials were included if they addressed stages IIB and IIIABC disease (including inflammatory breast cancer), as were RCTS that addressed stage II (unspecified) and stage IIA disease, provided that stage I plus stage IIA disease constituted fewer than half the cases or that subgroup results for either or both of stages IIB and III were available. Studies in which the title and abstract indicated only "early breast cancer" with no mention of stage or other indication that patients meeting our definition of LABC might form all or part of the population were excluded. An exception was made for RCTS located based on another publication about LABC (review, guideline, or RCT): in such cases, the Methods and Results of the original RCT publication were reviewed to determine whether the study group actually met our definition of LABC despite a title and abstract indicating otherwise. Studies in which the cancer was described as metastatic were excluded unless metastasis only to regional lymph nodes was mentioned. Randomized controlled studies were the preferred publications. Cohort studies were considered in the initial screening, but were included only if the comparison groups were equivalent—for example, they had a similar tumour stage distribution. Cohort studies were excluded if the patients were assigned to treatment based on patient and disease factors instead of randomly, such that the prognoses in the groups (before treatment) were not equivalent.

For question 2(b) about the extent of RT (whole breast or chest wall, or locoregional), studies were excluded if they focused on partial compared with whole-breast irradiation (for example, accelerated partial breast irradiation, brachytherapy, intensity-modulated radiation therapy) or on intraoperative techniques (for example, targeted intraoperative radiotherapy or intraoperative radiotherapy with electrons), or if they compared RT techniques (dose-density, boost, hypofractionation) or focused on simulation or treatment planning.

2.5 Development of Recommendations

The working group drafted recommendations based on the systematic review. Where evidence from RCTS was limited, recommendations were based on the authors' professional experience, together with a consideration of current practice and recommendations in other guidelines. Such limitations are clearly indicated in the key evidence and qualifying statements that follow each recommendation.

2.6 Internal and External Review Process

Before submission of the draft report for external review, the systematic review and practice guideline were reviewed by the members of the Breast Cancer DSG and the PEBC Report Approval Panel (RAP). The latter group consists of the PEBC director and two other members with expertise in clinical and methodology issues. The DSG and RAP members reviewed the draft systematic review and practice guideline and provided feedback, which was incorporated into the guideline. The revised draft document was then distributed for external review. External review included both targeted peer review (intended to obtain direct feedback from a small number of content experts) and 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[8].

3. RESULTS

After removal of duplicate citations, the searches in MEDLINE and EMBASE resulted in 42,138 publications. After application of the inclusion and exclusion criteria, 143 publications of trials, 18 clinical practice guidelines, and 27 systematic reviews or meta-analyses remained. Most studies included a mix of cancer stages. The full systematic review[8] provides details of the methodologic characteristics and clinical outcomes of the included trials.

No studies meeting the inclusion criteria were located for question 1 (BCS vs. mastectomy after good response to NACT). Several RCTs dealt with question 2(a) (RT after mastectomy), with some studies including patients receiving anthracycline-based chemotherapy, but not taxanes. For question 2(b) (extent of RT), one prospective nonrandomized study[10] met the inclusion criteria. Three RCTs were relevant (two published only as abstracts), but they included both early cancer and LABC and therefore did not meet the threshold of 50% or more of the patients having stage IIB–III cancer. A large number of studies compared the technical feasibility of SLNB and ALND, but they did not compare long-term survival outcomes. Data for question 4 were also very limited.

4. DOCUMENT REVIEW PROCESS

4.1 Internal Review

During the internal review by DSG members (other than those of the working group), 16 approved the document, 1 had strong concerns about the inclusion of stage IIB in the guideline and did not approve, and 1 abstained because the document was outside his area of expertise. Most of the comments received were related to the definition of LABC. Although 1 reviewer preferred that stage IIB be removed from the definition of LABC, the working group decided that it was neither feasible nor desirable to redo the evidence summary, because most studies reported a heterogeneous patient group, and few dealt specifically with stage III cancers. As suggested by 1 reviewer, we incorporated a footnote describing the rationale and limitations of the LABC definition into the text describing the target population, because those aspects are essential to the document and address some of the other comments.

