

# Management of the Axilla in Early-Stage Breast Cancer: Ontario Health (Cancer Care Ontario) and ASCO Guideline

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**PURPOSE** To provide recommendations on the best strategies for the management and on the best timing and treatment (surgical and radiotherapeutic) of the axilla for patients with early-stage breast cancer.

**METHODS** Ontario Health (Cancer Care Ontario) and ASCO convened a Working Group and Expert Panel to develop evidence-based recommendations informed by a systematic review of the literature.

**RESULTS** This guideline endorsed two recommendations of the ASCO 2017 guideline for the use of sentinel lymph node biopsy in patients with early-stage breast cancer and expanded on that guideline with recommendations for radiotherapy interventions, timing of staging after neoadjuvant chemotherapy (NAC), and mapping modalities. Overall, the ASCO 2017 guideline, seven high-quality systematic reviews, 54 unique studies, and 65 corollary trials formed the evidentiary basis of this guideline.

**RECOMMENDATIONS** Recommendations are issued for each of the objectives of this guideline: (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 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 is when NAC is used, and (5) to determine which are the best methods for identifying sentinel nodes.

Additional information is available at [www.asco.org/breast-cancer-guidelines](http://www.asco.org/breast-cancer-guidelines).

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## ASSOCIATED CONTENT

Appendix

### Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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## INTRODUCTION

Axillary staging for breast cancer has been a standard part of initial surgical treatment since 2002 when Fisher et al published the National Surgical Adjuvant Breast and Bowel Project (NSABP) B06,<sup>1</sup> but axillary lymph node dissection (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, sentinel lymph node biopsy (SLNB) became the standard of care for axillary staging in Canada in 2009 with the Cancer Care Ontario (CCO) guideline by George et al.<sup>2</sup>

Over the ensuing decade, the standard of care for patients with a pathologically positive sentinel lymph node was a completion ALND, with the resultant morbidity risks mentioned above. More recently, data emerged to suggest that a completion ALND for some patients with positive nodes from SLNB did not confer an improved survival or regional recurrence benefit.<sup>3,4</sup> Therefore, in a selective cohort of non–high-risk tumors, positive sentinel nodes were no longer being followed by ALND. At the same time, a Canadian trial<sup>5</sup> found that locoregional nodal irradiation (LRNI) after axillary dissection for patients with node-positive or high-risk node-negative disease conferred a disease-free survival (DFS) advantage. There has thus continued to be clinical confusion regarding the benefit of LRNI, whether it can supplant completion ALND and how to synthesize both these trials.<sup>3–5</sup> Given the breast

## THE BOTTOM LINE

### Management of the Axilla in Early-Stage Breast Cancer: Ontario Health (Cancer Care Ontario) and ASCO Guideline

#### Guideline Objectives

To provide recommendations on the best strategies for the management and on the best timing and treatment (surgical and radiotherapeutic) of the axilla in early-stage breast cancer. Specific objectives are presented before each recommendation.

#### Target Population

Patients with early-stage breast cancer (ie, stages I, IIA, and IIB; prognostic groups T1, T2, N0, N1mi, N1, and M0; and primary tumor size  $\leq$  5 cm).

#### Target Audience

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

#### Methods

A joint OH (CCO) and ASCO Expert Panel was convened to develop clinical practice guideline recommendations on the basis of a systematic review of the medical literature.

#### Preamble to Recommendations

The focus of this guideline is the management of the axilla in patients with early-stage breast cancer. This includes interventions such as surgery, radiotherapy, imaging, and systemic treatment. For all recommendations, we recommend a patient-centered approach. Each recommendation corresponds to a specific objective of this guideline. An algorithm for the management of the axilla in patients with early-stage breast cancer is presented in [Figure 1](#).

#### Recommendations

##### Objective 1

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

##### Recommendation 1

- For patients age  $\geq$  70 years with clinically node-negative (T1N0) early-stage invasive breast cancer, that is hormone receptor–positive and human epidermal growth factor receptor 2 (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<sup>8</sup> that stated, “Don’t routinely use sentinel node biopsy in clinically node negative women  $\geq$  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 (Type: informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate).
- For patients age  $<$  70 years without significant competing comorbidities, SLNB should be considered for axillary staging of early-stage breast cancer (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate to high for staging by ALND v no ALND; insufficient for staging by SLNB v no staging; Strength of recommendation: strong).

##### 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.

##### 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<sup>9,10</sup>) (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).
- In some selected patients (eg, 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

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## THE BOTTOM LINE (CONTINUED)

ipsilateral internal mammary lymph nodes in addition to the breast and/or chest wall (see the Qualifying Statement). For the majority of patients (ie, 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) (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate to low; Strength of recommendation: weak).

### 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 age < 18 or > 80 years, 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 (ie, 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.

#### *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 5 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.

### 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,<sup>9,10</sup> Recommendation 2.1) (Type: evidence based; benefits outweigh harms; Evidence quality: high for patients who received breast-conserving surgery; Strength of recommendation: strong for those who had breast-conserving surgery. For patients who had mastectomy and for those excluded from the trials, the strength of the body of the evidence is insufficient and the recommendation is weak).

#### *(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 (Type: evidence based; benefits may outweigh harms; Evidence quality: low; Strength of recommendation: weak).

#### *(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 are recommended if  $\geq 3$  sentinel lymph nodes are positive. In patients who receive mastectomy and have one to two positive nodes, postmastectomy radiation (PMRT) to the axilla is recommended and ALND can be safely omitted. In patients declining PMRT (ie, 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  $\geq 3$  positive nodes, ALND followed by LRNI can be considered (Type: informal consensus; benefits outweigh harms in the short term; Evidence quality: low; Strength of recommendation: weak).

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**THE BOTTOM LINE (CONTINUED)***(D) Radiotherapy compared with no treatment*

In patients with unilateral invasive cancer of small size (ie, T1a), favorable tumor features (eg, estrogen receptor–positive 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 (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: weak).

**Qualifying statement for recommendation 3***(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, and 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 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 and N3 disease) falls outside the scope of this guideline. Please refer to OH (CCO) Program in Evidence-Based Care (PEBC) guideline 19-1 guideline: locoregional therapy of locally advanced breast cancer (LABC).<sup>11</sup> 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.

*(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.

*(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.

*(D) Radiotherapy compared with no treatment*

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

**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 or core needle biopsy, and were treated with NAC should receive SLNB at the time of surgery as their axillary staging procedure (Type: informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong).

*(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 to minimize the false-negative rate (FNR) and optimize accuracy of the procedure. At this time, we also recommend LRNI for these patients, regardless of pathologic status of sentinel lymph nodes.

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## THE BOTTOM LINE (CONTINUED)

- 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 (ie, 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.

(Type: evidence based; benefits outweigh harms; Evidence quality: low; Strength of recommendation: weak.)

### (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 (Type: informal consensus; benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).

### Qualifying statement for recommendation 4

#### (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.

### 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 (eg, 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 before incision is recommended, and blue dye can be added before 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) (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

#### (B) US-guided staging versus standard guided (dye or isotope) staging

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

In patients with clinically palpable (ie, clinically positive) lymph nodes, it is recommended to conduct US-guided core biopsy of the axillary node to prove pathologic 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 (Type: evidence based; benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).

#### (C) US-guided staging versus surgical staging

We recommend that diagnostic staging by US only (ie, not confirmed by a biopsy) should not be used instead of traditional SLNB staging (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

### Qualifying statement for recommendation 5

(A) Dual tracer should be used in settings where it is expected to be a learning curve for the operators performing the procedure (eg, low-volume centers and surgeons in training or post-training).

(C) 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 that 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.

### 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](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](http://www.asco.org/breast-cancer-guidelines). Patient information is available at [www.cancer.net](http://www.cancer.net).

**ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.**



cancer population heterogeneity, there are always patients presenting with variations on the theme (slight extranodal extension, high grade, 2 v 3 positive nodes, etc) and the indications for avoiding completion ALND are ever expanding without clear data. Additionally, ongoing trials (NSABP B51,<sup>6</sup> Alliance/MAC19 [NCT01901094]) are looking to further de-escalate the axillary surgery for patients who are biopsy-proven lymph node–positive at diagnosis and are rendered clinically sentinel node–negative after neoadjuvant chemotherapy (NAC).

Given the new, mounting evidence around axillary staging, the Working Group of the Breast Advisory Group of Ontario Health (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. The systematic review has been registered in PROSPERO<sup>7</sup> with the number CRD42017056859.

## GUIDELINE OBJECTIVES

The general objective of this joint guideline is to provide recommendations on the best strategies for the management and on the best timing and treatment (surgical and radiotherapeutic) of the axilla in early-stage breast cancer. 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 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 is when NAC is used, and (5) To determine which are the best methods for identifying sentinel nodes.

## METHODS

### Guideline Development Methods

This guideline was developed with the PEBC practice guidelines development cycle<sup>12,13</sup> (see the [PEBC Handbook](#) and the [PEBC Methods Handbook](#)) and the ASCO guideline development methods (available at [www.asco.org/guideline-methodology](http://www.asco.org/guideline-methodology)). This includes a systematic review, interpretation of the evidence, drafting of recommendations, and internal and external review by health research methodologists, clinicians, and other stakeholders.

A periodic review and evaluation of the scientific literature, with the addition of newer evidence to the original

document if necessary, guarantees the currency of this document (see the [PEBC Document Assessment and Review Protocol](#)). A list of implementation considerations is provided along with the recommendations for information purposes. This is the most recent information as of the publication date.

