Management of the Axilla in Early-Stage Breast Cancer: OH (CCO) and ASCO Guideline

Brackstone et al.
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Background & Methodology
Introduction

• Axillary staging for breast cancer has been a standard part of initial surgical treatment since 2002 when Fisher et al published the NSABP B06\textsuperscript{1}, but ALND was associated with significant morbidity. Some centers have used axillary ultrasound (US) as an adjunctive imaging modality to assess the axilla at diagnosis. Patients with clinically or sonographically suspicious lymph nodes undergo needle biopsy--core needle biopsy or fine needle aspiration biopsy--with image guidance. For patients with clinically negative axillae, SLNB became the standard of care for axillary staging in Canada in 2009 with the CCO guideline by George et al\textsuperscript{2}.

• Given new, mounting evidence around axillary staging, the Working Group of the Breast Advisory Group of (OH [CCO]) felt that a pragmatic guideline for the management of the axilla would be of great help to clinicians and patients alike. Using high-quality data to answer how best to manage the axilla, minimizing unnecessary treatment but supporting effective or necessary treatment, fits the mandate of OH (CCO) and ASCO, and this provided the impetus to pursue this systematic review and clinical practice guideline.
Guideline Development Methodology

- PEBC (an initiative of OH [CCO]) and ASCO collaborated on the development of this guideline, with PEBC taking the lead.

- The guideline process includes:
  - a systematic literature review
  - an expert panel provides critical review and evidence interpretation to inform guideline recommendations
  - internal and external review by health research methodologists, clinicians, and other stakeholders
  - final guideline approval by participating organizations

- See the *PEBC Handbook*, the *PEBC Methods Handbook*, and the *ASCO Guideline methodology manual* for additional information on the guideline development process.
Guideline Objectives

The guideline addresses five specific objectives:

1. To determine which patients with early-stage breast cancer require axillary staging.
2. To determine whether any further axillary treatment is indicated for women with early-stage breast cancer who did not receive neoadjuvant chemotherapy (NAC) and are sentinel lymph node negative at diagnosis.
3. To determine which axillary strategy is indicated for women with early-stage breast cancer who did not receive NAC and are pathologically sentinel lymph node positive at diagnosis (after a clinically node-negative presentation).
4. To determine what axillary treatment is indicated and what the best timing of axillary treatment for women with early-stage breast cancer treated with NAC.
5. To determine which are the best methods for identifying sentinel nodes.
Target Population and Audience

Target Population

• Patients with early-stage breast cancer (i.e., stages I, IIA, IIB; and prognostic groups T1, T2, N0, N1mi, N1, M0; and primary tumor size ≤5 cm).

Target Audience

• Surgeons, radiation oncologists, medical oncologists, and other clinicians (e.g., pathologists, radiologists, oncology nurses, genetic counselors) involved in the staging, radiation, systemic treatment, and in the management of the axilla in patients with early-stage breast cancer.
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Summary of Recommendations
Summary of Recommendations

Objective 1

• To determine which patients with early-stage breast cancer require axillary staging.

Recommendation 1.

• For patients ≥70 years of age with clinically node-negative (T1N0) early-stage invasive breast cancer that is hormone receptor positive and HER2-negative, SLNB is not required. This is supported by the Choosing Wisely statement released on July 12, 2016, and updated on June 20, 2019 by the Society of Surgical Oncology\(^3\) that stated: “Don’t routinely use sentinel node biopsy in clinically node negative women ≥70 years of age with early stage hormone receptor positive, HER2 negative invasive breast cancer” if they will be treated with hormonal therapy. If omission of SLNB is considered, a consultation with a medical oncologist can be considered before surgery to discuss hormonal therapy.
Summary of Recommendations

Recommendation 1. (cont.)

- For patients <70 years of age without significant competing comorbidities, SLNB should be considered for axillary staging of early-stage breast cancer

Qualifying Statements for Recommendation 1.

- The information acquired from SLNB would be helpful in guiding adjuvant treatment decision making.
- Patients should be evaluated on a case-by-case basis to ensure appropriate patient-centered decision making.
- Patients who are clinically node-negative on physical examination but are found to be sonographically abnormal on imaging with or without confirmatory biopsy can be offered SLNB as first-line axillary staging.
Summary of Recommendations

Objective 2

• To determine whether any further axillary treatment is indicated for women with early-stage breast cancer who did not receive NAC and are sentinel lymph node-negative at diagnosis.

Recommendation 2.

• Clinicians should not recommend ALND for women with early-stage breast cancer who do not have nodal metastases (endorsed from Recommendation 1 of the ASCO 2017 update guideline\(^4,5\)).
Summary of Recommendations

Recommendation 2. (cont.)