There was concern that, in recommendation 1, modified radical mastectomy was said to be the standard of care for LABC (that is, for all patients with LABC) and that such treatment did not really apply to patients with stage IIB breast cancer. Although the working group did not feel it appropriate to list all situations in which BCS might be considered, recommendation 1 was modified to clarify that mastectomy does not apply to everyone and that the judgment of the surgeon—and patient preference—is required. A qualifying statement was also revised to clarify that evidence for BCS in LABC is weak overall, but that exceptions exist.

As a result of 2 comments, we included a qualifying statement for recommendation 1 indicating that the type of surgery offered (for example, skin-sparing mastectomy with immediate reconstruction) continues to evolve, but that such advancements are beyond the scope of the guideline.

A comment about question 4 suggested that some patient groups (for example, estrogen receptor–positive, lobular histology) do not respond as well to chemotherapy. The working group believes that recommendation 4(b) (consider second-line chemotherapy, hormonal therapy if appropriate, RT, or immediate surgery) is sufficient. A separate guideline on lobular cancer could be useful, but addressing that variant in the current guideline is not feasible.

The RAP members had several suggestions that were addressed in the revised document. The key evidence and qualifying statements were edited to be less narrative and more succinct; the reader should review the evidence summary[8] (literature review) for more details. The description of the study selection criteria was reworded to be clearer to the reader. The Recommendations and Key Evidence and Literature Search sections were both revised to ensure that studies for question 2(b) are clearly understood to have been conducted in a broad group of patients with stages I–III cancer and not specifically LABC. Those studies do not meet the inclusion criteria of approximately 50% or more LABC cases in either the full study or a reported subgroup analysis; however, two studies were reported only as abstracts and might include subgroup data relevant to LABC when fully reported. Adverse effects had been included in the recommendations during the development process; additional details for some questions were added to the Discussion section of the systematic review.

4.2 External Review

Responses were received from 7 targeted peer reviewers (2 surgical oncologists, 3 radiation oncologists, 2 medical oncologists) considered to be clinical experts on the topic of the guideline. The documents and a brief questionnaire were also distributed to professions in our database with an interest in breast cancer. During the latter professional consultation, 28 responses were received: 10 from medical oncologists, 4 from pathologists, 6 from radiation oncologists, 5 from surgeons, and 3 from surgical oncologists. Most reviewers considered the guideline to be of high quality and said that they would make use of it in their practice. Most comments were related to choice of wording or unclear phrasing, and revisions were made accordingly. Some reviewers wanted further or more specific recommendations, but available RCT data would not allow for that. Other queries related to items outside the scope of the questions and the literature review.

Detailed comments and responses from the authors are reported in the full evidence document[8].

5. RECOMMENDATIONS AND KEY EVIDENCE

5.1 Preamble

Communication between oncologists, surgeons, radiologists, and pathologists is essential. A multidisciplinary case conference is the recommended forum for discussion of cases.

The experience of the authors is that use of neoadjuvant treatment is frequently not indicated when specimens are submitted for pathology examination. This type of clinical information can be vitally important for directing the pathology examination and determining the extent of response to treatment.

It is recommended that surgical clips marking the original (pretreatment) tumour location be inserted before administration of NACT. Neoadjuvant therapy can result in a change in the extent or distribution of tumour, including complete disappearance (a clinical complete response or pCR). The consensus reached at the 2011 meeting of the Canadian Consortium for LABC[11] was that clips should be inserted at the time of diagnosis to mark tumour location, and that clip insertion should be considered the standard of care. Use of clips allows for more accurate identification of the original tumour site (especially if a complete response is achieved), resection of all (previously) cancerous tissue with adequate margins, pathology interpretation of the most appropriate area of resected specimens, and greater accuracy of molecular analyses.

5.2 Recommendation 1

For most patients with LABC, mastectomy should be considered the standard of care. For some patients with noninflammatory LABC, BCS can be considered on a case-by-case basis when the surgeon deems that the disease can be fully resected and the patient expresses a strong preference for breast preservation. [See questions 2(b) and 3 for issues concerning axillary management and staging.]

5.2.1 Key Evidence

The literature review[8] found no RCTs that directly compared BCS with mastectomy in patients with LABC.

