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Evidence-Based Series 1-19 REQUIRES UPDATING

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

Locoregional Therapy of Locally Advanced Breast Cancer (LABC)

Muriel Brackstone, Glenn G. Fletcher, Ian S. Dayes, Yolanda Madarnas, Sandip K. SenGupta, Shailendra Verma, and Members of the Breast Cancer Disease Site Group[1]

Report Date: September 29, 2014

An assessment conducted in December 2023 indicated that Evidence-based Series (EBS) 1-19 REQUIRES UPDATING. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Evidence-Based Series 1-19 is comprised of three sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/336

Section 1:	**Guideline Recommendations**
Section 2:	**Evidentiary Base**
Section 3:	**Development Methods, Recommendations Development, and External Review Process**

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[1] see Appendix A for a full list of members

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Evidence-Based Series #1-19

Evidence-Based Series #1-19: Section 1

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

Locoregional Therapy of Locally Advanced Breast Cancer (LABC): Guideline Recommendations

Muriel Brackstone, Glenn G Fletcher, Ian Dayes, Yolanda Madarnas, Sandip SenGupta, Shailendra Verma, and Members of the Breast Cancer Disease Site Group[2]

Report Date: September 29, 2014

QUESTIONS

1. In female patients with locally advanced breast cancer with good response to neoadjuvant therapy, what is the role of breast-conserving surgery (BCS) compared with mastectomy?

2a. In female patients with locally advanced breast cancer who have had a mastectomy is radiotherapy indicated?

2b. In female patients with locally advanced breast cancer does locoregional irradiation result in higher survival and lower recurrence rates compared with breast/chest wall irradiation alone?

2c. In female patients with locally advanced breast cancer and pathologically complete response to neoadjuvant therapy is radiotherapy indicated?

3. In female patients with locally advanced breast cancer who receive neoadjuvant chemotherapy is sentinel lymph node biopsy (SLNB) or axillary dissection the most appropriate axillary staging procedure? Is SLNB indicated before neoadjuvant chemotherapy rather than at the time of surgery?

4. How should female patients with locally advanced breast cancer who do not respond to initial neoadjuvant therapy be treated?

TARGET POPULATION

[2] see Appendix A for a full list of members

This guideline is pertinent to female patients with locally advanced breast cancer (LABC). For purposes of this guideline, LABC includes Stages IIB and IIIABC and inflammatory cancer, as defined in *the AJCC Cancer Staging Manual, 6th edition* (1). Most studies in the evidentiary base (see Section 2) included heterogeneous populations spanning Stages IIB – IIIC and sometimes included inflammatory breast cancer. Very few studies dealt only with Stage III or specific subgroups such as patients with T3N0 cancer. As most of the major studies did not report results separately for patients with Stage IIB and Stage III cancers, the evidence did not support recommendations based on a narrower definition of LABC or subdivided by stage. Although some people do not consider Stage IIB to be locally advanced, there is an increasing trend to treat less bulky disease (Stage IIB) in a similar manner, including neoadjuvant therapy; therefore, the recommendations may also be applicable to this group.

INTENDED USERS

The intended users are surgeons and medical and radiation oncologists specializing in breast cancer.

BACKGROUND

This guideline addresses several questions related LABC as defined previously. In early breast cancer, breast-conserving surgery (BCS) with adjuvant radiotherapy (RT) has been found equivalent to mastectomy (in patients meeting BCS selection criteria) for long-term outcomes and it 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, LABC has had poor outcomes. Although neoadjuvant (preoperative, induction) therapy was first introduced in an attempt to improve tumour resectability and overall survival (OS) rate with early adjuvant treatment, improved OS was not realized (2-6). However, other clinically important outcomes were observed, including disease downstaging and feasibility of breast conservation in select cases, which form the basis for continued use of this approach. Furthermore, neoadjuvant chemotherapy (NACT)[3] may also allow an in vivo assessment of chemosensitivity, potentially allowing 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 our understanding of this disease.

Although BCS becomes technically feasible in some patients with LABC with good response to NACT, there is uncertainty as to whether mastectomy or BCS is most appropriate. Conversely, optimal treatment when LABC 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.

NACT has expanded beyond classically unresectable LABC and it is being used more frequently for some smaller tumours, especially certain clinical subtypes (e.g., triple

[3] In this document we use NACT to indicate any neoadjuvant systemic treatment. In some cases, patients may receive neoadjuvant endocrine therapy and/or chemotherapy.

negative, HER2+ [human epidermal growth factor receptor 2 positive]). Although this document does not evaluate effectiveness of NACT, its expanded use means that clinical trials often cover a heterogeneous patient population (see Target Population).