• In some selected patients (e.g., patients with medially or centrally located tumors or with high-risk features), and using a patient-centered approach, it is reasonable to offer the option of LRNI to include at least the supraclavicular and ipsilateral internal mammary lymph nodes in addition to the breast and/or chest wall (see the Qualifying Statement). For the majority of patients (i.e., node-negative patients whose tumors are not medial or central in location and who do not have other high-risk features), we cannot recommend LRNI. A risk-benefit discussion should be undertaken on a case-by-case basis for these patients (see the Qualifying Statement).
Summary of Recommendations

Qualifying Statements for Recommendation 2.

Surgical interventions

• SLNB is currently the standard of practice for this population.

• The evidence regarding the omission of ALND upon which this recommendation is based did not include patients who had a history of another cancer, had a multicentric breast cancer, had a prior ipsilateral breast cancer surgery or prior ipsilateral axillary surgery, were <18 or >80 years of age, were pregnant or lactating, were allergic to blue dye or radioisotope, had evidence of metastatic disease, had tumors > 3 cm in diameter, suffered from chronic life-threatening diseases possibly preventing the use of adjuvant therapy, had stage T0 tumors (i.e. ductal carcinoma in situ), had multifocal tumors, and received previous NAC. For these patients, decisions regarding ALND should be made after discussion between patient and clinicians on a case-by-case basis, depending on the invasive component of the lesion, other clinical circumstances, and patient preferences.
Summary of Recommendations

Qualifying Statements for Recommendation 2. (cont.)

Radiotherapy interventions

• Patients with centrally or medially located tumors may modestly benefit (<5% difference) from LRNI compared with whole-breast irradiation (WBI) only (postlumpectomy) or no postoperative radiation (postmastectomy) in terms of DFS, distant DFS, and locoregional relapse, but not in terms of overall survival (OS).

• Postmastectomy patients with node-negative, triple-negative breast cancer who receive chemotherapy may benefit from chest wall radiotherapy compared with no radiotherapy in DFS and OS.

• A radiotherapy dose fractionation schedule of 50 Gy in 25 fractions over five weeks is the current standard used in the relevant clinical trials; however, we recognize that there are other regimens now considered clinically appropriate and/or equivalent to this traditional fractionation.
Summary of Recommendations

Objective 3

• To determine which axillary strategy is indicated for women with early-stage breast cancer who did not receive NAC and are pathologically sentinel lymph node-positive at diagnosis (after a clinically node-negative presentation).

Recommendation 3.

A) No further axillary surgery beyond SLNB compared with ALND.

• Clinicians should not recommend ALND for women with early-stage breast cancer who have one or two sentinel lymph node metastases and will receive breast-conserving surgery with conventionally fractionated whole-breast radiotherapy (endorsed from ASCO 2017 guideline,4,5 Recommendation 2.1).
Summary of Recommendations

Qualifying Statements for Recommendation 3A.

A) No further axillary surgery beyond SLNB compared with ALND

• The evidence upon which this recommendation is based did not include patients who: Were pregnant or breastfeeding, had a history of another malignancy in the previous 5 years, have bilateral breast cancer, have multicentric disease, have three or more positive sentinel lymph nodes, have a concomitant malignancy, previously received systemic therapy for breast cancer, received chemoprevention in the preceding year, have distant metastases or macrometastatic disease, have palpable axillary nodes, were <18 or >75 years old. For these patients, as well as for patients who are treated with mastectomy, decisions regarding completion of ALND should be made after discussion between the patient and clinicians on a case-by-case basis depending on the invasive component of the lesion, other clinical circumstances, and patient preferences, taking into account the limited data specific to mastectomy and considering that these recommendations represent an extrapolation, on the basis of expert opinion, from trials designed for patients undergoing breast conserving surgery.

• The management of the axilla for patients with four or more positive lymph nodes (N2, N3 disease) falls outside the scope of this guideline. Please refer to OH (CCO) PEBC guideline 19-1 guideline: “Loco-regional therapy of locally advanced breast cancer (LABC)”⁶ For exactly three positive lymph nodes, there is not enough evidence to make a recommendation, and therefore, we recommend proceeding with ALND and considering LRNI.
Summary of Recommendations

Recommendation 3. (cont.)

B) Radiotherapy of the axilla (LRNI) compared with no LRNI.

It is reasonable to offer the option of treating the axilla with radiotherapy in addition to breast or chest wall irradiation following surgery, particularly in patients with medial or central tumors, and in patients with high-risk features. Discussion of pros and cons with patients needs to occur, and the decision should be made on a case-by-case basis.

Qualifying Statements for Recommendation 3B.

B) LRNI compared with no LRNI.

Patients with estrogen receptor-negative (ER-) and progesterone receptor-negative (PR-) status may have a more favorable DFS when treated with LRNI in addition to surgery.
Summary of Recommendations

Recommendation 3. (cont.)