Evidence in early breast cancer is that BCS plus RT is equivalent to mastectomy alone[12,13]. Breast cancer stage is a continuum rather than a sharp cut-off between early and locally advanced (see the Target Population subsection). The guideline[13] from CCO's PEBC included all of stages I and II, although the Early Breast Cancer Trialists' Collaborative Group (EBCTCG)[14] defined "early" as "breast cancer in which all clinically apparent disease can be removed surgically." At least some cancers defined as LABC in the current guideline (for example, stage IIB) are therefore covered by the recommendations in those other guidelines.

Guidelines from the American College of Radiology[15], the U.S. National Comprehensive Cancer Network (NCCN)[16], and the Consensus Conference on Neoadjuvant Chemotherapy in Carcinoma of the Breast[17] indicate that BCS is appropriate for some patients with LABC after NACT. That group can include small N2 or N3 tumours with nodal response or large tumours (T3N0 or T3N1) with good response. The NCCN recommends that tumours initially staged IIIABC (except T3N1) with good response be treated with mastectomy or be considered for lumpectomy (plus ALND and RT). We endorse the criteria for BCS outlined in the guidelines from the American College of Radiology[15] and the Consensus Conference[17] and by the International Expert Panel on Inflammatory Breast Cancer[18].

5.2.2 Qualifying Statements

Patients should be informed that, for LABC as a whole, the data are insufficient to recommend BCS as a rule; however, some exceptions can be considered on a case-by-case basis.

The extent of surgery, including BCS, should be determined after full discussion between the patient and the treating oncologist, taking into consideration the patient's values and the fact that direct evidence about the relative benefit of BCS compared with mastectomy in this particular situation is lacking. Treatment of the axilla is discussed in recommendations 2 and 3.

When considering the choice between mastectomy and BCS (for patients meeting selection criteria), benefits and harms must be weighed. Breast-conserving surgery is considered to have generally better cosmetic effects, and for some female patients, it might have less impact on body image, self-esteem, and sexuality than complete breast removal by mastectomy. With BCS, additional reconstructive surgery is usually not needed, and the operation can be less complex. In some cases of BCS, positive margins might mandate re-excision. In cases of recurrence after BCS, further surgical procedures might be needed, and some patients might wish to eliminate that possibility by undergoing mastectomy as initial treatment.

Wide excision of the remaining tumour (in the region of the original pre-neoadjuvant treatment tumour bed) plus RT is recommended for patients with LABC who strongly desire BCS. The volume of tissue to excise will be less if there is a response to NACT. Surgical clips marking the original (pre-treatment) tumour location should be inserted before administration of NACT (see the Preamble).

Breast-conserving surgery is not advised in inflammatory breast cancer because the extent of tumour involvement cannot be reliably ascertained.

The types of surgical procedures offered (for example, skin-sparing mastectomy with immediate

reconstruction) are continuing to evolve, but evaluation of those procedures is beyond the scope of the present guideline.

5.3 Recommendation 2(a)

Radiotherapy after mastectomy is recommended for patients with LABC.

5.3.1 Key Evidence

The EBCTCG meta-analyses[19,20] (see Table 1 in the systematic review[8]) found that postmastectomy RT significantly reduced the 5-year and 10-year recurrence risk in patients with positive nodes (including the subgroups with 1–3 positive nodes and with ≥4 positive nodes) or patients who received systemic therapy [primarily cyclophosphamide–methotrexate–5-fluorouracil or tamoxifen, or both (>85% of patients with positive nodes received systemic therapy)]. The reduction in recurrence risk applied to patients who had undergone mastectomy plus ALND, mastectomy plus axillary sampling, and mastectomy only.

In the EBCTCG meta-analyses, postmastectomy RT significantly improved 20-year breast cancer mortality (including all subgroups). Postmastectomy RT also significantly improved 20-year overall mortality for node-positive patients receiving ALND (overall or with ≥4 positive nodes) or axillary sampling.

The benefit of RT in reducing the rates of breast cancer recurrence and mortality appears to be offset by adverse effects in older trials (primarily cardiovascular and lung adverse effects), especially in female patients at low risk of recurrence. The ratios of the breast cancer mortality rate to other mortality rates were strongly affected by nodal status, age, and decade of follow-up. The absolute benefit still favoured RT overall, but not necessarily in subgroups at particularly low risk of recurrence. More recent reviews found that the effectiveness of RT is increased and cardiopulmonary adverse effects are greatly reduced with modern RT planning and technique; the non-cancer mortality rate data in the EBCTCG meta-analyses might therefore not be relevant to current practice.