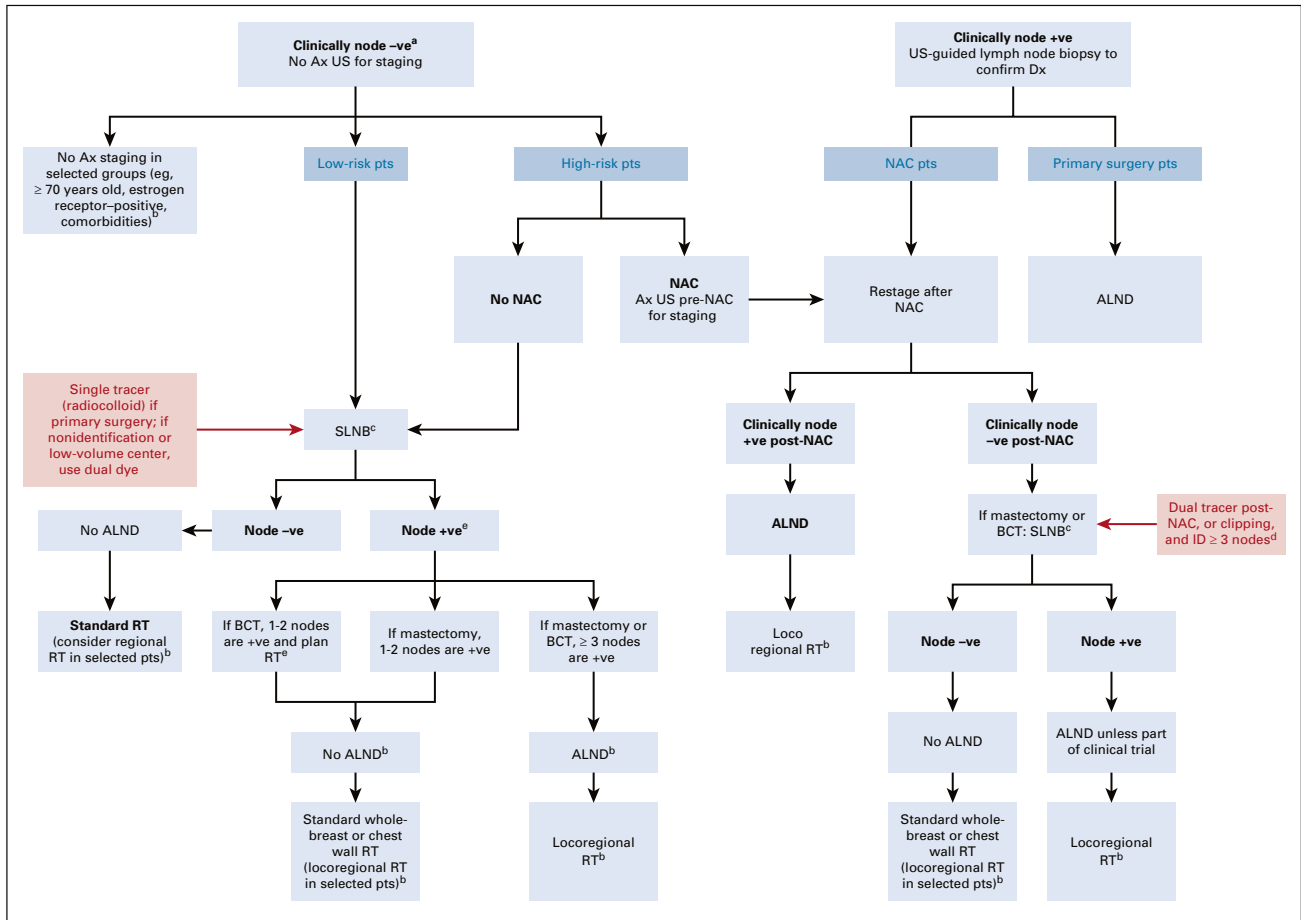
### Guideline Developers

PEBC and ASCO worked together in developing this guideline with PEBC taking the lead, and both organizations were involved from the early stages. The PEBC is an initiative of OH (CCO) supported by the Ontario Ministry of Health, and its mandate is to improve the lives of Ontarians affected by cancer. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health. The PEBC created the project plan, established the scope of the guideline, and formed the Working Group. ASCO provided four members of the Expert Panel, including a patient representative from the ASCO Practice Guideline Implementation Network, and provided some of the external reviewers. The Management of the Axilla in Early Breast Cancer Guideline Developing Group (MAEBCGDG) (Appendix [Table A1](#), online only) was convened at the request of the CCO Breast Cancer Advisory Committee. A small Working Group of the MAEBCGDG led this project by reviewing the evidence base, drafting the recommendations, and responding to comments of internal and external reviewers. Other members of the MAEBCGDG served as the Expert Panel and were responsible for the review and approval of the guideline at the internal review stage. Members of the multidisciplinary MAEBCGDG were radiation oncologists, surgical oncologists, medical oncologists, radiologists, pathologists, genetic counselors, general surgeons, and health research methodologists. The internal review consisted of a review by the Expert Panel and by the PEBC Report Approval Panel.

### Conflict of Interest (COI)

All members of the MAEBCGDG completed a COI disclosure form. Declared conflicts were evaluated against both PEBC<sup>14</sup> and ASCO<sup>15</sup> policies. PEBC Report Approval Panel and ASCO Clinical Practice Guideline Committee members with any potential COIs were not eligible to review or approve the guideline, and those involved in the process had no conflicts. Targeted external reviewers had to complete a COI form; however, for them, COI was not a barrier to participation. For purposes of publication, the authors completed an additional *Journal of Clinical Oncology/ASCO COI* form and declarations are available at <https://ascopubs.org/journal/jco>.

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines (Policy, found at <http://www.asco.org/rwc>). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a



**FIG 1.** Algorithm for the management of the axilla in patients with early-stage (clinical stage T1, T2, N0, and N1 [stage I to stage IIB]) breast cancer. <sup>a</sup>Refers to all patients with no palpable axillary nodes on physical examination, including those who might have had an US that was equivocal, abnormal, or even biopsy-proven positive. <sup>b</sup>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. <sup>c</sup>Do not recommend SLNB prechemotherapy except in special circumstances after multidisciplinary discussion. <sup>d</sup>Evidence supports the use of dual localizing tracer (blue dye and radioisotope) and harvesting ≥ 3 nodes or else perform ALND to minimize FNR; any clipped positive nodes should be localized for surgery. <sup>e</sup>In rare circumstances (eg, a small T1aN1), it is possible to avoid radiation (see Justification of Recommendation 3D). +ve, positive; -ve, negative; ALND, axillary lymph node dissection; Ax, axillary; BCT, breast-conserving therapy; Dx, diagnosis; ER, estrogen receptor; FNR, false-negative rate; HT, hormonal therapy; NAC, neoadjuvant chemotherapy; pts, patients; RT, radiation treatment; SLNB, sentinel lymph node biopsy; US, ultrasound.

result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker’s bureau; research funding; patents, royalties, and other intellectual property; expert testimony; travel, accommodations, and expenses; and other relationships. In accordance with the Policy, the majority of members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

**Search for Existing Guidelines**

A search for existing guidelines was conducted using known guideline-developer websites and practice-guideline databases. Guidelines were considered for endorsement if the Working Group members answered yes to the following questions:

- Do you agree with the recommendations and think that no new evidence would change the recommendations?
- Do you think that the recommendations would be acceptable in Ontario?

The ASCO guideline<sup>9,10</sup> met this requirement for some of its recommendations relative to the use of SLNB and ALND. The overall quality of the guideline was assessed independently by two methodologists (F.G.B. and N.V.) with the AGREE II tool.<sup>16</sup>

**Guideline Disclaimers**

Care has been taken in the preparation of the information contained herein. Nevertheless, any person seeking to consult the report or apply its recommendations is expected to use independent medical judgment in the context of individual clinical circumstances or to seek out the

supervision of a qualified clinician. CCO makes no representations or guarantees of any kind whatsoever regarding the report content or its use or application and disclaims any responsibility for its use or application in any way.

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## LITERATURE REVIEW

### Specific Research Questions

On the basis of the objectives of this guideline, the Expert Panel derived the five research questions outlined below:

1. Which patients with early-stage breast cancer require axillary staging (ie, SLNB, ALND, or US)?
2. For women with early-stage breast cancer who did not receive NAC and are sentinel lymph node–negative at diagnosis:
  - a. Is further axillary treatment (ie, radiation or surgery) indicated?

- b. What sentinel node–negative patient subgroups are most likely to benefit from further axillary treatment with radiation therapy?
3. For women with early-stage breast cancer who did not receive NAC and are pathologically sentinel lymph node–positive at diagnosis:
  - a. Which axillary strategy is indicated?
  - b. What sentinel node–positive patient subgroups are most likely to benefit from further axillary treatment with radiation or with surgery or both?
4. For women who were treated with NAC:
  - a. If the lymph node is negative at diagnosis, what axillary treatment (ie, radiation or surgery) is indicated after chemotherapy?
  - b. If the lymph node is positive at diagnosis, what axillary treatment (ie, radiation or surgery) is indicated after chemotherapy?
  - c. When is the best timing for performing sentinel node excision: before or following NAC?
5. Among patients with early breast cancer appropriate for axillary staging:
  - a. Is there a better identification rate (IR) with single or dual tracer?
  - b. Is there a better IR with US-guided SLNB or traditional SLNB?
  - c. Is there a better IR with US or SLNB?

For all questions, measures of survival and disease control were considered critical outcomes. Quality of life, adverse events, and surgical complication rates were considered important outcomes.

### Literature Search Methods

The Expert Panel searched for systematic reviews published from January 2011 to June 2017 and primary studies to integrate and update the evidence from included systematic reviews from January 2007 to February 2020. Search terms included a combination of terms specific to the axilla, breast cancer, and design in the databases MEDLINE, EMBASE, EPISTEMONIKOS, and the Cochrane Library. Panel members searched their own files and the proceedings (from January 2016 to December 2019) of the ASCO, American Society for Therapeutic Radiology and Oncology, European Society for Medical Oncology, and European Society for Radiotherapy and Oncology conferences and of the San Antonio Breast Cancer Symposium. Additionally, the Expert Panel searched the reference lists of the included systematic reviews, guidelines, and primary studies.

### Study Selection Criteria and Process

Inclusion criteria comprised studies of  $\geq 100$  patients with early-stage breast cancer (ie, stage I, IIA, and IIB; prognostic groups T1, T2, N0, N1mi, N1, and M0; and tumor size  $\leq 5$  cm). The studies had to include surgical and radiotherapy interventions to the axilla or combinations thereof. Outcomes measured included survival, disease



control, quality of life, adverse events, ability to map, procedure completion rate, FNR, and IR. Studies of experimental treatments were excluded. The focus was on randomized controlled trials (RCTs) and comparative observational studies that controlled for confounding.