C) Radiotherapy to the axilla compared with further surgery (ALND).

We recommend radiotherapy of the axilla in lieu of ALND in patients who are clinically node negative and pathologically sentinel lymph node positive with tumors of up to 5 cm, and unifocal or multifocal disease restricted to one quadrant. In patients who receive breast-conserving surgery, we recommend no ALND if one or two sentinel lymph nodes are positive. LRNI is a reasonable option, especially when there are high-risk features as in (B). ALND and LRNI to the axilla is recommended if ≥ 3 sentinel lymph nodes are positive. In patients who receive mastectomy and have one to two positive nodes, post-mastectomy radiation (PMRT) to the chest wall and the axilla is recommended and ALND can be safely omitted. In patients declining PMRT (i.e., patients with immediate reconstruction), either radiation to the axilla without the chest wall or completion ALND can be considered. In patients who receive mastectomy and have ≥ 3 positive nodes, ALND followed by LRNI can be considered.
Summary of Recommendations

Qualifying Statements for Recommendation 3C.

C) Radiotherapy to the axilla compared with further surgery (ALND).

The ongoing MA39 (NCT00005957) study addresses the incremental benefit of LRNI of the axilla in lower-risk, node-positive patients. At this time, no studies comparing SLNB alone without LRNI have been identified in the mastectomy or lumpectomy setting.
Summary of Recommendations

Recommendation 3. (cont.)

D) Radiotherapy compared with no treatment

In patients with unilateral invasive cancer of small size (i.e., T1a), favorable tumor features (e.g., ER+ undergoing hormonal therapy), clear margins, and one to three positive nodes, treated with chemotherapy or hormonal therapy, clinicians might offer the option of omitting LRNI.

Qualifying Statements for Recommendation 3D.

D) Radiotherapy compared with no treatment.

• Patients ≥ 65 years of age may benefit less from the addition of radiotherapy.
• Receptor-negative patients may benefit more from radiotherapy treatment.
Summary of Recommendations

Objective 4

• To determine what axillary treatment is indicated and what the best timing of axillary treatment for women with early-stage breast cancer is when NAC is used.

Recommendation 4.

A) Initially node-negative patients

• Patients who are initially clinically node negative on physical examination, and those who had clinically suspicious nodes on physical examination but deemed to be pathologically negative at fine needle aspiration/core needle biopsy, and were treated with NAC, should receive SLNB at the time of surgery as their axillary staging procedure.
Summary of Recommendations

Recommendation 4. (cont.)

B) Initially node-positive patients

• For patients who were initially clinically and biopsy-proven node positive, and who remained clinically node positive after NAC, we recommend ALND.

• For patients who were initially clinically and biopsy-proven node positive, and became node negative after NAC, we recommend SLNB to restage the axilla. Restaging can be achieved by placing a biopsy clip into the biopsied positive node at diagnosis and localizing it at surgery along with sentinel node biopsy, or, in institutions where the use of biopsy clips for nodes is not available, by performing sentinel node biopsy with dual tracer and excising at least three sentinel nodes in order to minimize the false negative rate and optimize accuracy of the procedure. At this time, we also recommend LRNI for these patients, regardless of pathologic status of sentinel lymph nodes.
Summary of Recommendations

Recommendation 4. (cont.)

B) Initially node-positive patients (cont.)

• Postmastectomy patients who are node-positive on surgical pathology after NAC can be offered PMRT after a completion ALND

• We recommend LRNI for the postmastectomy node-positive cohort after NAC while awaiting data from ongoing trials (i.e., the MAC19 study).

• We recommend LRNI after ALND for patients clinically and biopsy-proven node-positive at breast-conserving surgery who remain pathologically node-positive after NAC.

• Shared decision-making processes should be put in place while we await mature clinical trial data, to enable patient value-based decision making.
Summary of Recommendations

Qualifying Statements for Recommendation 4B.

B) Initially clinically positive and biopsy-proven node-positive patients

• To date, the clinical standard of care for node-positive patients who fail to respond clinically in the axilla to NAC requires maximal therapy to the axilla, which includes ALND followed by LRNI.

Recommendation 4. (cont.)

C) SLNB Timing: before or after NAC

We recommend against performing lymph node sampling twice, before and after NAC. We recommend to time the SLNB after NAC and not before in clinically node-negative patients who will receive NAC.
Summary of Recommendations

Objective 5

• To determine which are the best methods for identifying sentinel nodes.

Recommendation 5.