RECOMMENDATIONS

Preamble

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

Any prior use of neoadjuvant therapy should be indicated when specimens are submitted for pathologic examination. Clinical details often affect the pathologic examination and interpretation, whereas details of pathology reports will determine appropriate treatment. Prior therapy (including neoadjuvant therapy) can change the nature of the specimen and what should be reported. The experience of the authors is that use of neoadjuvant treatment is frequently not indicated when submitting specimens.

It is recommended that surgical clips marking the original (pretreatment) tumour location be inserted before administration of neoadjuvant therapy. Neoadjuvant therapy may result in a change in the extent or distribution of tumour, including complete disappearance (clinically or pathologically complete response). The consensus reached at the Canadian Consortium for Locally Advanced Breast Cancer (COLAB) in 2011 (7) was that clips should be inserted at the time of diagnosis to mark tumour location and that this should be considered the standard of care. Use of clips allows for more accurate identification of the original tumour site (especially if there is complete response), resection of all (previously) cancerous tissue with adequate margins, pathologic interpretation of the most appropriate area of specimens, and greater accuracy of molecular analyses.

Question 1. In female patients with locally advanced breast cancer (LABC) with good response to neoadjuvant therapy, what is the role of breast-conserving surgery (BCS) compared with mastectomy?

Recommendation 1

For most patients with LABC, mastectomy should be considered to be the standard of care. [See Question 2b and 3 for issues on axillary management and staging.]

BCS may be considered for some patients with non-inflammatory LABC on a case-by-case basis when the surgeon deems the disease can be fully resected and there is strong patient preference for breast preservation.

Key Evidence ***(go to Results in Section 2)***

- No randomized controlled trials (RCTs) that directly compared BCS with mastectomy in patients with LABC were found in the literature review (see Section 2).
- Evidence in early breast cancer is that BCS plus radiation is equivalent to mastectomy alone (8,9). There is a continuum in breast cancer stage, as opposed to a sharp cut-off between early and locally advanced (see Target Population). The Cancer Care Ontario/Program in Evidence-Based Care (CCO/PEBC) guideline (9) included all of Stage I and II, although the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) defined

early as "breast cancer in which all clinically apparent disease can be removed surgically" (10). Therefore, at least some cancers defined as LABC in the current guideline (e.g., Stage IIB) are covered in the recommendations of these other guidelines.

- Guidelines by the American College of Radiology (ACR) (11), National Comprehensive Cancer Network (NCCN) (12), and the Consensus Conference on Neoadjuvant Chemotherapy in Carcinoma of the Breast (13) indicate BCS is appropriate for some patients with LABC after NACT. This may include small N2/N3 tumours with nodal response, or large (T3N0 or T3N1) tumours with good response. NCCN recommends patients initially Stage IIIABC (except T3N1) with good response be treated with mastectomy or consider lumpectomy (plus ALND plus RT). We endorse the criteria for BCS as outlined in the ACR (11) and Consensus Conference guidelines (13) and The International Expert Panel on Inflammatory Breast Cancer (14).

Qualifying Statements

- Patients should be informed that for LABC as a whole the data are insufficient to recommend BCS as a rule; however, there may be some exceptions that 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 lack of direct evidence regarding the relative benefit of BCS vs mastectomy in this particular situation. Treatment of the axilla is discussed in Recommendations 2 and 3.
- When considering between mastectomy and BCS (for those meeting selection criteria), benefits and harms must be weighed. BCS is considered to have generally better cosmetic effects, and for some female patients may have less impact on body image, self-esteem and sexuality than complete breast removal by mastectomy. With BCS there is usually no need for additional reconstructive surgery and the operation may be less complex. In some cases of BCS, there may be positive margins requiring re-excision. In cases of recurrence after BCS, further surgical procedure may be needed, and some patients may wish to reduce this possibility by having 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 decreased if there is response to neoadjuvant therapy. Surgical clips marking the original (pretreatment) tumour location should be inserted before administration of neoadjuvant therapy (see Preamble).
- BCS is not advised in inflammatory breast cancer because the extent of tumour involvement cannot be reliably ascertained.
- There is continuing evolution in the type of surgical procedures offered (e.g., skin-sparing mastectomy with immediate reconstruction), but these are beyond the scope of this guideline.