The methodologist (F.G.B.) reviewed the titles and the abstracts of citations identified by the searches and excluded those that were most obviously irrelevant. The methodologist and one of the clinicians (M.B. and F.E.P.) reviewed each full text of the remaining articles independently. Discrepancies were resolved by discussion. When clinically homogeneous results from two or more trials were available, the methodologist conducted a meta-analysis using the Review Manager software (RevMan 5.3).<sup>17</sup>

## RESULTS

### Literature Search Results

Table 1 presents the evidence that forms the basis for this guideline.

**Objective 1.** The systematic review by Liang et al<sup>18</sup> compared ALND with no dissection and pooled two RCTs with a population of older women with early-stage breast cancer.<sup>21,22</sup> We updated the review by Liang et al<sup>18</sup> with two additional RCTs of pre- and postmenopausal women.<sup>19,20</sup> We identified six ongoing trials of clinically negative women of any age, and of a subgroup of women with 1-2 positive nodes, which explore the option of abandoning staging by SLNB: the SOUND trial,<sup>23</sup> the BOOG 2013-08 trial,<sup>24</sup> the INSEMA trial,<sup>25</sup> the Italian trial,<sup>84</sup> the NCT01821768 trial,<sup>26</sup> and the NCT02167490 trial.

**Objective 2.** For women with early-stage breast cancer without nodal metastases, who did not receive NAC, we endorsed Recommendation 1 of the ASCO guideline<sup>9,10</sup> for surgical interventions. For radiotherapy interventions, we included the Early Breast Cancer Collaborative Group<sup>32</sup> individual patient data meta-analysis and we supplemented this evidence with three primary studies.<sup>33-35</sup> In addition, 10% of participants in the MA.20 trial<sup>5</sup> had node-negative disease with high-risk features.

**Objective 3.** For pathologically sentinel lymph node-positive women with early-stage breast cancer who were not treated with NAC, we considered four comparisons: (A) no further axillary surgery beyond SLNB versus ALND; (B) radiotherapy plus surgery versus no LRNI; (C) radiotherapy versus ALND; and (D) radiotherapy versus no treatment. For comparison (A), we endorsed Recommendation 2.1 from the ASCO guideline.<sup>9,10</sup> For comparison (B), the MA.20 RCT<sup>5</sup> included a small percentage of women with high-risk node-negative disease. For comparison (C), we updated the systematic review by Schmidt-Hansen et al<sup>37</sup> with an individual patient data meta-analysis of 22 trials<sup>32</sup> that collected data from 1964 to 2009. For comparison (D), we identified two trials of women treated with mastectomy

and either chemotherapy (premenopausal women)<sup>52</sup> or hormonal therapy (postmenopausal women).<sup>53</sup>

**Objective 4.** For women treated with NAC, the evidence provided by the ASCO guideline,<sup>9,10</sup> and by three systematic reviews that initially met our inclusion criteria,<sup>67,85,86</sup> was outdated and we did not identify any RCTs. For patients who were initially pathologically node-negative, we did not identify any completed studies. For patients who were pathologically node-positive, we included three observational studies that reported on direct patient outcomes.<sup>54-56</sup> Kim et al<sup>54</sup> reported on surgical interventions (ie, SLNB v ALND), and Rusthoven et al<sup>55</sup> and Krug et al<sup>56</sup> on radiotherapy interventions. We did not locate any completed trial comparing radiotherapy with ALND. We did not conduct a meta-analysis because the included studies were heterogeneous. We are aware of two RCTs that are recruiting patients at this time: The MAC.19 trial (NCT01901094) (<https://sunnybrook.ca/trials/item/?i=172&page=49335>) and the NSABP-B-51 trial (NCT01872975) (<https://sunnybrook.ca/trials/item/?i=240&page=49335>).

**Objective 5.** No existing guidelines provided any relevant recommendations to direct the use of different modalities for axillary staging in women with early-stage breast cancer. Three systematic reviews met our inclusion criteria,<sup>67,74,75</sup> and they provided evidence for diagnostic outcomes related to comparisons (A) *single versus dual tracer*<sup>67</sup> and (B) *US-guided versus traditional SLNB*.<sup>74,75</sup> For comparison (A), we also included a primary study<sup>58</sup> reporting on direct patient outcomes and nine studies of diagnostic outcomes. For comparison (C), *US versus SLNB*, two studies<sup>58,78</sup> reported on direct patient outcomes and 15 studies<sup>58,64-66,68-73,78-82</sup> reported on test accuracy outcomes. We did not combine the results of the studies in meta-analysis because the trials were heterogeneous.

### Study Design and Quality

**Objective 1.** The included studies comprise a noninferiority RCT,<sup>20</sup> a multicenter equivalence RCT,<sup>19</sup> a multicenter RCT,<sup>22</sup> and a single-center RCT.<sup>21</sup> Four of the ongoing trials are noninferiority RCTs,<sup>23,24,26,87</sup> and two<sup>84,88</sup> are multicenter RCTs. The Institute Bergonié trial<sup>19</sup> was at high overall risk of bias; therefore, we did not pool it in meta-analysis. All other trials were at moderate to low risk of bias. None of the studies reported whether outcome assessors were blinded or described the surgeons' expertise.

**Objective 2.** The ASCO update guideline<sup>9,10</sup> was of high quality. The overall risk of bias of the body of evidence it contained for surgical and radiotherapy interventions was moderate and moderate to low, respectively. The included studies were clinically heterogeneous; therefore, we did not pool the results in meta-analysis.

### Objective 3.

**(A) No further surgery beyond SLNB versus ALND** The ASCO guideline<sup>9,10</sup> is of high quality. The overall certainty of the evidence for this comparison was moderate to high. The

**TABLE 1.** Literature Search Results

Comparison		Endorsed Guidelines	Included High-Quality SRs	Included RCTs	Included Observational Comparative Trials	Ongoing Trials
Intervention	Control					
Question 1						
Axillary staging (by surgery or imaging)	No staging	NA	Liang et al <sup>18</sup>	Avril et al, <sup>19</sup> Agresti et al, <sup>20</sup> Martelli et al, <sup>21</sup> and Rudenstam et al <sup>22</sup>	NA	Gentilini et al, <sup>23</sup> van Roozendaal et al, <sup>24</sup> Reimer et al, <sup>25</sup> Tinterri et al, <sup>84</sup> (NCT02167490), and Tucker et al <sup>26</sup>
Question 2						
Further axillary treatment (eg, with radiation therapy)	No further axillary treatment	Surgical interventions		All identified studies <sup>27-31</sup> were also included in the endorsed guideline	NA	NCT02651142
		ASCO 2017 guideline <sup>9,10</sup>	NA			
		Radiotherapy interventions				
		NA	EBCTCG <sup>32</sup> IPD meta-analysis	EORTC 22922/10925 <sup>33</sup> ; MA.20, 2015 <sup>5</sup> ; and Wang et al <sup>34</sup>	Zurrada et al <sup>35</sup> (subgroup of GRISO 053 RCT <sup>36</sup> )	PMRT-NNBC 1602 (NCT02992574) and TAILOR RT trial (NCT03488693)
Question 3						
(A) No further axillary surgery beyond SLNB	ALND	ASCO 2014, 2017 <sup>9,10</sup>	Schmidt-Hansen et al <sup>37</sup>	ATTRM-048-13-2000, 2013 <sup>38</sup> ; IBCSG-23-01 2011, 2013 <sup>39-41</sup> ; and ACOSOG Z0011 <sup>42-44</sup>	NA	SENOMAC (NCT02240472, NCT03083314, and NCT01468883), <sup>45</sup> INSEMA (NCT02466737), and SERC <sup>46</sup> (NCT01717131)
(B) RT + ALND	No RT to the regional lymph nodes	NA	NA	MA.20 trial <sup>5</sup>	NA	POSNO <sup>47,48</sup> (NCT02401685)
(C) RT	ALND	NA	Schmidt-Hansen et al <sup>37</sup>	OTOASOR <sup>49</sup> , AMAROS <sup>4,50,51</sup> ; and EBCTC, 2014 <sup>32</sup>	NA	MA39 (NCT03488693 and NCT00005957) and HypoG01 (NCT03127995)
(D) RT	No treatment	NA	NA	Killander et al <sup>52,53</sup>	NA	Optimal (NCT02335957)
Question 4						
Patients who were node-negative at diagnosis						
Further axillary treatment	No further axillary treatment	NA	NA	NA	NA	NA
Patients who were node-positive at diagnosis						
Surgical interventions		NA	NA	NA	Kim et al <sup>54</sup>	NA
SLNB surgery	ALND, no treatment					

(continued on following page)

**TABLE 1.** Literature Search Results (continued)

Comparison		Endorsed Guidelines	Included High-Quality SRs	Included RCTs	Included Observational Comparative Trials	Ongoing Trials
Intervention	Control					
Radiotherapy interventions		NA	NA	NA	Rusthoven et al <sup>55</sup> and Krug et al <sup>56</sup>	MAC.19 trial (NCT01901094) and RTOG 1304/NSABP B51 (NCT01872975)
RT plus surgery, RT	No treatment, surgery (ALND)					
Timing of SLNB						
SLNB before NAC	SLNB after NAC	NA	NA	NA	Studies of direct patient outcomes: Fernandez-Gonzalez et al, <sup>57</sup> Hunt et al, <sup>58</sup> and Papa et al <sup>59</sup>	NA
					Studies of diagnostic outcomes: Classe et al, <sup>60</sup> Zetterlund et al, <sup>61,62</sup> van der Heiden-van der Loo et al, <sup>63</sup> Kuehn et al, <sup>64</sup> Tausch et al, <sup>65</sup> Papa et al, <sup>59</sup> and Gimbergues et al <sup>66</sup>	
Question 5						
Single tracer	Dual tracer	NA	Geng et al <sup>67</sup> (accuracy outcomes, patients treated with NAC)	Studies of direct patient outcomes NA Studies of diagnostic outcomes O'Reilly et al <sup>68</sup> and Jung et al <sup>69</sup>	Hunt et al <sup>58</sup> Kuehn et al, <sup>64</sup> Boughey et al, <sup>70</sup> Boileau et al, <sup>71</sup> Kang et al, <sup>72</sup> Nathanson et al, <sup>73</sup> Tausch et al, <sup>65</sup> Hunt et al, <sup>58</sup> and Gimbergues et al <sup>66</sup>	NA
US-guided SLNB	Traditional SLNB	NA	Van Wely et al <sup>74</sup> and Houssami et al <sup>75-77</sup>	Studies of direct patient outcomes NA Studies of diagnostic outcomes NA	Verheuvél et al <sup>78</sup> Kramer et al, <sup>79</sup> Kim et al, <sup>80</sup> Cools-Lartigue et al, <sup>81</sup> Stachs et al, <sup>82</sup> and Caudle et al <sup>83</sup>	CK19B (NCT03280134)
US	SLNB	NA	NA	Studies of direct patient outcomes NA Studies of diagnostic outcomes NA	Stachs, 2013 <sup>82</sup> and Kuehn et al <sup>64</sup>	CK19B (NCT03280134)

Abbreviations: ACOSOG, American College of Surgeons Oncology Group; ALND, axillary lymph node dissection; NA, not applicable; NAC, neoadjuvant chemotherapy; NSABP, National Surgical Adjuvant Breast and Bowel Project; PMRT, postmastectomy radiation; RCT, randomized controlled trial; RT, radiation therapy; SLNB, sentinel lymph node biopsy; SRs, systematic reviews; US, ultrasound.

included studies<sup>39,40,42-44</sup> may suffer from selection and recruitment bias. Consequently, the results are applicable only to low-risk patients who meet the inclusion criteria of these studies.