A) Single versus dual tracer

For patients having primary surgery, we recommend using a sentinel node tracer (e.g., it is not necessary to add blue dye on a regular basis for SLNB if the radiocolloid signal successfully identifies the sentinel node(s) in the axilla). In cases of non-identification, blue dye can be added. Screening for radiocolloid signal prior to incision is recommended, and blue dye can be added prior to making the incision. In patients who receive NAC, we recommend either placing a biopsy clip into the positive node at diagnosis and localizing it at time of surgery or using dual tracer (radiocolloid plus blue dye).
Summary of Recommendations

Qualifying Statement for Recommendation 5A.

A) Single versus dual tracer

• Dual tracer should be used in settings where it is expected to be a learning curve for the operators performing the procedure (e.g. low volume centers, surgeons in training/post training).
Summary of Recommendations

Recommendation 5. (cont.)

B) US-guided staging versus standard guided (dye/isotope) staging.

In clinically node-negative patients with early-stage breast cancer where the sentinel lymph node is likely to be negative (i.e., T1 and T2), preoperative axillary US staging is not recommended.

In patients with clinically palpable (i.e., clinically positive) lymph nodes it is recommended to conduct US-guided core biopsy of the axillary node to prove pathological positivity. If patients are pathologically negative on image-guided lymph node biopsy, see Recommendation 2. If they are pathologically positive on image-guided lymph node biopsy, see Recommendation 3.
Summary of Recommendations

Recommendation 5. (cont.)

C) US-guided staging versus surgical staging.

We recommend that diagnostic staging by US only (i.e., not confirmed by a biopsy) should not be used instead of standard SLNB staging.

Qualifying Statements for Recommendation 5C.

C) US-guided staging versus surgical staging

If a clip is used to identify a biopsied lymph node at diagnosis, the node containing the clip needs to be localized to make sure it is excised. If dual tracer is used, three or more sentinel nodes have to be identified. If three or more sentinel nodes are not identified in a patient who has had NAC according to standard sentinel lymph node techniques, an axillary dissection is recommended.
Discussion
Abbreviations. ALND, axillary lymph node dissection; BCT, breast conserving therapy; ER, estrogen receptor; NAC, neoadjuvant chemotherapy; RT, radiation therapy; SLNB, sentinel lymph node biopsy; yrs, years

Notes.

a Refers to all patients with no palpable axillary nodes on physical examination, including those who may have had an ultrasound that was equivocal, abnormal, or even biopsy-proven positive.

b Decision making should be made on a case-by-case basis, and include a patient-centered approach; that is, consider and discuss pros and cons of various options in light of patient’s specific circumstances, values, and preferences.

c Do not recommend SLNB before chemotherapy except in special circumstances after multidisciplinary discussion.

d Evidence supports the use of dual localizing tracer (blue dye and radio-isotope) and harvesting ≥3 nodes or else do ALND to minimize false negative rate; any clipped positive nodes should be localized for surgery.

e In rare circumstances (e.g., a small T1aN1) it is possible to avoid radiation (see Justification of Recommendation 3D).
Limitations of the Research and Future Research

• Among the limitations of this work is the total lack of evidence for male patients with early-stage breast cancer, which makes our recommendations generalizable only to female patients. However, we support the generalization of these guidelines to male patients with early-stage breast cancer.

• Other potential limitations of this work include the lack of focus on new or emerging technologies for axillary staging, a body of evidence that is still partly immature with several studies still ongoing; and the almost complete lack of evidence on quality of life in all its dimensions (including patient-centered outcomes such as morbidity from interventions, such as lymphedema rates in patients treated by axillary radiation rather than ALND.

• Hopefully, these gaps will be filled with future updates to this document.
Additional Resources

• For more information, please refer to the OH (CCO) version of this guideline, available at: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/breast?f%5B0%5D=field_type_of_cancer%3A746.

• A supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/breast-cancer-guidelines

• Patient information is available at www.cancer.net
# Guideline Panel Members

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Abbreviations

- ALND, axillary lymph node dissection
- ASCO, American Society of Clinical Oncology
- BCT, breast conserving therapy
- CCO, Cancer Care Ontario
- DCIS, ductal carcinoma *in situ*
- DFS, disease free survival
- ER, estrogen receptor
- HER2, human epidermal growth factor receptor 2
- LABC, locally advanced breast cancer
- LRNI, loco-regional nodal irradiation
- NAC, neoadjuvant chemotherapy
- NSABP, National Surgical Adjuvant Breast and Bowel Project
- OH, Ontario Health
- OS, overall survival
- PEBC, Program in Evidence-Based Care
- PMRT, postmastectomy radiotherapy
- PR, progesterone receptor
- RT, radiation therapy
- SLNB, sentinel lymph node biopsy
- SSO, Society of Surgical Oncology
- US, ultrasound
- WBI, whole breast irradiation
References

2. George R, Quan ML, McCready DR, et al: Sentinel lymph node biopsy in early-stage breast cancer. Toronto (ON), Cancer Care Ontario; Program in Evidence-based Care, 2009
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