Question 2a. In female patients with locally advanced breast cancer who have had a mastectomy is radiotherapy indicated?

Recommendation 2a

Radiotherapy following mastectomy is recommended for patients with LABC.

Key Evidence ***(go to Results in Section 2)***

- The EBCTCG meta-analyses (15,16) (see Section 2 Table 1) found postmastectomy radiotherapy (PMRT) significantly reduced 5-year and 10-year recurrence risk in patients with positive nodes (including subgroups with 1-3 positive nodes or with ≥4 positive nodes) or who received systemic therapy (primarily cyclophosphamide + methotrexate + fluorouracil [CMF] and/or tamoxifen; >85% of patients with positive nodes received systemic therapy). This recurrence risk reduction applied to patients who had mastectomy plus ALND, mastectomy plus axillary sampling, or mastectomy only.
- In the EBCTCG meta-analyses PMRT significantly improved 20-year breast cancer mortality (including all subgroups). PMRT also significantly improved 20-year overall mortality for node positive patients with ALND (overall or with ≥4 positive nodes) or with axillary sampling.
- The benefit of RT in reducing breast cancer recurrence and mortality rates appears to be offset by adverse effects in older trials (primarily cardiovascular and lung adverse effects) especially in female patients with lower risk of recurrence. The ratio of breast cancer mortality rate to other mortality rates was strongly affected by nodal status, age, and decade of follow-up. The absolute benefit still favoured RT overall, but not necessarily in subgroups with 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; therefore, the non-cancer mortality rate data in the EBCTCG meta-analyses may not be relevant to current practice.

Qualifying Statements

- The use of three-dimensional (3D) treatment planning is important to minimize the dose to the lung and heart to ensure improvements in breast-cancer-specific survival rates are not offset by non-breast cancer mortality rates. Treatments provided 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, although these were not evaluated in this guideline series.
- Radiotherapy after BCS was not part of this review, however guidelines for early breast cancer recommend radiation following BCS (8,9) and this is the current standard of care. In the absence of RCTs to the contrary, it is logical that radiation be used following BCS for LABC as well. Radiotherapy following BCS for LABC is the current standard of care.
- The EBCTCG meta-analyses found RT improved recurrence and survival rates in the subgroup of patients with systemic treatment. Several of the studies used older regimens such as CMF. Whelan et al (17) also found RT reduced mortality in patients with node-positive breast cancer who received systemic treatment. Figure 1 of Section 2 indicates RT significantly improved the local recurrence rate in patients receiving anthracycline-based chemotherapy but there was no effect on survival rate. No studies were included in the systematic review (Section 2) using taxane-based chemotherapy. Newer chemotherapies and targeted therapies may reduce the absolute benefit of RT for some patients, although in the absence of RCTs, RT is still recommended.
- Patients should be informed that improvements in recurrence and disease-specific survival rates have not necessarily translated into advantages in OS, possibly related to radiation-induced adverse effects in older studies. This applies especially in patients at lower risk of recurrence; however, most LABC patients who receive NACT would not be considered at low risk. Of patients with LABC, those with T3N0 confirmed by SLNB as N0 prior to chemotherapy are of lower risk than N+ patients. RT reduced the recurrence rates in all groups reported, but the absolute benefit in patients with very low risk of recurrence due

to disease characteristics and systemic therapy may be small, and some may consider the incremental benefit of RT, although statistically significant, to be clinically unimportant.

- Lymphedema is more likely when surgical procedures include ALND or/and when RT includes the nodal areas (see Section 2). Decreased shoulder mobility, decreased strength, arm weakness, and paresthesia/hypesthesia have also been reported. The German Breast-Cancer Study Group trial (also referred to as the Bundesministerium für Forschung und Technologie [BMFT] 03 study) (18) found that 25% of RT patients had acute skin reactions, and 28% had long-term skin alterations (1-2 years after RT). Radiation pneumonitis in the MA.20 trial was reported in 1.3% of patients receiving RT and 0.2% without. In some older RT regimens there was a significant increase in contralateral breast cancer and non-cancer mortality rates, primarily from heart disease and lung cancer (15,19). Careful treatment planning is likely to reduce (but not eliminate) risks other than lymphedema and skin effects.
- The benefit of PMRT in patients with node-negative LABC (T3-4N0) is less clear because they have not been reported separately from smaller (T2N0) cancers. Additionally, in patients clinically T3N0 the rate of pathological node positivity exceeds 50% and these patients may be considered T3Nx unless deemed N0 by SLNB before NACT or by ALND. The EBCTCG fifth cycle analysis (16) found that patients with node-negative cancer (primarily early cancer) treated with mastectomy + ALND + RT had no difference in recurrence risk (3.0% RT vs 1.6%, p>0.1)due to RT but significantly higher overall mortality rate (47.6% vs 41.6%, p=0.03). Control patients (no RT) with node negative cancer in studies using mastectomy + axillary sampling had higher recurrence than in studies with ALND (17.8% vs 1.6%); RT in patients treated with axillary sampling resulted in significantly lower recurrence risk (3.7% vs 17.8%) and no difference in 20-year mortality (46.1% vs 49.9%, RR=1.0, p>0.1). Patients with T3N0 cancer remain a group with limited data and should be discussed individually with regards to risks and benefits.

