Guideline 1-23-A

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Ontario Health (Cancer Care Ontario) in Collaboration with the American Society of Clinical Oncology (ASCO)

Management of the axilla in early-stage breast cancer

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An assessment conducted in December 2023 deferred the review of Guideline 1-23-A. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 1-23-A is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/69736

Section 1:	**Recommendations**
Section 2:	**Guideline – Recommendations and Key Evidence**
Section 3:	**Guideline Methods Overview**
Section 4:	**Systematic Review**
Section 5:	**Internal and External Review**

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PUBLICATIONS RELATED TO THIS REPORT

- Brackstone M, Baldassarre F, Perera F, Cil, T, Dayes I, et al. Management of the axilla in early-stage breast cancer. J Clin Oncol. 2021; publish ahead of print July 19, 2021, DOI: https://doi.org/10.1200/JCO.21.00934.
- Lyman GH, Temin S, Edge SB, Newman LA, Turner RR, Weaver DL, 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. 2014;32:1365-83.
- Lyman GH, Somerfield MR, Bosserman LD, Perkins CL, Weaver DL, Giuliano AE. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology Clinical practice guideline update. J Clin Oncol. 2017;5:561-4 JCO2016710947
- 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 Sep 29. Program in Evidence-Based Care Evidence-Based Series No.: 1-19.

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Management of the axilla in early-stage breast cancer

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES

General Objectives:

To provide recommendations on the best strategies for the management, and on the best timing and treatment (surgical and radio-therapeutic) of the axilla in early-stage breast cancer.

Specific Objectives:

Specific objectives are listed before each recommendation.

TARGET POPULATION

These recommendations apply to patients with early-stage breast cancer (i.e., stages I, IIA, IIB; and prognostic groups T1, T2, N0, N1mi, N1, M0; and primary tumour size ≤5 cm).

INTENDED USERS

This guideline is targeted for:

1. General surgeons involved in the staging of early breast cancer and management of the axilla.
2. Radiation oncologists involved in the radiation treatment of patients with early-stage breast cancer.
3. Medical oncologists involved in the systemic treatment of patients with early-stage breast cancer.
4. Other clinicians involved in the management of women with early-stage breast cancer (e.g., pathologists, radiologists, oncology nurses, genetic counselors).

DEFINITIONS:

1) A **patient-centred approach** involves considering each patient on a case-by-case basis, discussing pros and cons of various options with the patient, in light of her or his circumstances, values and preferences, and using a shared decision-making process for choosing treatment.
2) **Clinical versus pathological positivity:** We define a clinically positive axilla as clinically palpable disease where the determination is made by physical examination only. Pathological positivity means that metastatic cells are identified in the axillary nodes at histopathology, conducted either by fine needle or core biopsy at diagnosis, or postoperatively as a result of sentinel lymph node biopsy (SLNB), or axillary lymph node dissection (ALND). In this document, when we describe patients as positive or negative, we mean that they are pathologically positive or negative, unless otherwise specified. We do not consider lymph nodes to be pathologically positive if they only contain isolated tumour cells.

3) **Radiotherapy of the axilla:** Axillary radiation delivered by standard 2-field tangents to the breast/chest wall that will cover the level 1 and 2 lymph nodes in the axilla, without additional fields to the axilla as is utilized in loco-regional nodal radiation.
4) **Early-stage breast cancer** is defined by the US National Cancer Institute as breast cancer that has not spread beyond the breast or the axillary lymph nodes. This includes ductal carcinoma in situ (DCIS) and stages I, IIA, IIB, and IIIA breast cancers (https://www.cancer.gov/publications/dictionaries/cancer-terms/def/early-stage-breast-cancer). For this report we excluded women with DCIS because they are stage 0 and should not require staging since the cells, by definition, do not spread beyond the basement membrane of the lactiferous duct. We did not include women with stage IIIA because stage III is considered locally advanced and it is covered by our Evidence-Based Series #1-19: "Loco-regional Therapy of Locally Advanced Breast Cancer" [1] available at: https://archive.cancercare.on.ca/common/pages/UserFile.aspx?fileId=334821.
5) **Cancer staging** definitions, see the American Joint Committee on Cancer (AJCC) manual, 8th edition, last updated 05 June, 2018, available at: https://cancerstaging.org/references-tools/deskreferences/Documents/AJCC%20Cancer%20Staging%20Form%20Supplement.pdf [2]
6) Patients with negative nodes and with high-risk features are patients younger than 50 years of age, or premenopausal, or with primary tumour measuring ≥5 cm, or ≥2 cm with <10 axillary nodes removed and at least one of: grade III histologic categorization, estrogen-receptor negativity, or lymphovascular invasion (e.g., with triple-negative breast cancer).
7) In this document, loco-regional radiotherapy refers to whole breast, chest wall, and regional nodal basins irradiation.

SPECIFIC OBJECTIVES AND RECOMMENDATIONS

For all recommendations we recommend a patient-centred approach.

An algorithm for the management of the axilla in patients with early-stage breast cancer is presented in Figure 1.

Specific objective 1: To determine which patients with early-stage breast cancer require axillary staging.