**(B) Radiotherapy of the axilla compared with no LRNI** The MA.20 randomized trial<sup>5</sup> was at overall moderate risk of bias.

**(C) Radiotherapy to the axilla compared with further surgery (ALND)** The systematic review by Schmidt-Hansen et al<sup>37</sup> is of high quality. The OTOASOR trial<sup>49</sup> and the AMAROS trial<sup>4,50,51</sup> that form its evidentiary base were considered at high risk of bias; however, both trials randomly assigned patients before SLNB. Therefore, the populations are representative of patients seen in clinical practice. Given the shortcomings of the included studies, the results are applicable to patients who strictly meet their inclusion criteria and considered on a case-by-case basis. We did not use the evidence from the individual patient data meta-analysis<sup>32</sup> that we found during our update search because radiotherapy treatment has changed since the included patients were treated.

**(D) Radiotherapy compared with no treatment to the axilla** Both the included trials<sup>52,53</sup> were randomized, phase III trials. The follow-up<sup>89</sup> evaluated adverse effects of irradiation after the second decade postintervention. Both included trials were at high overall risk of bias, and the evidence provided was indirect. The certainty of this body of evidence is moderate to low.

#### Objective 4.

**(A) Patients who were initially clinically node-negative** We did not identify any studies for this population.

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

*Surgery trials.* The study by Kim et al<sup>54</sup> was a retrospective institutional cohort study. The overall risk of bias was serious to very serious. The certainty of the evidence for this comparison is low to very low.

*Radiotherapy trials.* The trial by Rusthoven et al<sup>55</sup> was a retrospective analysis of a very large sample from the National Cancer Database. Krug et al<sup>56</sup> conducted a pooled retrospective analysis of three RCTs. Both trials are at moderate risk of bias.

**(C) Timing of SLNB** The body of evidence for direct patient outcomes<sup>57-59</sup> was at moderate to serious risk of bias. The certainty of this body of evidence is moderate to low because of imprecision and indirectness. Among the studies of diagnostic outcomes, the trials by Classe et al,<sup>60</sup> Zetterlund et al,<sup>61</sup> Tausch et al,<sup>65</sup> and Gimbergues et al<sup>66</sup> and the SENTinel NeoAdjuvant (SENTINA) trial<sup>64</sup> were prospective cohort studies, whereas the study by Van der Heiden-van der Loo et al<sup>63</sup> was a retrospective study. All the studies used ALND as a reference standard. The studies that included pathologically positive populations<sup>60,62,64-66</sup> were at a variable risk of bias. Tausch et al<sup>65</sup> reported on the expertise of the operator.

#### Objective 5.

**(A) Single tracer compared with dual tracer** For direct patient outcomes, the study by Hunt et al<sup>58</sup> was at moderate

risk of bias. For diagnostic outcomes, the systematic review by Geng et al<sup>67</sup> was at low risk of bias as assessed using the ROBIS tool,<sup>90</sup> but the evidence it provided was partially indirect. Additionally, we identified 10 primary studies<sup>58,64-66,68-73</sup>; two were RCTs,<sup>68,69</sup> the others were observational studies, and all but one<sup>72</sup> had a prospective design. The risk of bias of these studies was unclear or high. A confounding factor such as the expertise of the surgeons with less-experienced surgeons reaching a lower IR with a single tracer was inconsistently reported by the studies.

**(B) US-guided staging compared with traditional SLNB** For direct patient outcomes, we identified a very large population-based retrospective trial,<sup>78</sup> which was at critical risk of bias. For diagnostic outcomes, we included the systematic reviews by Houssami et al<sup>75</sup> and by van Wely et al<sup>74</sup> and five retrospective trials.<sup>79-83</sup> The systematic review by Houssami et al<sup>75</sup> failed to meet our quality criteria at the first step of the ROBIS tool.<sup>90</sup> The systematic review by van Wely et al<sup>74</sup> was at unclear risk of bias, and the evidence was partially indirect. In node-positive patients treated with NAC, Caudle et al<sup>83</sup> reported a prospective evaluation of the use of clipped nodes for the selective localization and removal of positive axillary nodes. Three retrospective trials<sup>79-81</sup> evaluated patients who did not receive NAC. Overall, for diagnostic outcomes, the risk of bias was unclear to high. We did not pool the results into a meta-analysis because the studies were heterogeneous.

**(C) US compared with SLNB** We did not identify any systematic review for this comparison; no studies reported on direct patient outcomes and on IR for this comparison. Stachs et al,<sup>82</sup> a retrospective study at unclear risk of bias, reported on FNR of preoperative US. The SENTINA trial<sup>64</sup> gives us an estimate of the FNR of US. This body of evidence is indirect and imprecise, and it is not possible to exclude publication bias.

**Outcomes** Details on outcomes in the studies included in the guideline's systematic review are reported in the Data Supplement (online only).

## RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

### Preamble and Implementation Considerations

This guideline focuses on the management of the axilla in patients with early-stage breast cancer: the proposed interventions are feasible, often already part of the current standard of care, and they would not require any significant changes or additional costs in the current systems, which is an enabler to the implementation of this guideline. We involved patient representatives since the planning stages of this guideline, and we anticipate that patients and clinicians will view the recommendation as acceptable and that they will value outcomes in a similar way. Application of the recommendations on a case-by-case basis, the shared

decision making that we recommended, and consideration of comorbidities will reduce the risk of increased morbidity, especially in vulnerable, older women. The Algorithm and the Bottom Line section will facilitate implementation of this guideline in a variety of settings.

**Objective 1.** To determine which patients with early-stage breast cancer require axillary staging.

### Recommendation 1

- For patients age  $\geq 70$  years 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<sup>8</sup> that stated, “Don’t routinely use sentinel node biopsy in clinically node negative women  $\geq 70$  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 (Type: informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate).
- For patients age  $< 70$  years without significant competing comorbidities, SLNB should be considered for axillary staging of early-stage breast cancer (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate to high for staging by ALND v no ALND; insufficient for staging by SLNB v no staging; Strength of recommendation: strong).

### Qualifying statement 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.

### Key evidence for recommendation 1

- The meta-analysis of two studies<sup>21,22</sup> by Liang et al<sup>18</sup> concluded that omission of axillary staging by ALND in women age 70 years or older, with clinically negative axilla, resulted in increased risk of regional recurrence (relative risk [RR] 0.24; 95% CI, 0.06 to 0.95;  $I^2 = 0\%$ ;  $P = .04$ ), but did not affect overall and breast cancer–specific mortality (RR, 0.99; 95% CI, 0.79 to 1.24;  $I^2 = 0\%$ ;  $P = .92$  and RR 1.07; 95% CI, 0.72 to 1.57;  $I^2 = 0\%$ ;  $P = .75$ , respectively).
- Our update of the meta-analysis by Liang et al<sup>18</sup> with one additional study<sup>20</sup> confirmed these results for OS (hazard ratio [HR], 1.09; 95% CI, 0.85 to 1.39;  $P = .5$ ;

$I^2 = 0\%$ ) and for DFS (HR, 1.06; 95% CI, 0.81 to 1.38;  $P = .69$ ;  $I^2 = 0\%$ ).

- One of the included studies<sup>22</sup> reported on quality of life defined as a physician and self-assessed report of pain or restriction in movement of the arm. Physicians and patients alike reported a significant increase in pain (23% v 7%,  $P = .00006$ ) and restriction of movement (39% v 15%,  $P = .000001$ ) for the ALND group compared with the SLNB-only group.
- Data will be forthcoming in the next several years from four ongoing clinical trials<sup>23-26</sup> comparing SLNB with no axillary staging.

### Interpretation of evidence for recommendation 1

- By choosing SLNB over ALND, patients will experience a substantial reduction in adverse events, such as lymphedema and sensory neuropathy, for the same effect on OS and DFS, which are outcomes critical to patients. This is also true for patients who have sonographically abnormal imaging with or without confirmatory biopsy. In fact, the majority of these patients would be able to avoid ALND had the US not been performed, as they are most likely to have only 1-2 positive nodes.
- Some patients may experience axillary recurrence if ALND is avoided; therefore, we suggested this possibility to be discussed and evaluated, according to individual patient’s circumstances, values, and preferences.
- No evidence is available at this time for staging by SLNB compared with observation, and we are awaiting the results of ongoing trials that will appear in the next several years.
- Applying the Choosing Wisely guideline to low-risk,  $\geq 70$ -year-old women with hormone-positive early-stage cancer should be made on a case-by-case basis because although omitting SLNB has no impact on survival, it is associated with an increased risk of recurrence. Therefore, patients’ preferences should be balanced against their comorbidities and competing risks for death.
- Although the CALGB 9343 trial<sup>91</sup> did not meet the inclusion criterion for intervention in our systematic review, as it was an RCT evaluating the role of breast radiation (as opposed to axillary radiation) in patients age  $> 70$  years who received tamoxifen for early-stage breast cancer, two thirds of the patients in this study had no axillary staging procedure. Long-term follow-up has demonstrated low rates of in-breast recurrence and low rates of axillary recurrence. This finding supports our recommendation that sentinel node biopsy can be safely avoided in these patients.
- The overall certainty of this body of evidence was moderate to high for staging performed by ALND compared with no ALND.