Question 2b. In female patients with locally advanced breast cancer does locoregional irradiation result in higher survival and lower recurrence rates compared with breast/chest wall irradiation alone?

Recommendation 2b

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

Key Evidence *(go to Results in Section 2)*

- The recommendation for breast/chest wall irradiation is based on several RCTs as summarized in the EBCTCG meta-analyses (10,15,20-23) and is discussed in Question 2a.
- A prospective nonrandomized study (24) in high-risk patients with Stage II-III breast cancer found improved disease-free survival (DFS) rates at median 77 months follow-up (73% with internal mammary (IM) node RT vs 52% without, p=0.02), whereas OS was 78% vs 64%, p=0.08. Subgroups at higher risk of recurrence may have greater benefit, as has been reported for patients with positive nodes.
- A meta-analysis of the role of RT to regional nodes included three trials (two abstracts and one full publication) in patients with early/LABC (25) and concluded that regional RT to IM and medial supraclavicular (MS) nodes improves DFS, OS, and distant metastasis-free survival (DMFS) in Stage I-III breast cancer. This analysis did not meet our inclusion

criteria because only approximately 36% of patients had LABC; therefore, the results need to be confirmed when the trials are fully published including subgroup data.

- The recommendation to include local node-bearing areas is consistent with current practice and other clinical practice guidelines. The NCCN guideline (12) 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. NCCN also states that RT to the infraclavicular region and supraclavicular area is recommended for patients with ≥4 positive nodes and should be strongly considered if 1-3 nodes are positive, and considered for patients with T3N0 cancer (especially if inadequate axillary evaluation or extensive lymphovascular invasion).
- The ACR (26) recommends PMRT for T1-2N2+ and T3-4N+, usually including ipsilateral supraclavicular fossa for patients with positive nodes. There is more variation for IM nodes, but IM RT is considered for patients at risk of IM involvement such as those with medial or centrally located tumours and positive axillary lymph nodes. PMRT treatment of T1-2N1 and T3NO is controversial and should be individualized.

Qualifying Statements

- Locoregional treatment (compared with breast/chest wall alone) increases the risk for cardiovascular/pulmonary adverse effects. The additional fields are more technically complex to administer. The use of 3D treatment planning is important to minimize the dose to the lung and heart to ensure improvements in breast-cancer-specific survival are not offset by non-breast cancer mortality.
- The risk of long-term adverse effects from locoregional radiation 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 regarding the role of regional radiation to specific nodal groups (e.g., IMC, MS, apical axilla, full axilla) in LABC are significantly limited. Although some studies attempted to isolate the role of irradiation to the IM nodes (27,28), others included additional radiation to the MS nodes (29-31) or all locoregional nodes (32,33).
- The additional benefit of regional nodal RT is small, but significant for the overall patient groups studied in RCTs (early cancers plus LABC combined).
- The incidence and/or severity of lymphedema is higher with locoregional RT. Especially in patients with lower-risk disease, the risk of long-term adverse effects from locoregional radiation should be weighed against the potential benefit of reduced recurrence rates and increased survival rates.
- Patients with T3N0 cancer (verified to be node negative [N0] pre- and post-neoadjuvant therapy) remain a heterogeneous group with limited data and should be discussed individually with regards to risks and benefits. In patients clinically T3N0 the rate of pathological node positivity exceeds 50% and these patients may be considered T3Nx unless deemed N0 by SLNB before NACT or by ALND. In the latter case, they may be similar to T2N0 patients and less RT to the chest wall may be considered.