Recommendation 1
• For patients ≥70 years of age with clinically node-negative (T1N0) early-stage invasive breast cancer which 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 (SSO) available at: http://www.choosingwisely.org/clinician-lists/sso-sentinel-node-biopsy-in-node-negative-women-70-and-over/ that stated: "Don't routinely use sentinel node biopsy in clinically node negative women ≥70 years of age with early stage hormone receptor positive, HER2 negative invasive breast cancer" if they will be treated with hormonal therapy. If omission of SLNB is considered, a consultation with a medical oncologist can be considered before surgery to discuss hormonal therapy. • For patients <70 years of age without significant competing comorbidities, SLNB should be considered for axillary staging of early-stage breast cancer.
Qualifying Statements for Recommendation 1
• The information acquired from SLNB would be helpful in guiding adjuvant treatment decision making. • Patients should be evaluated on a case-by-case basis to ensure appropriate patient-centred 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.

Specific objective 2: To determine whether any further axillary treatment is indicated for women with early-stage breast cancer who did not receive neoadjuvant chemotherapy (NAC) and are sentinel lymph node negative at diagnosis.

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 American Society of Clinical Oncology [ASCO] 2017 update guideline [3,4]).

In some selected patients (e.g., patients with medially or centrally located tumours or with high-risk features), and using a patient-centred approach, it is reasonable to offer the option of loco-regional radiation to include at least the supraclavicular and ipsilateral internal mammary lymph nodes in addition to the breast and/or chest wall (see Qualifying Statement).

For the majority of patients (i.e., node-negative patients whose tumours are not medial/central in location, and who do not have other high-risk features), however, we cannot recommend loco-regional node irradiation. Risk-benefit discussion should be undertaken on a case-by-case basis for these patients (see Qualifying Statement).

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 (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 <18 or >80 years of age, were pregnant or lactating, were allergic to blue dye or radioisotope, had evidence of metastatic disease, had tumours >3 cm in diameter, suffered from chronic life-threatening diseases possibly preventing the use of adjuvant therapy, had stage T0 tumours (e.g., ductal carcinoma in situ), had multifocal tumours, and received previous NAC. For these patients, decisions regarding ALND should be made after discussion between the patient and clinicians on a case-by-case basis, depending on the invasive component of the lesion, other clinical circumstances and patient preferences.

Radiotherapy interventions

- Patients with central or medially located tumours may modestly benefit (<5%) from loco-regional irradiation compared with whole breast only (post lumpectomy) or no post-operative radiation (post-mastectomy) in terms of disease-free survival (DFS), distant DFS, and loco-regional relapse, but not in terms of overall survival (OS).
- Post-mastectomy patients with node-negative, triple-negative breast cancer who receive chemotherapy may benefit in DFS and OS from chest wall radiotherapy compared with no radiotherapy.
- A radiotherapy dose fractionation schedule of 50 Gy in 25 fractions over five weeks is the current standard schedule 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.

Specific 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 [3,4], Recommendation 2.1). **B) Radiotherapy of the axilla (loco-regional node irradiation) compared with no radiation to the loco-regional lymph nodes.** 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/central tumours, and in patients with high-risk features. Discussion of pros and cons with patients needs to occur, and decisions should be made on a case-by-case basis. **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 tumours 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. Loco-regional radiation is a reasonable option, especially when there are high-risk features as in (B) above. ALND and loco-regional radiation to the axilla is recommended if ≥3 sentinel lymph nodes are positive. In patients who undergo mastectomy and have one to two positive nodes, post-mastectomy radiation (PMRT) to the chest wall and the axilla is recommended and ALND can be safely omitted.In patients declining PMRT (i.e., patients with immediate reconstruction), either radiation to the axilla without the chest wall or completion ALND can be considered. In patients who undergo mastectomy and have ≥3 positive nodes, ALND followed by loco-regional radiation can be considered. **D) Radiotherapy compared with no treatment** In patients with unilateral invasive cancer of small size (i.e., T1a), favourable tumour features (e.g., 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 radiotherapy of the regional nodes.
Qualifying Statements 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 five years, had bilateral breast cancer, had multicentric disease, had ≥3 or more positive sentinel lymph nodes, had a concomintant malignancy, were previously treated with systemic therapy for

breast cancer, had chemoprevention in the preceding year, had distant metastases or macrometastatic disease, had palpable axillary nodes, were <18 or >75 years old

For these patients, as well as for patients who are treated with mastectomy, decisions regarding completion of ALND should be made after discussion between the patient and clinicians on a case-by-case basis depending on the invasive component of the lesion, other clinical circumstances, and patient preferences, taking into account the limited data specific to mastectomy and considering that these recommendations represent an extrapolation, based on expert opinion, from trials designed for patients undergoing breast-conserving surgery.

For a detailed description of patients who were included in the studies upon which this recommendation is based, see Appendix 7, Tables A to D.

The management of the axilla for patients with four or more positive lymph nodes (N2, N3 disease) falls outside the scope of this guideline. Please refer to Cancer Care Ontario PEBC guideline 19-1 guideline: "Loco-regional therapy of locally advanced breast cancer (LABC)" [1]. For exactly three positive lymph node there is not enough evidence to make a recommendation; therefore, we recommend proceeding with ALND and considering regional radiation.