**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<sup>9,10</sup>) (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).
- In some selected patients (eg, 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 (ie, 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) (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate to low; Strength of recommendation: weak).

**Qualifying statement for recommendation 2***Surgical interventions*

- LNB is currently the standard of practice for this population.
- The evidence regarding the omission of ALND upon which this recommendation is based (see key evidence for Recommendation 2) 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 age < 18 or > 80 years, 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 (ie, 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.

*Radiotherapy interventions*

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

**Key evidence for recommendation 2***Surgical interventions*

- We endorsed the recommendation from the ASCO 2017 update guideline.<sup>9,10</sup>
- The systematic search of the literature for this guideline did not uncover any new evidence that would change the ASCO recommendations<sup>9,10</sup> for this treatment for women who were node-negative at diagnosis.

*Radiotherapy interventions*

- There are currently no published clinical trials of LRNI in exclusively pathologically node-negative patients. Two pivotal trials included a small portion of node-negative patients.<sup>5,33</sup> The EORTC 22922/10925 trial<sup>33</sup> selected patients with centrally and medially located tumors, who may be less likely to present with axillary node-positive disease. These patients may benefit more from LRNI. Among women who received ALND, the EORTC 22922/10925 trial<sup>33</sup> reported no statistically significant difference in OS at a 10-year follow-up between patients who received LRNI, in addition to WBI and thoracic wall irradiation compared with those who received WBI or thoracic irradiation alone: 82.3% versus 80.7%, HR, 0.87; 95% CI, 0.76 to 1.0;  $P = .06$ . However, a statistically significant difference was noted in breast cancer-specific death rate in favor of the LRNI group: 12.5% versus 14.4%, HR, 0.82; 95% CI, 0.70 to 0.97,  $P = .02$ .
- The EORTC 22922/10925 trial<sup>33</sup> reported a better DFS (HR for disease progression, 0.89; 95% CI, 0.80 to 1.00;  $P = .04$ ), distant DFS rate (78% v 75%,  $P = .02$ ), and a lower rate of first recurrence (19.4% v 22.9%,  $P = .02$ ) at a 10-year follow-up for patients who had LRNI compared with those who did not.
- In the EORTC 22922/10925 trial,<sup>33</sup> 44% of women had centrally and medially located tumors treated with mastectomy, or breast-conserving surgery and ALND, and most patients received systemic therapy. In this trial,<sup>33</sup> at a 10-year follow-up, patients who received LRNI experienced more pulmonary fibrosis (4.4% v 1.7%,  $P < .001$ ) than those who had radiotherapy of the thoracic wall and WBI. No statistically significant difference was detected for cardiac disease or cardiovascular death.
- In the MA.20 trial,<sup>5</sup> 10% of included patients had high-risk node-negative disease (9.7% [n = 89] in the WBI group and 9.6% [n = 88] in the WBI plus LRNI group).

- The MA.20 trial<sup>5</sup> showed that LRNI in all patients, those with positive nodes or those with negative nodes and high-risk features, was associated with improved DFS at 10 years (estrogen receptor–negative [ER–] 61.6% v 76.2; HR, 0.56; 95% CI, 0.39 to 0.81;  $P = .04$ ; progesterone receptor–negative [PR–] 70.5% v 81.9%; HR, 0.57; 95% CI, 0.41 to 0.80;  $P = .03$ ) and distant DFS at 10 years (86.3% in the LRNI group v 82.4% in the WBI group; HR, 0.76; 95% CI, 0.60 to 0.97;  $P = .03$ ).
- When comparing chest wall radiotherapy with no radiation in patients with triple-negative breast cancer, Wang et al<sup>34</sup> reported that patients experienced better outcomes with chest wall radiation compared with no radiation: OS at 5 years (90.4% v 78.7%; HR, 0.79; 95% CI, 0.74 to 0.97;  $P = .03$ ), distant metastases (24.2% v 38.5%, for those with 1-2 distant metastases; 75.8% v 61.5% for those with > 2 metastases,  $P < .05$ ), and relapse-free survival (88.3% v 74.6%; HR, 0.77; 95% CI, 0.72 to 0.98;  $P = .02$ ), with no statistically significant between-group difference in neutropenia and nausea or emesis.
- None of the included radiotherapy trials reported on quality of life.
- The included studies involved women of variable age. Radiotherapy was delivered at a dose of 50 Gy in 25 fractions. Techniques might have improved since the time when the studies were performed, and currently, some fractionation schedules exist for accelerated WBI and partial breast radiation.
- The overall certainty of the evidence in support of this recommendation is moderate to low because of risk of bias, imprecision, and indirectness.

**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,<sup>9,10</sup> Recommendation 2.1) (Type: evidence based; benefits outweigh harms; Evidence quality: high for patients who received breast-conserving surgery; Strength of recommendation: strong for those who had breast-conserving surgery. For patients who had mastectomy and for those excluded from the trials, the strength of the body of the evidence is insufficient and the recommendation is weak).

#### (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 (Type: evidence based; benefits may outweigh harms; Evidence quality: low; Strength of recommendation: weak).

#### (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 are recommended if  $\geq 3$  sentinel lymph nodes are positive. In patients who receive mastectomy and have one to two positive nodes,

## Interpretation of evidence for recommendation 2

### Surgical interventions

- Patients are concerned with the possibility of overtreatment in those who have negative sentinel nodes. We agree with the ASCO recommendation to not perform ALND for women with negative sentinel nodes; that recommendation aimed at reducing overtreatment and its consequent burden of adverse effects.
- Benefits of treatment with SLNB alone, as compared with SLNB and ALND, outweighed the morbidity of SLNB and ALND in women with negative nodes.
- The certainty of the body of evidence for surgical interventions was moderate.

### Radiotherapy interventions

- Patients may value differently the pros and cons of receiving axillary radiotherapy, and they may differ on how they value outcomes; therefore, we issued a weak recommendation for this treatment and we recommended an in-depth discussion between clinicians and patients of various aspects of each individual situation on a case-by-case basis. OS, DFS, and local control are considered critical outcomes; quality of life and adverse effects are also important outcomes to patients.
- After axillary surgery, patients did not experience any difference in overall or breast cancer mortality when treated with or without axillary radiotherapy; DFS was better, and recurrence was reduced in the treatment arm of the studies compared with control. The included studies had a follow-up of about 10 years.

PMRT to the axilla is recommended and ALND can be safely omitted. In patients declining PMRT (ie, 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  $\geq 3$  positive nodes, ALND followed by LRNI radiation can be considered (Type: informal consensus; benefits outweigh harms in the short term; Evidence quality: low; Strength of recommendation: weak).

#### (D) Radiotherapy compared with no treatment

- In patients with unilateral invasive cancer of small size (ie, T1a), favorable tumor features (eg, estrogen receptor–positive 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 (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: weak).

#### Qualifying statement for recommendation 3

##### (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, and 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 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 and N3 disease) falls outside the scope of this guideline. Please refer to OH (CCO) PEBC guideline 19-1 guideline: locoregional therapy of LABC.<sup>9</sup> 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.

##### (B) LRNI compared with no LRNI

- Patients with ER and PR status may have a more favorable DFS when treated with LRNI in addition to surgery.

##### (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.

##### (D) Radiotherapy compared with no treatment

- Patients age 65 years or older may benefit less from the addition of radiotherapy.
- Receptor–negative patients may benefit more from radiotherapy treatment.

#### Key evidence for recommendation 3

##### (A) No further axillary surgery beyond SLNB compared with ALND

- We endorsed the recommendation for women with early-stage breast cancer with one or two positive nodes at SLNB from the ASCO 2017 guideline.<sup>9,10</sup> The ASCO guideline<sup>9,10</sup> was based on the evidence from two randomized trials, the Z0011<sup>3,42-44</sup> and the IBCSG 23-01.<sup>39,40</sup> These studies showed that SLNB was noninferior to ALND. We included the Schmidt-Hansen systematic review,<sup>37</sup> which included the above trials, and an additional smaller study.<sup>38</sup> The results of the ATTRM-048-13-2000 study<sup>38</sup> point in the same direction as the previously existing evidence.
- A subgroup analysis of the IBCSG 23-01 trial<sup>39,40</sup> examined 86 women (approximately 9% of the total sample) treated with mastectomy who experienced nine events. The observed HR was lower than 1.25, the set noninferiority margin (HR, 0.52; 95% CI, 0.09 to 3.10), and the group without ALND was significantly (ie,  $P < .10$ ) noninferior to the group with ALND.
- At this time, evidence from randomized trials is not available to support the recommendation to omit ALND for women who received mastectomy and for women with multicentric tumors and prior breast or axillary surgery (ie, patients who were excluded from the studies that support Recommendation 3A). We believe that clinicians and patients should discuss advantages and disadvantages of all options depending on the characteristics of the tumor, other clinical circumstances, and patient preferences.

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

- At a 9.5-year follow-up, the MA.20 trial<sup>5</sup> did not detect any statistically significant difference in OS between patients treated with WBI plus LRNI and those treated with WBI alone (HR, 0.91; 95% CI, 0.72 to 1.13;  $P = .38$ ). All patients received some form of axillary surgery (SLNB or ALND) in addition to breast surgery and WBI. DFS was statistically significantly better for patients treated with the additional LRNI (HR, 0.76; 95% CI, 0.61 to 0.94;  $P = .01$ ).

- The MA.20 trial<sup>5</sup> showed that patients with hormone receptor–negative status may have a better DFS at a 10-year follow-up when treated with additional LRNI than with WBI alone (ER–: 81.3% v 73.9%; HR, 0.69; 95% CI, 0.47 to 1.00;  $P = .05$ ; test for interaction: 0.08 and PR–: 83.5% v 78.9%; HR, 0.76; 95% CI, 0.55 to 1.06; test for interaction: 0.20).
- Patients in the LRNI group experienced more pneumonitis and radiation dermatitis than patients in the WBI group (1.2% v 0.2%,  $P = .01$  and 49.5% v 40.1%,  $P < .001$ , respectively).
- No data on LRNI versus none in patients who only had SLNB are available as we are awaiting results from the ongoing MA-39 trial. Despite MA-20<sup>5</sup> node-positive patients having all had axillary dissection, benefit was modest: breast cancer–specific mortality at 10 years was not statistically significantly different for surgery only versus surgery and LRNI (10.3% v 12.3%; HR, 0.80; 95% CI, 0.61 to 1.05;  $P = .11$ ); there was a 5% improvement in DFS with a small cost of increased pneumonitis (1.2% v 0.2%,  $P = .01$ ) and worse grade 2 lymphedema rates for the LRNI group (8.4% v 4.5%,  $P = .001$ ). Therefore, this recommendation is based on our expert opinion.