Question 2c. In female patients with locally advanced breast cancer and pathologically complete response to neoadjuvant therapy is radiotherapy indicated?

Recommendation 2c

It is recommended that postoperative radiotherapy remains the standard of care for patients with LABC who have pathologically complete response to neoadjuvant therapy.

Qualifying Statements *(go to Results in Section 2)*

- No prospective randomized studies were found in the literature review (see Section 2) that compared treatment with vs without RT in female patients with pathologically complete response (pCR) to neoadjuvant therapy. 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. These range from 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 requires the added disappearance of axillary lymph node metastasis for a pCR.
- Randomized trials such as those planned by the Athena Breast Cancer Network (34,35) and the NSABP B51/RTOG 1304 trial may provide data to re-evaluate the recommendation for specific subgroups in the future.

Question 3. In female patients with locally advanced breast cancer who receive neoadjuvant chemotherapy is sentinel lymph node biopsy (SLNB) or axillary dissection the most appropriate axillary staging procedure? Is SLNB indicated before neoadjuvant chemotherapy rather than at the time of surgery?

Recommendation 3-1

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.

Key Evidence *(go to Results in Section 2)*

- The median sentinel lymph node (SLN) identification rates (SLN ID rates) for the trials in Section 2 were 88% overall, 93% in patients with cN0 cancer and 85% in patients with clinically positive nodes. SLN ID rates depend on the experience of surgeons and the techniques used (see Section 2 for details).
- The ACOSOG Z1071 trial (36,37) conducted with 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. This study found detection with radiolabeled colloid much better than blue dye alone (94% colloid + dye, 91% colloid, 79% dye).
- For the studies in Section 2, median false negative (FN) rates were 10% overall, 7% cN0, and 13% clinically node positive. The SN FNAC study (38,39) found the FN rate decreased with the number of sentinel nodes removed (FN rate 19% for 1 SN, 7% for 2+ SN) and is consistent with the SENTINA trial findings. Using radiolabelled tracer plus blue dye and removing at least 2-3 SLNs, the best teams achieved FN rates of 5-7%. The FN rate is not dissimilar to the FN rates of 5-10% for early breast cancer surgery (40-42).

- Although the studies indicate that SLNB is technically feasible in both early and locally advanced breast cancer, a small percentage of patients will be understaged using SLNB alone. This risk needs to be weighed against the increased adverse effects of ALND.
- This recommendation is based on the authors' valuing 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 may decide that for less advanced LABC (e.g, Stages 2b-3a) the adverse effects of ALND are greater than the benefits.

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 FN SLNB is not known in these patients (see Discussion in Section 2).
- The benefit of ALND is that more nodes are removed and examined, giving more accurate staging for some patients. Provided that locoregional RT is to be administered in all patients, as recommended in Questions 2a and 2b, the staging may have no impact on treatment. However, some patients may 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.
- More than 80% of female patients undergoing ALND have at least one postoperative complication in the arm and psychological distress is common (43). In the Z0011 trial (44,45) ALND added to SLNB resulted in more wound infections, axillary seromas, paresthesias, and subjective reports of lymphedema than SLNB alone.
- The NCCN guideline (12) (not specifically on NACT) indicates "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". They recommend that cN0 plus SLN negative (including T3N0) need no further ALND. However, the authors of the current guideline note that most patients with LABC are pathologically node positive before neoadjuvant therapy, even those considered clinically negative; therefore, a high portion may still be pathologically node positive after neoadjuvant therapy.
- None of the studies included inflammatory breast cancer; therefore, these findings cannot be extrapolated to that cohort of patients.

Recommendation 3-2

Although SLNB before or after NACT is technically feasible, there is insufficient data to make any recommendation regarding the optimal timing of SLNB with respect to NACT. Limited data suggests higher SLN ID rates and lower FN rates when SLNB is conducted before NACT; however, this must be balanced against the requirement for two operations if SLNB is not performed at the time of resection of the main tumour.

Key Evidence *(go to Results in Section 2)*

- Only three of the studies in Table 6 of the evidence summary (46-48) compared timing of SLNB (before or after NACT) and one additional study (abstract only) performed SLNB before neoadjuvant therapy (49). The rest of the studies performed SLNB and ALND after completion of NACT. Before NACT the SLN ID rate was 98-99%, whereas after NACT it was

a median of 93% in patients with clinically node-negative cancer and 88% overall. The studies also suggest FN rates are lower when SLNB is conducted before NACT.