B) Radiotherapy of the axilla (loco-regional node irradiation) compared with no irradiation to the loco-regional lymph nodes.
Patients with estrogen- and progesterone-negative receptor status may have a more favourable DFS when treated with **loco-regional** irradiation in addition to surgery.

C) Radiotherapy to the axilla compared with further surgery (ALND)
The ongoing MA39 (NCT00005957) study addresses the incremental benefit of loco-regional nodal irradiation of the axilla in lower-risk, node-positive patients. At this time, no studies comparing SLNB alone without loco-regional node irradiation have been identified in the mastectomy or lumpectomy setting.

D) Radiotherapy compared with no treatment
Patients 65 years of age or older may benefit less from the addition of radiotherapy. Receptor-negative patients may benefit more from radiotherapy treatment.

Specific objectives 4: to determine what axillary treatment is indicated and what is the best timing of treatment for women with early-stage breast cancer treated with NAC.

Recommendation 4

A) Initially node-negative patients
Patients who are initially clinically node negative on physical examination, and those who had clinically suspicious nodes on physical examination but deemed to be pathologically negative at fine needle aspiration/core needle biopsy, and have been treated with NAC, should have SLNB at the time of surgery as their axillary staging procedure.

B) Initially node-positive patients

1. For patients who were initially clinically and biopsy-proven node positive, and who remained clinically node positive after NAC we recommend ALND.
2. 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 SLNB, or, in institutions where the use of biopsy clips for nodes is not available, by performing SLNB with dual tracer and excising at least three sentinel nodes in order to minimize the false negative rate and optimize accuracy of the procedure. At this time, we also recommend loco-regional radiation for these patients, regardless of pathologic status of sentinel lymph nodes.

3. Post-mastectomy patients who are node positive on surgical pathology after NAC can be offered PMRT after a completion ALND.
4. We recommend loco-regional nodal irradiation for post-mastectomy node-positive patients after NAC while awaiting data from ongoing trials (i.e., the MAC19 study).
5. We recommend loco-regional irradiation after ALND for patients clinically and biopsy-proven node positive at breast-conserving surgery who remain pathologically node positive after NAC.
6. Shared decision-making processes should be put in place while we await mature clinical trial data, to enable patient value-based decision making.

C) SLNB Timing: before or after NAC

We recommend against performing lymph node sampling twice, before and after NAC. We recommend that SLNB be performed after NAC and not before in clinically node-negative patients who will receive NAC.

Qualifying Statements for Recommendation 4

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

- To enable patient value-based decision making, shared decision making processes should be put in place, and a decision aid could be developed while we await mature clinical trial data.
- To date, the clinical standards of care for node-positive patients who fail to respond clinically in the axilla to NAC require maximal therapy to the axilla, which includes ALND followed by loco-regional nodal irradiation.

Specific 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 single sentinel node tracer (e.g., it is not necessary to add blue dye on a regular basis for SLNB if the radiocolloid signal successfully identifies the sentinel node(s) in the axilla).

In cases of non-identification, blue dye can be added. Screening for radiocolloid signal prior to incision is recommended, and, in cases of non-identification, blue dye can be added prior to making the incision.

In patients who receive NAC, we recommend either placing a biopsy clip into the positive node at diagnosis and localizing it at time of surgery, or using dual tracer (radiocolloid plus blue dye).