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

- The OTOASOR<sup>49</sup> and AMAROS<sup>4,50,51</sup> studies showed no statistically significant difference in OS, DFS, and axillary recurrence between treatment arms. In these trials, the patients in the surgical arm experienced significantly worse adverse events. The trials presented results at 5 years, and data on second cancers are available in two conference abstracts<sup>92,93</sup> that presented the 10-year update results of the AMAROS trial<sup>4,50,51</sup> and showed equivalent local control and OS, but a small increase in second breast cancers in the LRNI arm. The OTOASOR trial has been updated at an 8-year follow-up,<sup>94</sup> and no changes in outcomes have been detected.
- While awaiting the full publication of the MA39 (NCT03488693) trial, the recommendation about the incremental use of radiation therapy and its combination with surgery is based on the expert opinion of Working Group members. At this time, no studies comparing SLNB alone without LRNI have been identified in the mastectomy or lumpectomy setting.

### (D) Radiotherapy compared with no treatment

- In the included studies,<sup>52,53</sup> in older women treated with LRNI with or without tamoxifen compared with tamoxifen alone, a benefit was seen in 20-year recurrence rates (locoregional recurrence rate: 5.3% radiotherapy plus tamoxifen v 18.5% tamoxifen,  $P < .001$ ; recurrence rate of systemic disease: 40% v 50%, respectively,  $P = .047$ ), with no difference

shown in OS. As well, in younger women, a benefit for locoregional recurrence at 20 years (radiotherapy v cyclophosphamide: 3.5% v 13.9%,  $P = .0071$ ) was noted with no statistically significant between-group difference in OS.

- In the included studies, adding radiotherapy to either cyclophosphamide or tamoxifen increased mortality from heart disease from zero to 0.8% ( $P = .04$ ), and from 10.5% to 18.4% ( $P = .005$ ), respectively, in pre- and postmenopausal women. In older women, mortality because of cerebrovascular disease increased from 3.4% to 8.7% by adding radiotherapy to hormonal therapy ( $P = .015$ ), whereas in premenopausal women, there was no statistically significant difference by adding radiotherapy to chemotherapy (cumulative cerebrovascular mortality: cyclophosphamide: 0.8% v radiotherapy plus cyclophosphamide: 1.7%,  $P = .52$ ).

## Interpretation of evidence for recommendation 3

### (A) No further axillary surgery beyond SLNB compared with ALND

- Patients highly value reduction in adverse events and quality-of-life outcomes obtained by omitting ALND.
- Benefits outweigh harms for patients similar to those included in the trials reviewed for this guideline. The IBCGS 23-01 trial<sup>39,40</sup> examined a subgroup of patients who received mastectomy. According to their results, the omission of axillary dissection might also be acceptable in patients undergoing mastectomy. However, this result was based on a small subgroup of patients who experienced a very small number of events. We consider this evidence insufficient to be able to generalize to all women who received mastectomy. Omitting ALND is an option for these women, but all clinical circumstances need to be carefully considered, and patient preferences taken into account.
- As well, for women who would have been excluded from the trials on which this recommendation is based, a careful consideration of all clinical circumstances and preferences is warranted. Until more data become available, we believe that it is reasonable to extend the recommendation to avoid ALND and to treat the axilla with radiation in those patients who have one or two positive nodes on SLNB as well.
- SLNB is acceptable as it is a less invasive intervention than ALND.
- The generalizability of this recommendation is limited to women similar to those included in the included trials. For male patients, refer to Generalizability statement in Recommendation 1.
- This body of evidence was of overall moderate certainty.

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

- Patients value the reduction in short-term adverse effects. Patients treated with WBI and additional LRNI experienced more short-term adverse effects than



patients treated with WBI only. Patients also value survival, DFS, and local control. One study (MA.20<sup>5</sup>) did not show a difference in survival, but did show improved DFS with the addition of LRNI, which came at the cost of an increase in more severe short-term adverse events. There is no information about late adverse events, second cancers, or quality of life. The addition of LRNI may be an option for high-risk patients. Discussion of pros and cons with patients has to occur, and decisions have to take place on a case-by-case basis.

- Patients with ER– and PR– status may benefit more from this treatment.
- Not all patients may agree on the balance of benefits and harms on the basis of the evidence available to date. No data are available on quality of life, and some groups of patients may benefit more than others.
- Some patients, particularly those who underwent immediate implant-based breast reconstruction following mastectomy, may find radiation less acceptable if the risk of morbidity and resultant further surgeries to correct capsular contractions or implant loss is significant.
- This recommendation is generalizable to women with fewer than three positive sentinel lymph nodes.

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

- Patients value the reduction in short-term adverse effects. Patients treated with axillary irradiation experienced, in the short term, less adverse events than those treated with ALND, and no evidence is available on second cancers yet. No statistically significant difference was detected in quality of life at one or five years.<sup>4,50,51</sup> Even in patients with three or more positive sentinel lymph nodes (25% of patients in the AMAROS trial<sup>4,50,51</sup>), LRNI was equivalent to ALND; thus, either treatment strategy is an option. However, radiotherapy has lower lymphedema risk, and therefore, we recommended it.
- Studies are ongoing in low-risk, node-positive patients such as the Canadian Cancer Trial Group MA39 study (NCT03488693) that addresses the incremental benefit of LRNI of the axilla. At this time, no studies comparing SLNB alone without LRNI have been identified in the mastectomy or lumpectomy setting.
- No statistically significant between-group difference was noted in both the OTOASOR<sup>49</sup> and the AMAROS<sup>4,50,51</sup> trials for OS, DFS, and recurrence in the axilla. Short-term (ie, 0-11 months) adverse events were not reported. The AMAROS trial<sup>4,50,51</sup> reported statistically significantly worse lymphedema and arm circumference increase at one, three, and five years in patients treated surgically compared with those given irradiation. The certainty we have in the evidence regarding adverse events is low, because only one of two trials reported on this outcome; however, the existing evidence cannot be ignored. Therefore, the

balance of benefits and harms weighs in favor of the radiotherapy treatment.

- Some patients may consider radiotherapy interventions acceptable and others less so.
- The OTOASOR and AMAROS trials randomly assigned women after SLNB; therefore, the results are applicable to patients with early-stage breast cancer found in clinical practice.
- The overall certainty of this body of evidence was moderate.

### (D) Radiotherapy compared with no treatment

- Patients highly value a reduction in adverse events; therefore, we suggested the omission of irradiation for older women. However, studies on which this recommendation is based<sup>52,53,89</sup> collected data from 1978 to 1985. Therefore, the adverse events of radiotherapy that were seen at a 25-year follow-up (eg, cardiac events and second cancers) may not be as relevant for patients treated with more modern radiotherapy techniques, but there is no evidence of this yet.
- OS, DFS, and local control are considered critical outcomes for all comparisons; quality of life and adverse effects are also important outcomes to patients.
- Adding radiotherapy of the locoregional nodes demonstrated a reduction in recurrence at 20 years, but did not change survival in the studies of older and younger women included here.<sup>52,53</sup>
- This recommendation is generalizable to women with the same characteristics as those included in the studies that form its evidentiary basis.
- We can consider the overall certainty of this body of evidence as moderate.

**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 or core needle biopsy, and were treated with NAC should receive SLNB at the time of surgery as their axillary staging procedure (Type: informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong).

### (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 to minimize the FNR and optimize accuracy of the procedure. At this time, we also recommend LRNI for these patients, regardless of pathologic status of sentinel lymph nodes.

- 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 (ie, 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.

(Type: evidence based; benefits outweigh harms; Evidence quality: low; Strength of recommendation: weak).

**(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 (Type: informal consensus; benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).

#### Qualifying statement for recommendation 4

##### **(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.

#### Key evidence for recommendation 4

##### **(A) Patients who were initially clinically node-negative**

- None of the included trials reported on women who were initially node-negative, and therefore, this recommendation is based on the expertise of the Working Group members.

##### **(B) Initially clinically and biopsy-proven node-positive patients**

- The evidence available at this time for surgical interventions is a nonrandomized, retrospective study<sup>54</sup> that compared 386 patients in five groups.
- The currently available evidence for radiotherapy interventions is a very large (N = 15315) retrospective cohort trial with a 39-month follow-up<sup>55</sup> and a retrospective analysis of three randomized trials with a 51.5-month follow-up.<sup>56</sup> In the trial by Rusthoven

et al,<sup>55</sup> patients treated with mastectomy and NAC who received PMRT (with or without LRNI) had a significantly better OS compared with patients who did not receive PMRT, irrespective of nodal status. On propensity score–matched analysis, 92% of patients who were node-negative after NAC survived with PMRT compared with 90% without PMRT: HR, 0.695; 95% CI, 0.518 to 0.929;  $P = .014$ ; and 80% of patients who were node-positive after NAC survived with PMRT compared with 76% without PMRT: HR, 0.845; 95% CI, 0.738 to 0.968;  $P = .015$ . In patients treated with breast-conserving surgery, the trial by Rusthoven et al<sup>55</sup> showed that adding LRNI did not provide a statistically significant OS benefit; among patients who were node-negative after NAC, 93% survived with breast irradiation and LRNI compared with 92% with breast irradiation: HR, 1.028; 95% CI, 0.716 to 1.477;  $P = .880$ ; among patients who were node-positive after NAC, 84% were alive with breast irradiation and LRNI and 85% survived with just breast irradiation: HR, 0.962; 95% CI, 0.785 to 1.175;  $P = .704$ . The trial by Krug et al<sup>56</sup> included only women treated with mastectomy; in the subgroup of patients with T1-T2 tumors, PMRT did not improve locoregional recurrence (HR, 0.94; 95% CI 0.45 to 1.95;  $P = .86$ ).