5.3.2 Qualifying Statements

The use of three-dimensional treatment planning is important to minimize the dose to lung and heart so that improvements in breast-cancer-specific survival rates are not offset by non–breast cancer mortality rates. Treatments should conform to accepted standards with respect to tissue coverage and dose. Techniques such as gated RT or active breath-hold are used in some centres to reduce cardiotoxicity, but were not evaluated in this guideline series.

Radiotherapy after BCS was not part of the review, but guidelines for early breast cancer recommend RT after BCS[12,13], and that combination is the current standard of care. In the absence of RCTs to the contrary, it is logical that RT also be used after BCS for LABC. Radiotherapy after BCS for LABC is the current standard of care.

The EBCTCG meta-analysis found that RT improves rates of recurrence and survival in the subgroup of patients receiving systemic treatment. Several of the studies used older regimens such as cyclophosphamide–methotrexate–5-fluorouracil. Figure 1 in the systematic review[8] indicates that RT significantly improves the local recurrence rate in patients receiving anthracycline-based chemotherapy; however, no effect on the survival rate is observed. Whelan *et al.*[21] also found that RT reduces mortality in patients with node-positive breast cancer who receive systemic treatment. No studies using taxane-based chemotherapy were included in the systematic review. Newer chemotherapies and targeted therapies might reduce the absolute benefit of RT for some patients, although in the absence of RCTs, RT is still recommended.

Patients, especially those at lower risk of recurrence, should be informed that improvements in the rates of recurrence and disease-specific survival have not necessarily translated into OS advantages, possibly because of RT-induced adverse effects in older studies; however, most LABC patients who receive NACT would not be considered at low risk. For patients with LABC, the risk is lower in those with T3N0 disease (N0 confirmed by SLNB before chemotherapy) than in those who are node-positive. Radiotherapy reduced the recurrence rates in all groups reported, but the absolute benefit in patients with very low risk of recurrence because of disease characteristics and systemic therapy could be small, and some practitioners might consider the incremental benefit of RT, although statistically significant, to be clinically unimportant.

Lymphedema is more likely when surgical procedures include ALND and when RT includes the nodal areas. Reduced shoulder mobility, reduced strength, arm weakness, and paresthesia or hypesthesia have also been reported. The German Breast Cancer Study Group trial[22] [also known as the Bundesministerium für Forschung und Technologie (BMFT) 03 study] found that 25% of patients receiving RT experienced acute skin reactions and that 28% experienced long-term skin alterations (1–2 years after RT). In the MA.20 trial, radiation pneumonitis was reported in 1.3% of patients receiving RT and in 0.2% of patients not receiving RT[23]. Some older RT regimens were associated with a significant increase in contralateral breast cancer and in non-cancer mortality rates, primarily related to heart disease and lung cancer[19,24]. Careful treatment planning is likely to reduce (but not to eliminate) risks other than those of lymphedema and skin effects.

The benefit of postmastectomy RT in patients with node-negative LABC (T3–4N0) is less clear, because those patients have not been reported separately from patients with smaller (T2N0) cancers. Additionally, in patients clinically staged T3N0, the

rate of pathologic node positivity exceeds 50%; such patients can be considered T3Nx unless deemed N0 by SLNB before NACT or by ALND. The EBCTCG 5th cycle analysis[20] found that patients with node-negative cancer (primarily early cancer) treated with mastectomy plus ALND and RT showed no difference in recurrence risk (3.0% vs. 1.6%, $p > 0.1$) attributable to RT, but experienced a significantly higher overall mortality rate (47.6% vs. 41.6%, $p = 0.03$). Control (no RT) patients with node-negative cancer experienced higher recurrence rates in studies using mastectomy plus axillary sampling than in studies using ALND (17.8% vs. 1.6%); in patients treated with axillary sampling, RT was associated with a significantly lower recurrence risk (3.7% vs. 17.8%) and no difference in 20-year mortality (46.1% vs. 49.9%; relative risk: 1.0; $p > 0.01$). Data for patients with T3N0 cancer remain limited; such patients should be discussed individually with regard to risks and benefits.

5.4 Recommendation 2(b)

It is recommended that patients with LABC receive locoregional radiation encompassing the breast or chest wall and local node-bearing areas after BCS or mastectomy.