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

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

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

C) US staging versus surgical staging

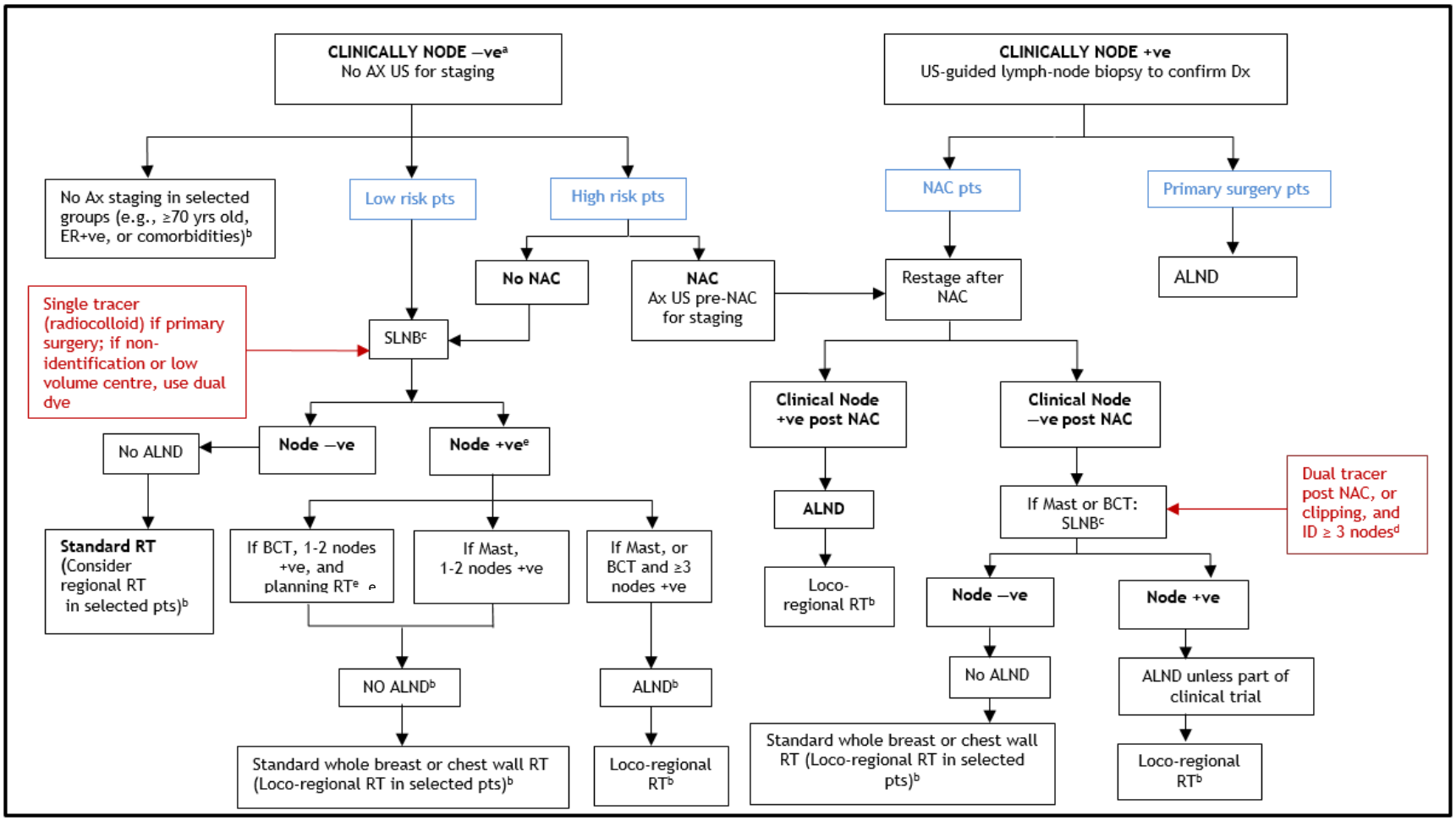
We recommend that diagnostic staging by US only (i.e., not confirmed by a biopsy) not be used instead of standard SLNB staging.

Qualifying Statements 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 (e.g. low volume centers, surgeons in training/post training).

B) If a clip is used to identify a biopsied lymph node at diagnosis, the node containing the clip needs to be localized to make sure it is excised. If dual tracer is used, three or more sentinel nodes have to be identified. If three or more sentinel nodes are not identified in a patient who has had NAC according to standard sentinel lymph node techniques, an axillary dissection is recommended.

Figure 1-1. Algorithm for the management of the axilla in patients with early-stage (clinical stage T1,T2, N0,N1 [Stage I to Stage IIB]) breast cancer



a Refers to all patients with no palpable axillary nodes on physical examination, including those who may have had an ultrasound that was equivocal, abnormal, or even biopsy-proven positive.
b Decision making should be made on a case-by-case basis, and include a patient centered approach, that is consider and discuss pros and cons of various options in light of patient's specific circumstances, values and preferences.
c Do not recommend SLNB before chemotherapy except in special circumstances after multidisciplinary discussion.
d Evidence supports the use of dual localizing tracer (blue dye and radio-isotopye) and harvesting ≥3 nodes or else do ALND to minimize false negative rate; any clipped positive nodes should be localized for surgery.
e In rare circumstances (e.g., a small T1aN1) it is possible to avoid radiation (see Justification of Recommendation 3D)

+ve = positive; -ve = negative; ALND = axillary lymph node dissection; Ax = axillary; BCT = breast conserving therapy; ER = estrogen receptor; HT = hormonal therapy; Mast = mastectomy; NAC = neo-adjuvant chemotherapy; pts = patients; RT = radiation treatment; SLNB = sentinel lymph node biopsy; US = ultrasound; yrs = years.

Management of the axilla in early-stage breast cancer

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

General Objectives:

To provide recommendations on the best strategies for the management, and on the best timing and treatment (surgical and radio-therapeutic) of the axilla in early-stage breast cancer.

Specific Objectives:

Specific objectives are listed before each recommendation.

TARGET POPULATION

These recommendations apply to patients with early-stage breast cancer (i.e., stages I, IIA, IIB; and prognostic groups T1, T2, N0, N1mi, N1, M0; and primary tumour size ≤5 cm).

INTENDED USERS

This guideline is targeted for:

1. General surgeons involved in the staging of early breast cancer and management of the axilla.
2. Radiation oncologists involved in the radiation treatment of patients with early-stage breast cancer.
3. Medical oncologists involved in the systemic treatment of patients with early-stage breast cancer.
4. Other clinicians involved in the management of women with early-stage breast cancer (e.g., pathologists, radiologists, oncology nurses, genetic counsellors).