- We are aware of two ongoing randomized trials: the MAC.19 trial (clinicaltrials.gov identifier [NCT01901094](https://clinicaltrials.gov/ct2/show/study/NCT01901094)), which will be completed in 2024, and the RTOG 1304/NSABP B51 trial ([NCT01872975](https://clinicaltrials.gov/ct2/show/study/NCT01872975)), which will be completed in 2028 with first data available in 2023. The MAC.19 trial is comparing ALND with LRNI in patients with breast cancer stage cT1-T3 N1 who remained node-positive after NAC; the RTOG 1304/NSABP B51 trial evaluates whether adding chest wall radiotherapy and LRNI after mastectomy compared with no radiation, or breast irradiation and LRNI compared with breast irradiation only, after breast-conserving surgery will significantly reduce event rates in a population of initially positive patients who converted to node-negative after NAC.

##### **(C) SLNB timing: before or after NAC**

- The SENTinel NeoAdjuvant (SENTINA) trial<sup>64</sup> evaluated timing of SLNB in relation to NAC. Arm B of this trial, which was stopped early, examined SLNB before NAC for clinically node-negative patients and repeated it again after NAC. In this cohort, the second SLNB was associated with low overall IR (60.8% [219 of 360 patients], 95% CI, 55.6 to 65.9) and high overall false-negative rates (51.6% [33 of 64 patients], 95% CI, 38.7 to 64.2).

#### Interpretation of evidence for recommendation 4

- Patients value survival, DFS, and local control. Patients also want to prevent increased morbidity from

treatments. For node-positive patients, there is a lack of evidence at this time; randomized trials are ongoing (NCT01872975 and NCT01901094), and data will not be available until 2023/2024. Data from these ongoing trials, once completed, will strengthen or change this recommendation.

- Some patients may select to undergo SLNB instead of ALND to minimize surgical morbidity. We recognize that this area remains controversial. A decision aid tool does not exist at the present time, and it would be helpful to provide support to those patients who want to avoid the potential for increased morbidity from ALND.
- We recognize that restaging the axilla after NAC and the role of clips remains controversial. Further work is ongoing in this area that may help clarify this in the future.
- OS, DFS, and local control are considered critical outcomes; quality of life and adverse effects are also important outcomes to patients.
- The certainty of the evidence for patients who were node-negative at diagnosis is very low at this time as no trials were identified for this population. When new evidence will become available, the recommendation will be updated as soon as possible.
- The certainty of this evidence for SLNB compared with ALND in patients who were node-positive at diagnosis is low to very low. The certainty of the evidence for radiotherapy interventions compared with no intervention is moderate because of risk of bias, indirectness, and imprecision.
- The benefits of the recommended course of action outweigh the undesirable effects; lymph nodes that are not proven to be positive by biopsy can be treated as negative and interrogated by SLNB at surgery, in an effort to minimize potentially unnecessary morbidity from an axillary dissection that might not be clinically indicated. These indeterminate lymph nodes could be reactive, and therefore, SLNB is the appropriate axillary staging procedure for them.
- For patients who are initially clinically and biopsy-proven node-positive, given the absence of data to guide management, we consider LRNI the safest approach. In patients who receive NAC and remain node-positive, the current standard is to recommend ALND with LRNI. Data from ongoing studies may change this practice.
- The studies that we included in this systematic review do not report data on adverse effects of ALND and of radiotherapy. However, adverse effects of ALND, such as lymphedema, and limitation in range of motion are well-known. This knowledge prompted us to issue the recommendation for patients who were initially clinically node-negative.
- With regard to timing of SLNB, patients planned for NAC who are taken to surgery for SLNB first, and are found to be node-positive, will require an axillary node dissection after NAC. This will result in increased morbidity without evidence of significant improvement in locoregional

control or DFS. The expert consensus of the Working Group members is to wait for SLNB on clinically or biopsy-proven node-negative patients until *after* NAC, so that definitive decisions on the management of the axilla can be made on the basis of this guideline. This is consistent with an evolving clinical practice leading to locoregional and systemic management decisions on the basis of residual disease after NAC rather than decisions based solely on presentation at diagnosis.

- We do not recommend taking clinically node-negative patients to surgery solely to perform SLNB. Rather, SLNB should be performed in one operation concurrently with the definitive breast surgery.
- We consider the proposed intervention acceptable to the majority of patients.
- These recommendations are generalizable to women who were initially node-positive or node-negative.

**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 (eg, 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 nonidentification, blue dye can be added. Screening for radiocolloid signal before incision is recommended, and blue dye can be added before 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) (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

### (B) US-guided staging versus standard guided (dye or isotope) staging

- In clinically node-negative patients with early-stage breast cancer where the sentinel lymph node is likely to be negative (ie, T1 and T2), preoperative axillary US staging is not recommended.
- In patients with clinically palpable (ie, clinically positive) lymph nodes, it is recommended to conduct US-guided core biopsy of the axillary node to prove pathologic 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 (Type: evidence based; benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).

### (C) US-guided staging versus surgical staging

- We recommend that diagnostic staging by US only (ie, not confirmed by a biopsy) should not be used instead

of traditional SLNB staging (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

### Qualifying statement for recommendation 5

#### (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 (eg, low-volume centers and surgeons in training or post-training).

#### (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 that 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.

### Key evidence for recommendation 5

#### (A) Single versus dual tracer

- No evidence is available on direct patient outcomes such as survival, disease control, quality of life, complication rate, ability to map, and procedure completion rate. For adverse events, O'Reilly et al<sup>68</sup> reported an anaphylaxis rate of 0.3% and a skin tattooing rate of 0.6% with blue dye.
- The SENTINA trial<sup>64</sup> reported that, when SLNB was performed before NAC, no difference was observed between IR with the combination of radiocolloid and blue dye (dual tracer) and radiocolloid alone (single tracer) (99.5% [399 of 401] v 98.8% [573 of 580],  $P =$  not reported). When SLNB was performed after NAC, the addition of blue dye was associated with a significant increase in IR; in clinically node-negative patients who had a pathologically positive sentinel node before NAC and received a second SLNB followed by ALND (arm B of the trial), the IR was 76.2% with dual tracer (80 of 105) compared with 52.9% with single tracer (126 of 238). In initially cN1 or cN2 patients who had NAC and then had SLNB and ALND if they converted to a clinically negative axillary status (arm C of the trial), the IR was 87.8% with dual tracer (144 of 164) versus 77.4% with single tracer (301 of 389),  $P =$  not reported. In arm C of the trial, dual tracer was identified by the authors as one of the factors affecting increased detection rate in multivariate analysis: odds ratio (OR), 2.13; 95% CI, 1.01 to 4.46;  $P = .046$ . This study included approximately 6% of patients with stage T3-T4 disease and 14% of patients for whom the clinical size of the tumor was unknown, making this evidence partially indirect.

- Tausch et al<sup>65</sup> reported an IR of 82% with blue dye alone, 85% with radioisotope alone, and 94% with the combination ( $P =$  not reported).
- In 13 studies of patients with breast cancer at stages T1-T4 treated with NAC, Geng et al<sup>67</sup> reported no statistically significant difference in IR between three mapping methods: blue dye 96% (95% CI, 91 to 100), radiocolloid 96% (95% CI, 94 to 99), or blue dye combined with radiocolloid 97% (95% CI, 96 to 98),  $P = .180$ .
- Nathanson et al,<sup>73</sup> in patients who did not receive NAC, reported that IR was higher with dual than with single tracer (in a multivariable regression model, OR, 2.9; 95% CI, 1.77 to 4.73) and that high-volume surgeons had a 2.6 higher odds of finding sentinel lymph nodes than less-experienced surgeons (95% CI, 1.7 to 4.1;  $P < .0001$ ).
- The SENTINA trial<sup>64</sup> reported no statistically significant difference in FNR for single versus dual tracer. The American College of Surgeons Oncology Group Z1071 trial<sup>70</sup> reported no statistically significant difference in FNR for dual tracer (10.8% [95% CI, 7.2 to 15.3]) compared with single tracer (20.3% [95% CI, 11.0 to 32.8],  $P = .05$ ). The SN-FNAC trial<sup>71</sup> also reported no statistically significant difference between dual tracer (5.2%) and isotope only (16%),  $P = .190$ .
- Hunt et al<sup>58</sup> showed a statistically significant lower FNR with blue dye combined with radiocolloid compared with blue dye alone (OR, 2.61; 95% CI, 0.78 to 8.76;  $P < .0001$ ).
- Gimbergues et al<sup>66</sup> reported that factors affecting false-negative rate when radiocolloid alone was used were larger tumor size (5.7% for T1-T2 v 28.5% for T3 cases,  $P = .045$ ) and positive clinical lymph node status before NAC.

#### (B) US-guided staging versus standard guided (dye or isotope) staging

- No data are available at this time on disease control, quality of life, adverse events or complication rate, ability to map, and procedure completion rate. The population study by Verheuel et al<sup>78</sup> reported on OS, but the study was considered at critical risk of bias and its results were not suitable to support our recommendation. Kramer et al,<sup>79</sup> Kim et al,<sup>80</sup> and Cools-Lartigue et al<sup>81</sup> reported variable FNR. The FNR was 6.4% (137 of 2,130 patients), 34.8% (8 of 23 patients), and 40.8% (20 of 49 patients) for the three studies, respectively.

#### (C) US-guided staging versus surgical staging

- No evidence is available at this time for direct patient outcomes. Stachs et al<sup>82</sup> examined factors associated with a false-negative result of axillary US as a staging procedure. With histopathology after ALND or SLNB as the reference standard, the FNR of axillary US was 23% (87 of 378 patients). The size of nodal

metastases  $\leq 10$  mm was an independent predictor for false-negative axillary US (OR, 2.66; 95% CI, 1.81 to 3.91;  $P = .001$ ).