5.4.1 Key Evidence

The recommendation for breast or chest wall RT is based on several RCTs as summarized in the EBCTCG meta-analyses[14,19,25–28] and discussed for question 2(a).

A prospective nonrandomized study[10] in high-risk patients with stages II–III breast cancer found improved disease-free survival rates at a median of 77 months' follow-up [73% receiving vs. 52% not receiving internal mammary (IM) node RT, $p = 0.02$], with OS being 78% and 64% in those groups ($p = 0.08$). Subgroups at higher risk of recurrence might experience greater benefit, as has been reported for patients with positive nodes.

A meta-analysis examining the role of RT to regional nodes included three trials (two abstracts and one full publication) in patients with early breast cancer or LABC[29] and concluded that regional RT to IM and medial supraclavicular nodes improves disease-free survival, OS, and distant metastasis-free survival in stages I–III breast cancer. This particular analysis did not meet our inclusion criteria because only approximately 36% of the patients had LABC; the results therefore have to be confirmed when the trials are fully published with subgroup data.

The recommendation to include local node-bearing areas is consistent with current practice and other clinical practice guidelines. The NCCN guideline[16] recommends that if IM lymph nodes are clinically or pathologically positive, RT should be administered to the IM nodes; otherwise, treatment to the IM nodes should be strongly considered in patients with node-positive and T3N0 cancer. The NCCN also states that RT to the infraclavicular region and supraclavicular area is recommended for patients with 4 or more positive nodes; should strongly be considered if 1–3 nodes are positive; and should be considered for patients with T3N0 cancer (especially if axillary evaluation is inadequate or extensive lymphovascular invasion is present).

The American College of Radiology[30] recommends postmastectomy RT for T1–2N2+ and T3–4N+ disease, usually including the ipsilateral supraclavicular fossa for patients with positive nodes. There is more variation for the IM nodes, but IM RT is considered for patients at risk of IM involvement—for example, those with medial or centrally located tumours and positive axillary lymph nodes. Postmastectomy RT treatment of T1–2N1 and T3N0 tumours is controversial and should be individualized.

5.4.2 Qualifying Statements

Locoregional treatment (compared with breast or chest wall alone) increases the risk for cardiovascular and pulmonary adverse effects, and the additional fields are more technically complex to administer. The use of 3-dimensional treatment planning is important to minimize the dose to lung and heart so that improvements in breast cancer–specific survival are not offset by non–breast cancer mortality.

The risk of long-term adverse effects from locoregional RT should be weighed against the potential benefits in patients with lower-risk disease, particularly those with left-sided tumours. Ideally, such patients should be discussed in a multidisciplinary setting.

In light of incomplete data, any recommendations about the role of regional RT to specific nodal groups (for example, IM chain, medial supraclavicular, apical axilla, full axilla) in LABC are significantly limited. Although some studies attempted to isolate the role of RT to the IM nodes[31,32], others included additional RT to the medial supraclavicular nodes[33–35] or to all locoregional nodes[23,36].

The absolute additional benefit of regional nodal RT is small but significant for the patient groups studied in RCTs overall (early cancers and LABC combined).

The incidence and severity of lymphedema are higher with locoregional RT. Especially in patients with lower-risk disease, the risk of long-term adverse effects from locoregional RT should be weighed against the potential benefit of reduced recurrence rates and increased survival rates.

For patients with T3N0 cancer [verified to be node-negative (N0) before and after NACT], data remain limited; such patients should be discussed individually with respect to risks and benefits. In patients who are clinically T3N0, the rate of pathologic node positivity exceeds 50%; those patients can be considered T3Nx unless deemed N0 by SLNB before NACT or by ALND. In the latter case, they might be similar to T2N0 patients, and less RT to the chest wall can be considered.

5.5 Recommendation 2(c)

It is recommended that postoperative RT remain the standard of care for patients with LABC who experience a pCR to neoadjuvant therapy.

5.5.1 Qualifying Statements

The literature review found no prospective RCTs that compared treatment with and without RT in female patients achieving a pCR to NACT. The consensus of the authors is that postoperative RT should therefore remain the standard of care.

When examining the evidence, it is important for the clinician to be aware of the various definitions for pCR that have been used in clinical studies: no microscopic evidence of viable tumour cells, only residual necrotic or nonviable tumour cells, or only residual intraductal tumour cells in the resected specimen. The MD Anderson Cancer Center additionally requires the disappearance of axillary lymph node metastasis for a pCR.