DEFINITIONS:

1) A **patient-centred approach** involves considering each patient on a case-by-case basis, discussing pros and cons of various options with the patient, in light of her or his circumstances, values and preferences, and using a shared decision-making process for choosing treatment.
2) **Clinical versus pathological positivity:** We define a clinically positive axilla as clinically palpable disease where the determination is made by physical examination only. Pathological positivity means that metastatic cells are identified in the axillary nodes at histopathology, conducted either by fine needle or core biopsy at diagnosis, or postoperatively as a result of sentinel lymph node biopsy (SLNB), or axillary lymph node dissection (ALND). In this document, when we describe patients as positive or negative, we mean that they are pathologically positive or negative, unless otherwise specified.We do not consider lymph nodes to be pathologically positive if they only contain isolated tumour cells.
3) **Radiotherapy of the axilla:** Axillary radiation delivered by standard 2-field tangents to the breast/chest wall which will cover the level 1 and 2 lymph nodes in the axilla, without additional fields to the axilla as is utilized in loco-regional nodal radiation.
4) **Early-stage breast cancer** is defined by the US National Cancer Institute as breast cancer that has not spread beyond the breast or the axillary lymph nodes. This includes ductal carcinoma in situ (DCIS) and stages I, IIA, IIB, and IIIA breast cancers (https://www.cancer.gov/publications/dictionaries/cancer-terms/def/early-stage-breast-

cancer). For this report we excluded women with DCIS because they are stage 0 and should not require staging since the cells, by definition, do not spread beyond the basement membrane of the lactiferous duct. We did not include women with stage IIIA because stage III is considered locally advanced and it is covered by our Evidence-Based Series #1-19: "Loco-regional Therapy of Locally Advanced Breast Cancer" [1] available at: https://archive.cancercare.on.ca/common/pages/UserFile.aspx?fileId=334821.

5) **Cancer staging** definitions, see the American Joint Committee on Cancer (AJCC) manual, 8th edition, last updated 05 June, 2018, available at https://cancerstaging.org/references-tools/deskreferences/Documents/AJCC%20Cancer%20Staging%20Form%20Supplement.pdf [2]
6) Patients with negative nodes and with high-risk features are patients younger than 50 years of age, or premenopausal, or with primary tumour measuring ≥5 cm, or ≥2 cm with <10 axillary nodes removed and at least one of: grade III histologic categorization, estrogen-receptor negativity, or lymphovascular invasion (e.g., with triple-negative breast cancer).
7) In this document, loco-regional radiotherapy refers to whole breast, chest wall, and regional nodal basins irradiation.

SPECIFIC OBJECTIVES, RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

For all recommendations we recommend a patient-centred approach.

An algorithm for the management of the axilla in the patients with early-stage breast cancer is presented in Figure 2-1.

Specific objective 1: To determine which patients with early-stage breast cancer require axillary staging.

Recommendation 1
• For patients ≥70 years of age with clinically node-negative (T1N0) early-stage invasive breast cancer which 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 (SSO) available at: http://www.choosingwisely.org/clinician-lists/sso-sentinel-node-biopsy-in-node-negative-women-70-and-over/ that stated: "Don't routinely use sentinel node biopsy in clinically node negative women ≥70 years of age with early stage hormone receptor positive, HER2 negative invasive breast cancer" if they will be treated with hormonal therapy. If omission of SLNB is considered, a consultation with a medical oncologist can be considered before surgery to discuss hormonal therapy. • For patients <70 years of age without significant competing comorbidities, SLNB should be considered for axillary staging of early-stage breast cancer.
Qualifying Statements for Recommendation 1
• The information acquired from SLNB would be helpful in guiding adjuvant treatment decision making. • Patients should be evaluated on a case-by-case basis to ensure appropriate patient-centred 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 [5,6] by Liang et al. [7] concluded that omission of axillary staging by ALND in women of 70 years of age or older, with clinically negative axilla, resulted in increased risk of regional recurrence (relative risk [RR] 0.24, 95% confidence interval [CI], 0.06 to 0.95; I^2=0%; p=0.04), but did not impact overall, and breast cancer-specific mortality (RR, 0.99; 95% CI, 0.79 to 1.24; I^2=0%; p=0.92; RR 1.07; 95% CI, 0.72 to 1.57; I^2=0%; p=0.75, respectively).
Our update of the Liang et al. meta-analysis [7] with one additional study [8] confirmed these results for overall survival (OS) (hazard ratio [HR], 1.09; 95% CI, 0.85 to 1.39; p=0.5; I^2=0%), and for disease-free survival (DFS) (HR, 1.06; 95% CI, 0.81 to 1.38; p=0.69; I^2=0%). We could not pool the results for recurrence statistically because of differences in measurement of outcomes.
One of the included studies [5] 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% vs. 7%, p=0.00006), and restriction of movement (39% vs. 15%, p=0.000001) for the ALND group compared with the SLNB-only group (see Section 4 for detailed results).

We identified four ongoing clinical trials [9-12] comparing SLNB versus no axillary staging, and data will be forthcoming in the next several years.

Justification and Interpretation of the Evidence for Recommendation 1

Patient Values

Patients who receive management of the axilla face a very important risk of suffering significant morbidity from the treatment, which may not translate into a difference in survival for them. When recommending SLNB as a standard of practice, we took into consideration the adverse effects burden of this procedure, and the excess of treatment associated with more invasive surgery such as ALND. OS, DFS, and local control are considered critical outcomes; quality of life, and adverse effects are also important outcomes to patients.