## Interpretation of evidence for recommendation 5

### (A) Single versus dual tracer

- Patients value reduced potentially life-threatening adverse effects, and expect a test with high positive IR and low FNR.
- In studies of single versus dual tracer, for outcomes such as survival, disease control, and quality of life, the certainty of the evidence can be considered low for all patients.
- For IR and FNR, the certainty of the evidence for patients treated with NAC can be considered moderate. The studies for these outcomes are at unclear or high risk of bias. A small portion of the included patients have T3-T4 disease; therefore, the evidence is indirect to a certain extent. The studies had generally a large sample size. However, event rates could be very small (eg, FNR with dual tracer: 5.2% [3 of 58 patients]<sup>71</sup> and FNR with isotope only: 16.0% [4 of 25 patients]),<sup>64</sup> giving way to imprecision.
- The included studies were consistently indicating no difference between single and dual tracer. A caveat should be made in regard to confounding factors such as the expertise of the surgeons, with less-experienced surgeons reaching a lower IR with a single tracer.
- The certainty of the evidence for patients treated with NAC was moderate because of indirectness and imprecision. The certainty of the evidence for patients who did not receive NAC was moderate to low. The studies included were of high<sup>68,72</sup> or unclear<sup>73</sup> risk of bias. The reported results were inconsistent (eg, Nathanson et al<sup>73</sup> reported a higher IR for dual compared with single tracer, whereas Kang et al<sup>72</sup> reported no difference). The studies included a portion of patients with stage T3 and T4, or the stage was not reported; therefore, this evidence can be considered partially indirect.
- Blue dye has been linked to anaphylactic reactions, and no statistically significant advantage has been demonstrated in terms of FNR by using dual tracer in patients having surgery first before NAC.
- Most included studies reported very similar IR with single or dual tracer.
- When considering all the data, we recommend the use of dual tracer when performing an SLNB after NAC to optimize IR and minimize FNR by identifying at least three sentinel nodes. If two or fewer sentinel nodes are identified after NAC, the false-negative rate remains higher than considered acceptable. For this reason, we recommend proceeding to a completion ALND.

### (B) US-guided SLNB compared with SLNB

- The certainty of this evidence was low. Risk of bias was critical for direct patient outcomes and high to unclear for diagnostic outcomes. The evidence was partially indirect because the studies included a portion of patients with breast cancer stage T3-4. The study reporting direct patient outcomes<sup>78</sup> was considered at critical risk of bias. The other studies<sup>79-81,83</sup> reported on accuracy outcomes, which are an indirect measure. The three studies that reported on FNR<sup>80,81,83</sup> had very small samples. We did not pool the results into a meta-analysis because the studies were heterogeneous. FNR was higher in studies with smaller sample size. Inconsistencies in the results may be partly due to different definitions of FNR used in the studies. It is not possible to exclude publication bias.
- Axillary US and fine needle biopsy preoperative staging in clinically node-negative patients (especially those with tumors  $< 3$  cm) may lead to increased morbidity from more axillary surgery and clinical upstaging to node-positive at diagnosis, whereas these patients might otherwise have been eligible to SLNB alone according to the Z0011 trial<sup>42-44</sup> had the US not been performed. Therefore, we did not recommend US staging of the axilla in these patients. For patients with stage T3-T4 tumors, the likelihood of axillary disease is greater, and recommendations relative to this population are provided in the locoregional therapy of LABC, PEBC series 1-19 guideline.<sup>11</sup>

### (C) US compared with SLNB

- The trial by Stachs et al<sup>82</sup> was at unclear risk of bias because it was unclear whether the reference standard was interpreted without knowledge of the index test. No direct patient outcomes are reported. The trial by Stachs et al<sup>82</sup> was a single study with 470 patients, and therefore, this body of evidence can be considered imprecise. It is not possible to exclude publication bias.
- No data are available on direct patient outcomes. A relatively high FNR of axillary US, particularly for smaller-size metastases, is the reason for our recommendation.
- Together with the patient representatives, we consider the proposed interventions acceptable to the majority of patients.
- These recommendations are generalizable to node-positive or node-negative women, whether they had received treatment with NAC or not.

## OTHER IMPLEMENTATION CONSIDERATIONS

- Offering SLNB to selected low-risk, clinically node-negative patients with early-stage breast cancer is feasible; there are no current barriers to its implementation, and the procedure is available in all hospitals performing breast surgery.



- Both radiotherapy and surgical interventions are feasible. Both SLNB and radiotherapy are current clinical standards, and this can be considered an enabler to this recommendation.
- The timing of sentinel node to follow NAC in clinically node-negative or biopsy-proven node-negative patients is a confirmation of existing practice among experts, but has not yet been deemed a standard of care before this guideline.
- Potential barriers to implementation for the delivery of adjuvant radiotherapy may arise in the case of those patients, especially those at borderline-risk level, who may live far away from a radiation center and had chosen mastectomy to limit the risk of needing postoperative radiation.
- Clinicians in any of the relevant specialties (surgery, radiation, and medical oncology) may be accustomed to historical methods of care rather than decision making on the basis of response to NAC and may need to acquaint themselves with the medical literature referenced in this guideline.
- The clarification that dual tracer (radiocolloid and blue dye) should be used after NAC to minimize false-negative and non-IRs represents a change to the standard of care.
- Shifting from clinical decision making at diagnosis to post-NAC may represent a change in practice for some providers, particularly low-volume surgeons and radiation oncologists; however, the current data support this change and standardization in practice.
- We consider omission of completion ALND, in patients with one or two positive nodes, who are planned to undergo radiation, as the current standard of care. A change to the standard of care is to extend omission of completion ALND to patients with one or two positive nodes who received mastectomy.
- The timing of sentinel node to follow NAC in clinically node-negative or biopsy-proven node-negative patients is a confirmation of existing practice among experts, but has not yet been deemed a standard of care before this guideline.
- The role of NAC has been well-established in breast cancer, but the paradigm shift to make surgical and radiation clinical decisions on the basis of the results of the nodal status after NAC rather than before represents the current practice among experts and also a confirmation of this standard of care.
- All the studies that met the inclusion criteria for this systematic review included solely women. The results can be generalized to the population of women with early-stage breast cancer. However, it is clinically reasonable to extend the same recommendations to men as long as their primary breast disease is early-stage.

#### 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 and lymphedema rates in patients treated by axillary radiation rather than ALND). Hopefully, these gaps will be filled with future updates to this document.

#### EXTERNAL REVIEW

Comments on the draft guideline were received from three external reviewers with content expertise. Comments were also received from 34 among surgical oncologists, radiation oncologists, medical oncologists, and general surgeons as part of professional consultation. This document was rated as high quality, and most participants agreed that it would be useful in practice. We reviewed and integrated the comments into the final manuscript.

#### RELATED ASCO GUIDELINES

- Brackstone M, Baldassarre F, Perera F, et al: Management of the Axilla in Early-Stage Breast Cancer. PEBC 1-23 Toronto (ON): Ontario Health, Cancer Care Ontario; Program in Evidence-based Care Evidence-based Series: 1-23-A. Internet, Cancer Care Ontario, 2020
- Lyman GH, Temin S, Edge SB, et al. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 32:1365-1383, 2014 (<https://ascopubs.org/doi/10.1200/JCO.2013.54.1177>)
- Lyman GH, Somerfield MR, Bosserman LD, Perkins CL, Weaver DL, Giuliano AE. Sentinel lymph node biopsy for patients with early-stage breast cancer: ASCO Clinical practice guideline update. *J Clin Oncol* 5:561-564, 2017 (<https://ascopubs.org/doi/10.1200/JCO.2016.71.0947>)
- Brackstone M, Fletcher GG, Dayes IS, Madarnas Y, SenGupta SK, Verma S. Loco-regional therapy of locally advanced breast cancer (LABC). Toronto, ON, Cancer Care Ontario, 2014. Program in Evidence-Based Care Evidence-Based Series No.: 1-19. <https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/336>



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## EDITOR'S NOTE

This joint Ontario Health (Cancer Care Ontario) (OH [CCO]) and ASCO clinical practice guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at [www.cancer.net](http://www.cancer.net), is available at [www.asco.org/breast-cancer-guidelines](http://www.asco.org/breast-cancer-guidelines) and <https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/breast>. Published online ahead of print at [www.jco.org](http://www.jco.org) on July 19, 2021. **Clinical Practice Guidelines Committee approval:** April 7, 2021; Program in Evidence Based Care (PEBC) Report Approval Panel Approved: April 30, 2020.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

##### Management of the Axilla in Early-Stage Breast Cancer: Ontario Health (Cancer Care Ontario) and ASCO Guideline

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](#)).

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**Employment:** MD Anderson Physician's Network

**Honoraria:** Pfizer, Eisai

**Consulting or Advisory Role:** Roche/Genentech, AstraZeneca, Novartis, Pfizer, Asofar, Genomic Health

**Research Funding:** Novartis

**Expert Testimony:** Abbott Laboratories, Pfizer

**Travel, Accommodations, Expenses:** Pfizer

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## APPENDIX

**TABLE A1.** Ontario Health (Cancer Care Ontario)-ASCO Management of the Axilla in Early-Stage Breast Cancer Guideline Expert Panel Membership

<b>Name</b>	<b>Affiliation or Institution</b>	<b>Role or Area of Expertise</b>
Muriel Brackstone, MD, PhD (Working Group Chair)	London Health Sciences Centre, London, Ontario, Canada	Surgical Oncology
Fulvia G. Baldassarre, MSc	Program in Evidence-Based Care, McMaster University, Hamilton, Ontario, Canada	Health Research Methodologist
Francisco E. Perera, MD	London Health Sciences Centre, London, Ontario, Canada	Radiation Oncology
Tulin Cil, MD, MEd	University Health Network, Princess Margaret Hospital, Toronto, Ontario, Canada	Surgical Oncology
Mariana Chavez Mac Gregor, MD, MSc	University of Texas MD Anderson Cancer Center, Houston, TX	Medical Oncology
Ian S. Dayes, MD	Juravinski Cancer Centre, Hamilton, Ontario, Canada	Radiation Oncology
Jay Engel, MBCh	Cancer Center of Southeastern Ontario, Kingston General Hospital, Kingston, Ontario, Canada	Surgical Oncology
Janet K. Horton, MD	Research Triangle Park, Chapel Hill, NC	Radiation Oncology
Tari King, MD	Dana Farber/Brigham & Women's Cancer Center, Boston, MA	Surgical Oncology
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Ralph George, MD	St Michael's Hospital, CIBC Breast Centre, Division of General Surgery, Toronto, Ontario, Canada	Surgical Oncology
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Patricia A. Spears, BS	University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC	Patient Representative
Andrea F. Eisen, MD	University of Toronto, Odette Cancer Centre, Toronto, Ontario, Canada	Medical Oncology