Randomized trials such as those planned by the Athena Breast Cancer Network[37,38] and the National Surgical Adjuvant Breast and Bowel Project B51/Radiation Therapy Oncology Group 1304 trial could potentially provide data to re-evaluate the recommendation for specific subgroups in the future.

5.6 Recommendation 3(a)

It is recommended that axillary dissection remain the standard of care for axillary staging in LABC, with the judicious use of SLNB in patients who are advised of the limitations of current data.

5.6.1 Key Evidence

The median sentinel lymph node identification (SLN ID) rate for the trials was 88% overall, 93% in patients with cN0 cancer, and 85% in patients with clinically positive nodes. The SLN ID rate depends on the experience of the surgeon and the techniques used (see Section 2 of the systematic review for details[8]).

The American College of Surgeons Oncology Group Z1071 trial[39,40] conducted in patients with positive nodes (>85% LABC) is one of the largest and most recent studies. It found a 93% SLN ID rate for cN1 cancer and 89% for cN2 cancer. It also found that detection with radiolabeled colloid was much better than detection with blue dye alone (94% colloid plus dye, 91% colloid, 79% dye).

For the studies discussed in Section 2 of the systematic review, median false-negative rates were 10% overall, 7% for the cN0 group, and 13% for the clinically node-positive group. The SN FNAC study[41,42] found that the false-negative rate declined with the number of sentinel nodes removed (false-negative rate: 19% for 1 sentinel node, 7% for 2 or more sentinel nodes), a result consistent with the SENTINA trial findings. Using radiolabelled tracer plus blue dye and removing at least 2–3 SLNs, the best teams achieved false-negative rates of 5%–7%. Those false-negative rates are not dissimilar to the rates of 5%–10% for early breast cancer surgery[43–45].

Although studies indicate that SLNB is technically feasible in both early breast cancer and LABC, a small percentage of patients will be understaged by SLNB used alone. That risk has to be weighed against the increased adverse effects of ALND.

Our recommendation is based on the valuing, by the authors, of potentially increased survival rates with use of ALND over increased postoperative complications. Given the results of the Z0011 and EBCTCG studies for early or operable cancers, some patients might decide that, for less advanced LABC (for example, stages IIB–IIIA), the adverse effects of ALND are greater than the benefits.

5.6.2 Qualifying Statements

Although the SLNB technique in patients (mostly with LABC) receiving NACT is comparable to that in early breast cancer, the clinical implications of a false-negative SLNB in these patients is not known (see the discussion in Section 2 of the systematic review[8]).

The benefit of ALND is that more nodes are removed and examined, resulting in more accurate staging for some patients. Provided that locoregional RT is to be administered in all patients as recommended in questions 2(a) and 2(b), staging might have no effect on treatment. However, some patients might value the additional prognostic information. If a patient is not going to receive locoregional RT, then ALND is recommended. Trials in patients with LABC are ongoing.

There could be a secondary treatment benefit of ALND, in that involved nodes are removed and will therefore not metastasize further.

More than 80% of female patients undergoing ALND experience at least 1 postoperative complication in the arm, and psychological distress is common[46]. In the Z0011 trial[47,48], more wound infections, axillary seromas, paresthesias, and subjective reports of lymphedema resulted when ALND was added to SLNB than when SLNB alone was used.

The NCCN guideline[16] (not specifically on NACT) indicates that "in the absence of definitive data demonstrating superior survival [with axillary lymph node staging], the performance of ALND may be considered optional in patients who have particularly favourable tumours, patients for whom the selection of adjuvant systemic therapy is unlikely to be affected, for the elderly, or those with serious comorbid conditions." It recommends that cN0 plus SLN-negative (including T3N0) cancers need no further ALND. However, the authors of the current guideline note that most patients with LABC are pathologically node-positive before NACT, even those considered clinically negative; a high portion might therefore still be pathologically node-positive after NACT.

None of the studies included inflammatory breast cancer; findings therefore cannot be extrapolated to that cohort of patients.