Certainty of the Evidence

We considered the overall certainty of the existing body of evidence, as assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology, moderate to high for staging performed by ALND compared with no ALND.

No evidence is available at this time for staging by SLNB compared to observation, and we are awaiting the results of ongoing trials that will appear in the next several years.

Desirable, Undesirable Effects, and Balance of Effects

By choosing SLNB as the standard of practice, patients will experience a substantial reduction in adverse events, such as lymphedema, and sensory neuropathy, associated with staging performed by ALND for the same effect on OS and DFS. Therefore, in women with early-stage, clinically node-negative breast cancer, SLNB for axillary staging remains the standard of care.
This is true also for patients who have sonographically abnormal imaging with or without confirmatory biopsy. In fact, in our experience, the majority of these patients are most likely to have only one to two positive nodes, and therefore, they would be able to avoid completion axillary dissection according to ACOSOG Z0011 [13], had the ultrasound (US) not been performed.

Some patients may experience axillary recurrence if lymph node sampling is avoided; therefore, we suggest that this possibility be discussed and evaluated, according to individual patient's circumstances, values and preferences.

Applying the Choosing Wisely guideline to a patient should be made on a case-by-case basis. While omitting SLNB has no impact on survival, it is associated with an increased risk of recurrence. Therefore, patients' preferences should be balanced against their co-morbidities and competing risks for death. Avoiding SLNB is appropriate in these patients (i.e., low-risk women 70 years of age or older with hormone-positive early-stage cancer) according to the Choosing Wisely statement, given that there is no difference in OS.

While the CALGB 9343 trial 75 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 >70 years of age 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 as well as low rates of axillary recurrence. This finding supports our recommendation that sentinel node biopsy can be safely avoided in these patients.

Acceptability
At the present time, SLNB is the most acceptable option available. Loco-regional radiotherapy has been compared with no axillary treatment (e.g., the GRISO-053 trial [14]) in women who are clinically node negative; however, the majority of patients would have been pathologic node negative and exposed to radiation. Future research will provide further data on which patients this procedure can be omitted.

Generalizability
All the studies that met the inclusion criteria for this systematic review included women with early-stage breast cancer, of variable ages, and small tumours. The results can be generalized to the population of women with these characteristics. However, it is clinically reasonable to extend the same recommendations to men as long as their primary breast disease is early stage.

Specific objective 2: To determine whether any further axillary treatment is indicated for women with early-stage breast cancer who did not receive neoadjuvant chemotherapy (NAC) and are sentinel lymph node negative at diagnosis.

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 American Society of Clinical Oncology (ASCO) 2017 update guideline [3,4]). In some selected patients (e.g., patients with medially or centrally located tumours or with high-risk features), and using a patient-centred approach, it is reasonable to offer the option of loco-regional radiation to include at least the supraclavicular and ipsilateral internal mammary lymph nodes in addition to the breast and/or chest wall (see Qualifying Statement). For the majority of patients (i.e., node-negative patients whose tumours are not medial/central in location, and who do not have other high-risk features), however, we

cannot recommend loco-regional node irradiation. Risk-benefit discussion should be undertaken on a case-by-case basis for these patients (see Qualifying Statement).

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 (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 <18 or >80 years of age, were pregnant or lactating, were allergic to blue dye or radioisotope, had evidence of metastatic disease, had tumours >3 cm in diameter, suffered from chronic life-threatening diseases possibly preventing the use of adjuvant therapy, had stage T0 tumours, had multifocal tumours, or DCIS, and received previous NAC. For these patients, decisions regarding ALND should be made after discussion between the patient and clinicians on a case-by-case basis, depending on the invasive component of the lesion, other clinical circumstances and patient preferences.

Radiotherapy interventions

- Patients with central or medially located tumours may modestly benefit (<5%) from loco-regional irradiation compared with whole breast only (post lumpectomy) or no post-operative radiation (post-mastectomy) in terms of DFS, distant DFS, and loco-regional relapse, but not in terms of OS.
- Post-mastectomy patients with node-negative, triple-negative breast cancer who receive chemotherapy may benefit in DFS and OS from chest wall radiotherapy compared with no radiotherapy.
- A radiotherapy dose fractionation schedule of 50 Gy in 25 fractions over five weeks is the current standard schedule 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

SLNB is currently the standard of practice for this population.

We endorsed the recommendation from the ASCO 2017 update guideline [3,4] for surgical interventions in sentinel-node-negative patients. The systematic review that supports the ASCO guideline [3,4] went back further in time than this review did, and included women who were node negative and node positive at diagnosis. The authors included eight studies: the National Surgical Adjuvant Breast and Bowel Project (NSABP) B32 trial [15-17]; the Sentinella/Gruppo Interdisciplinare Veneto di Oncologia Mammaria (Sentinella/GIVOM) [18], the Canavese et al. trial [19]; the Royal Australasian College of Surgeons/Sentinel Node Versus Axillary Clearance (RACS/SNAC) trial [20,21]; and the Veronesi et al. (NCT00970983) trial [22]. Additionally, the Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial, and the Cambridge/East Anglia Study Group trial, which appeared before 2007, the cut-off date of this systematic review, were included.