- The SENTINA study (46) did not conduct ALND if the SLNB before NACT was negative so FN rates could not be determined for this subgroup. 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. SLN ID rate was 76% in the second SLNB and the FN rate based on the second SLNB was 61% compared with a SLN ID rate of 99% in patients with cN0 cancer when SLNB was performed before NACT. This suggests that SLNB should not be performed both before and after NACT.

Qualifying Statements

- It is often considered that adjuvant treatment should be based on the initial stage as determined before any treatment, although the extent of surgery depends on the size/extent of the tumour immediately before the surgical procedure (i.e., after any neoadjuvant treatment). Some studies suggest NACT often eliminates cancer from the SLN but not all the other nodes. For these reasons, there is theoretical justification for performing SLN biopsy before NACT. The very limited data would support this, but is considered insufficient at this time to make a strong recommendation due to the trade-off required in risk and inconvenience of needing 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 SLN (or ALND) in one operation.

Question 4. How should female patients with locally advanced breast cancer who do not respond to initial neoadjuvant therapy be treated?

Recommendation 4-1

It is recommended that patients receiving neoadjuvant anthracycline-taxane-based therapy (or other sequential regimens) whose tumours do not respond to the initial agent(s) or where there is disease progression be expedited to the next agent(s) of the regimen.

Recommendation 4-2

For patients who, in the opinion of the treating physician, fail to respond or who progress on first-line NACT, there are several therapeutic options to consider including second-line chemotherapy, hormonal therapy (if appropriate), radiotherapy, 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.

Key Evidence (Recommendations 4-1 and 4-2) ***(go to Results in Section 2)***

- Anthracycline-taxane is a standard therapy, with the taxane administered either concurrently or consecutively. The NSABP B-27 trial (50-52) found AC followed by docetaxel gave significantly improved clinical and pathological response and lower rates of local recurrence compared with neoadjuvant AC alone. Because most patients were not LABC and patients were not randomized based on response, the trial is not included in the evidence review of Section 2.
- The GeparTrio study (53) and a trial by Qi et al (54) evaluated early switching to second-line chemotherapy after nonresponse to two cycles of first-line chemotherapy and demonstrated conflicting findings: the GeparTrio demonstrated no improved response to

treatment but better tolerability and DFS; the other trial demonstrated some improved response but worse adverse effects and treatment delays. There is therefore insufficient evidence to switch chemotherapy mid-treatment.

- The recommendations are based on current practice and are consistent with the guidelines by NCCN (12), Health Canada (55), and the Consensus Panel for Neoadjuvant Chemotherapy (13).

Qualifying Statements (Recommendation 4-2)

- There is a body of literature including patients with locally advanced and metastatic disease (mostly single-arm case series, small pilot studies, or retrospective studies) that supports a variety of second-line single agent and multi-agent NACT and/or RT regimens to improve response (including pCR) and, thus, operability or survival. Although the data are limited and not within the rigorous inclusion criteria of the literature review, Table 8 of Section 2 lists some of these studies as examples of regimens in the medical literature that have been tried in this clinical scenario. These data are not systematically reviewed nor of quality sufficient to make a recommendation as to preferred regimens. It is advised that oncologists individualize the choice of therapy based on the patient and risk of adverse effects.

FUTURE RESEARCH

There is a need for prospective randomized clinical trials designed for patients with LABC who fail to respond to NACT so that more definitive treatment recommendations can be developed.

RELATED GUIDELINES

1. Breast Cancer Disease Site Group. Breast irradiation in women with early stage invasive breast cancer following breast-conserving surgery [Internet]. Version 2. Toronto (ON): Cancer Care Ontario; 2002 Mar [reviewed by Dayes I and Tey R, 2010; endorsed 2010 Nov; released 2011 Sep 15; cited 2013 Sep 17]. 28 p. Program in Evidence-Based Care Evidence-Based Series No.: 1-2; Available from: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/841.

2. Breast Cancer Disease Site Group. Surgical management of early-stage invasive breast cancer [Internet]. Version 3. Toronto (ON): Cancer Care Ontario; 2002 Mar [reviewed by Brackstone M and Tey R 2010; endorsed 2010 Nov; released 2011 Sept 15; cited 2013 Sep 17]. 33 p. Program in Evidence-Based Care Evidence-Based Series No.: 1-1. Available from: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/1001.

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as described in the PEBC Document Assessment and Review Protocol.

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