5.7 Recommendation 3(b)

Although SLNB before or after NACT is technically feasible, the data are insufficient to make any recommendation regarding the optimal timing of SLNB with respect to NACT. Limited data suggest higher SLN ID rates and lower false-negative rates when SLNB is conducted before NACT. However, those findings must be balanced against the requirement for two operations if SLNB is not performed at the time of resection of the main tumour.

5.7.1 Key Evidence

Only three of the studies[49–51] in Table 6 of the systematic review[8] examine the timing of SLNB (before or after NACT), and one additional study[52] (abstract only) performed SLNB before NACT. The remaining studies performed SLNB and ALND after completion of NACT. Before NACT, the SLN ID rate was 98%–99%; after NACT, it was a median of 93% in patients with clinically node-negative cancer and 88% overall. These studies also suggest that false-negative rates are lower when SLNB is conducted before NACT.

The SENTINA study[49] did not conduct ALND if the SLNB before NACT was negative, and so false-negative rates could not be determined for that subgroup of patients. Arm B of the SENTINA trial included patients initially cN0 with a positive SLN ($pN1_{SN}$) before NACT and conducted a second SLNB plus ALND after NACT. The SLN ID rate was 76% in the second SLNB, and the false-negative rate based on the second SLNB was 61%, compared with a SLN ID rate of 99% in patients with cN0 cancer when a SLNB was performed before NACT. Those findings suggest that SLNB should not be performed both before and after NACT.

5.7.2 Qualifying Statements

It is often considered that adjuvant treatment should be based on tumour stage as determined before any treatment, although the extent of surgery depends on the size or extent of the tumour immediately before the surgical procedure (that is, after any neoadjuvant treatment). Some studies suggest that NACT often eliminates cancer from the SLN, but not all the other nodes. For those reasons, there is theoretical justification for performing SLNB before NACT. The very limited available data would support that approach, but the data are, at this time, considered insufficient to make a strong recommendation because of the required trade-off in risk and in the inconvenience of having to perform two separate operations (one for SLNB and one to remove the main tumour) compared with the normal procedure of removing the tumour and performing SLNB (or ALND) in a single operation.

5.8 Recommendations 4(a) and 4(b)

5.8.1 Recommendation 4(a)

It is recommended that patients receiving neoadjuvant anthracycline–taxane-based chemotherapy (or other sequential regimens) whose tumours do not respond to the initial agent or agents, or who experience disease progression, be expedited to the next agent or agents of the regimen.

5.8.2 Recommendation 4(b)

For patients who, in the opinion of the treating physician, fail to respond or who progress on first-line NACT, several therapeutic options can be considered, including second-line chemotherapy, hormonal therapy (if appropriate), RT, or immediate surgery (if technically feasible). Treatment should be individualized through discussion at a multidisciplinary case conference, considering tumour characteristics, patient factors and preferences, and risk of adverse effects.

5.8.3 Key Evidence [Recommendations 4(a) and 4(b)]

Anthracycline–taxane is a standard therapy, with the taxane administered either concurrently or consecutively. The National Surgical Adjuvant Breast and Bowel Project B-27 trial[53–55] found that, compared with neoadjuvant doxorubicin–cyclophosphamide alone, doxorubicin–cyclophosphamide followed by docetaxel resulted in significantly improved clinical and pathologic responses and lower rates of local recurrence. Because most patients did not have LABC and patients were not randomized based on response, that trial is not included in the evidence review[8].

The GeparTrio study[56] and a trial by Qi *et al.*[57] evaluated an early switch to second-line chemotherapy after nonresponse to 2 cycles of first-line chemotherapy; their findings were conflicting. GeparTrio demonstrated no improved response to treatment, but better tolerability and disease-free survival; the Qi *et al.* trial demonstrated some improved response, but worse adverse effects and treatment delays. The evidence for a switch in chemotherapy mid-treatment is therefore insufficient.

Our recommendations are based on current practice and are consistent with the guidelines from the NCCN[16], Health Canada[58], and the Consensus Conference on Neoadjuvant Chemotherapy in Carcinoma of the Breast[17].

5.8.4 Qualifying Statements [Recommendation 4(b)]

There is a body of literature that encompasses patients with LABC and metastatic disease (mostly single-arm case series, small pilot studies, or retrospective studies) that supports a variety of regimens using second-line single-agent and multi-agent NACT or RT, or both, to improve response (including PCR) and thus operability or survival. Although the data are limited and not within the rigorous inclusion criteria of our literature review,

Table 8 of the systematic review[8] lists some of those studies as examples of regimens that have been tried in this clinical scenario. The resulting data have not been systematically reviewed and are not of sufficient quality to make a recommendation for a preferred regimen. Oncologists are advised to individualize the choice of therapy based on the patient and the risk of adverse effects.