The systematic search of the literature for this guideline, as well as the ASCO 2017 guideline update [3] did not uncover any new evidence that would change the 2014 ASCO recommendations [4] for this treatment for women who were negative at diagnosis.

Radiotherapy interventions

There are currently no published clinical trials of loco-regional radiation in exclusively pathologically node-negative patients. Two pivotal trials included a small portion of node-

negative patients [23,24]. The EORTC 22922/10925 trial [23] selected patients with centrally and medially located tumours who may be less likely to present with axillary node-positive disease. These patients may benefit more from loco-regional radiation. Among women who received ALND, the EORTC 22922/10925 trial [23] reported no statistically significant difference in OS at 10-year follow-up between patients who received loco-regional irradiation, in addition to whole breast and thoracic wall irradiation compared with those who received whole breast or thoracic irradiation alone: 82.3% vs. 80.7%, HR, 0.87; 95% CI, 0.76 to 1.0; p=0.06. However, a statistically significant difference in rate of death from breast cancer in favour of the loco-regional irradiation group was noted: 12.5% vs. 14.4%, HR, 0.82; 95% CI, 0.70 to 0.97, p=0.02.
The EORTC 22922/10925 trial [23] reported a better DFS (HR for disease progression, 0.89; 95% CI, 0.80 to 1.00, p=0.04), and distant DFS rate (78% vs. 75%, p=0.02) at 10-year follow-up for patients who had loco-regional node irradiation compared with those who did not.
The EORTC 22922/10925 trial [23] reported a statistically significant lower 10-year rate of first recurrence for patients who had received loco-regional irradiation compared with patients who did not (19.4% vs. 22.9%, p=0.02).
In the EORTC 22922/10925 trial [23] 44% of women had centrally and medially located tumours treated with mastectomy, or breast-conserving surgery and ALND; in addition, the majority of the patients received systemic therapy. In this trial [23], at 10 years follow-up, patients who received loco-regional irradiation experienced more pulmonary fibrosis (4.4% vs. 1.7%, p<0.001) than patients who received thoracic wall and whole breast irradiation. No statistically significant difference was detected for cardiac disease or cardiovascular death.
In the MA.20 trial [24] included 10% of the included patients had high-risk node-negative disease (9.7% [89 patients] in the whole breast irradiation [WBI] group and 9.6% [88 patients] in the WBI plus regional node irradiation [RNI] group).
The MA.20 trial [24] showed that RNI 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 [ER] status negative: 61.6% vs. 76.2; HR, 0.56; 95% CI, 0.39 to 0.81, p=0.04; progesterone receptor [PR] status negative: 70.5% vs. 81.9%, HR 0.57; 95% CI, 0.41 to 0.80, p=0.03) and distant DFS at 10 years (86.3% in the RNI group vs. 82.4% in the WBI group; HR, 0.76; 95% CI, 0.60 to 0.97, p=0.03).

Overall, 86.1% of patients in the study by Wang et al. of post-mastectomy radiotherapy for triple-negative breast cancer were reported to be node negative. [25]; 80.6% of patients were node negative in the arm receiving chemo-radiation therapy. Chest wall radiotherapy was compared with no radiation. RNI could be added as clinically indicated to the irradiation, typically, in patients with >2 pathologically positive axillary nodes, or with a percentage of positive axillary nodes >25%.
Chemotherapy included older cyclophosphamide, methotrexate, and 5-fluorouracil chemotherapy, with no details on the percentage of women receiving such chemotherapy.
This trial [25] provided some information on the subgroup of patients who are triple negative. These patients experienced better outcomes with chest wall radiation compared with no radiation: OS at five years (90.4% vs. 78.7%; HR, 0.79; 95% CI, 0.74 to 0.97, p=0.03), distant metastases (24.2% vs. 38.5%, for those with one to two distant metastases; 75.8% vs. 61.5% for those with >2 metastases, p<0.05), and relapse-free survival (88.3% vs. 74.6%; HR, 0.77; 95% CI, 0.72 to 0.98, p=0.02), with no statistically significant between-groups difference in neutropenia and nausea/emesis.
None of the included radiotherapy trials reported on quality of life.

Justification and Interpretation of the Evidence for Recommendation 2

Patient values

Surgical interventions
Patients are concerned with the possibility of overtreatment in those who have negative sentinel nodes. We agree with the ASCO recommendation not to perform ALND for women with negative sentinel nodes; that recommendation aimed at reducing overtreatment and its consequent burden of adverse effects.

Radiotherapy interventions
Patients may value the pros and cons of receiving axillary radiotherapy differently (e.g., adverse events that may present 20 years after treatment may not be so relevant to some patients while they may be of utmost importance to others; to some patients travel restrictions due to the time/length of daily radiotherapy treatment may also be important). Therefore, we issued a weak recommendation for this treatment, and recommended an in depth discussion between clinicians and patients of various aspects of each individual situation.

OS, DFS, and local control are considered critical outcomes; quality of life and adverse effects are also important outcomes to patients.