6. FUTURE RESEARCH

Prospective RCTs designed for patients with LABC who fail to respond to NACT are needed so that more definitive treatment recommendations can be developed.

7. REVIEW AND UPDATE

Practice guidelines and literature reviews developed by the PEBC are regularly reviewed and updated. For the full evidence-based series 1-19 and subsequent updates, please visit the CCO Web site at: https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-ebs/.

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9. CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests, disclosed in accordance with the PEBC Conflict of Interest Policy:

- Of the working group, one author (MB) received a database grant from Roche Pharmaceuticals, is principal investigator of a trial of neoadjuvant chemotherapy and RT, and has published an opinion on surgical considerations in LABC patients receiving neoadjuvant chemotherapy; one author (ISD) indicated that the guideline could potentially increase the number of referrals for postmastectomy RT.
- Of the expert panel, 14 members declared no conflicts of interest, and 5 declared potential conflicts. Two declared grants or other research support from pharmaceutical companies. One of the two also declared involvement as principal investigator for clinical trials on a related topic. A third member declared a travel grant from Roche to attend a conference. Two other members declared managerial responsibility for a department that received funding from Roche for meetings. Of those five members, three have published editorials or opinions on topics addressed in this guideline.
- The RAP members declared no conflicts.
- Four targeted peer reviewers declared no conflicts. Of the other reviewers, one has received consulting fees from Roche and research grants or support from RNA Diagnostics, was principal investigator of related trials, and has co-authored a meeting report on neoadjuvant care in LABC; one has received research grants or support from Hoffman–La Roche, was chair of the LABC Canadian National Consensus during 2012–2014, and has published commentary or opinions on LABC treatment and knowledge translation; and one has received a grant from Hoffman–La Roche for a LABC clinic and has published an opinion on surgical considerations in LABC patients receiving neoadjuvant chemotherapy.

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Correspondence to: Muriel Brackstone, c/o Program in Evidence-Based Care, McMaster University, Juravinski Hospital, G Wing, 2nd Floor, 1280 Main Street West, Hamilton, Ontario L8S 4L8.
E-mail: ccopgi@mcmaster.ca

* Surgical Oncology, London Regional Cancer Program, London Health Sciences Centre; and Departments of Surgery and Oncology, Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON.
† Program in Evidence-Based Care, Cancer Care Ontario; and Department of Oncology, McMaster University, Hamilton, ON.
‡ Juravinski Cancer Centre, Hamilton Health Sciences; and Department of Oncology, Division of Radiation Oncology, McMaster University, Hamilton, ON.
§ Department of Oncology, Queen's University, Kingston, ON.
‖ Cancer Centre of Southeastern Ontario, Kingston General Hospital; and Department of Pathology and Molecular Medicine, Queen's University, Kingston, ON.
The Ottawa Hospital Cancer Centre; and Department of Medicine, Division of Medical Oncology, University of Ottawa, Ottawa, ON.
** A. Eisen, S. Gandhi, C. Holloway, and M. Trudeau, Sunnybrook Health Sciences, Toronto, ON; P. Bedard, Princess Margaret Hospital, Toronto, ON; D. McCready, Princess Margaret Hospital, Toronto, ON; J. Semple, Women's College Hospital, Toronto, ON; R. George, St. Michael's Hospital, Toronto, ON; B. Meyers, Credit Valley Hospital, Mississauga, ON; B. Dhesy–Thind and L. Elavathil, Hamilton Health Sciences, Hamilton, ON; F. Perera and T. Vandenberg, London Health Sciences Centre, London, ON; R. Gupta and C. Hamm, Windsor Regional Cancer Program, Windsor Regional Hospital, Windsor, ON; O. Freedman, Durham Regional Cancer Centre, Lakeridge Health, Oshawa, ON; M. Mates, Cancer Centre of Southeastern Ontario, Kingston General Hospital, Kingston, ON; M. Clemons and S. Dent, The Ottawa Hospital Cancer Centre, Ottawa, ON.