Certainty of the Evidence
The overall certainty of the evidence in support of this recommendation is moderate to low because of risk of bias, imprecision, and indirectness (there were no trials that included entirely node-negative patients, most patients had ALND, and the trial for triple-negative patients [25] used irradiation to the chest wall, while the axillary nodes were irradiated as clinically indicated) (see details in Section 4).

Patients may differ on how they value outcomes. Therefore, careful consideration of individual circumstances on a case-by-case basis is recommended.

Desirable Effects, Undesirable Effects, and Balance of Effects

Surgical interventions
The benefits of SLNB alone, as compared with SLNB and ALND, outweighed the morbidity of SLNB and ALND in women with negative nodes.

Radiotherapy interventions
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.

Acceptability
See Recommendation 1.

Generalizability
Surgical interventions
For male patients, refer to Generalizability statement in Recommendation 1.

Radiotherapy interventions
The included studies involved women of variable ages. Radiotherapy was delivered at a dose of 50 Gys in 25 fractions. Techniques may have improved since the time when the studies

were performed, and currently some fractionation schedules exist for accelerated whole breast radiation and partial breast radiation.

Specific 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 [3,4], Recommendation 2.1).

B) Radiotherapy of the axilla (loco-regional node irradiation) compared with no radiation to the loco-regional lymph nodes.
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/central tumours, and in patients with high-risk features. Discussion of pros and cons with patients needs to occur, and decisions should be made on a case-by-case basis.

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 tumours 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. Loco-regional radiation is a reasonable option, especially when there are high-risk features as in (B) above.

ALND and loco-regional radiation to the axilla is recommended if ≥3 sentinel lymph nodes are positive.

In patients who undergo mastectomy and have one to two positive nodes, post-mastectomy radiation (PMRT) to the chest wall and the axilla is recommended and ALND can be safely omitted. In patients declining PMRT (i.e., patients with immediate reconstruction), either radiation to the axilla without the chest wall or completion ALND can be considered.

In patients who undergo mastectomy and have ≥3 positive nodes, ALND followed by loco-regional radiation can be considered.

D) Radiotherapy compared with no treatment
In patients with unilateral invasive cancer of small size (i.e., T1a), favourable tumour features (e.g., ER positive [ER+] undergoing hormonal therapy), clear margins, and one to three positive nodes, treated with chemotherapy or hormonal therapy, clinicians might offer the option of omitting radiotherapy of the regional nodes.

Qualifying Statements 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 five years,

have bilateral breast cancer, have multicentric disease, have three or more positive sentinel lymph nodes, have a concomintant malignancy, previously received systemic therapy for breast cancer, received chemoprevention in the preceding year, have distant metastases or macrometastatic disease, have palpable axillary nodes, were <18 or >75 years old.

For these patients, as well as for patients who are treated with mastectomy, decisions regarding completion of ALND should be made after discussion between the patient and clinicians on a case-by-case basis depending on the invasive component of the lesion, other clinical circumstances, and patient preferences, taking into account the limited data specific to mastectomy and considering that these recommendations represent an extrapolation, based on expert opinion, from trials designed for patients undergoing breast-conserving surgery.

For a detailed description of patients who were included in the studies upon which this recommendation is based, see Appendix 7, Tables A to D.

The management of the axilla for patients with four or more positive lymph nodes (N2, N3 disease) falls outside the scope of this guideline. Please refer to Cancer Care Ontario PEBC guideline 19-1 guideline: "Loco-regional therapy of locally advanced breast cancer (LABC)" [1]. For exactly three positive lymph node there is not enough evidence to make a recommendation, therefore, we recommend proceeding with ALND and considering regional radiation.

B) Radiotherapy of the axilla (loco-regional node irradiation) compared with no irradiation to the loco-regional lymph nodes.
Patients with ER-negative and PR-negative (ER– and PR–) status may have a more favourable DFS when treated with loco-regional irradiation in addition to surgery.

C) Radiotherapy to the axilla compared with further surgery (ALND)
The ongoing MA39 (NCT00005957) study addresses the incremental benefit of loco-regional nodal irradiation of the axilla in lower-risk, node-positive patients. At this time, no studies comparing SLNB alone without loco-regional node irradiation have been identified in the mastectomy or lumpectomy setting.

D) Radiotherapy compared with no treatment
Patients 65 years of age 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 [3,4]. The ASCO guideline [3,4] was based on the evidence from two randomized trials, the Z0011 [13,26-28] and the IBCSG 23-01 [29,30]. These studies showed that SLNB was noninferior to ALND. We included the Schmidt-Hansen systematic review [31], which included the above trials, and an additional smaller study [32]. The results of the ATTRM-048-13-2000 study [32] point in the same direction as the previous evidence.

A subgroup analysis of the IBCSG 23-01 trial [29,30] 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 non-inferiority margin (HR, 0.52; 95% CI, 0.09 to 3.10), and the group without ALND was significantly (i.e., p<0.10) 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 undergo mastectomy, for women with multicentric tumours, and prior breast or axillary surgery (i.e., patients who were excluded from the studies that support Recommendation 3A). We believe that clinicians and patients should discuss the adantages and disadvantages of all options depending on the characteristics of the tumour, other clinical circumstances, and patient preferences.

B) Radiotherapy of the axilla (loco-regional node irradiation) compared with no irradiation to the regional lymph nodes.
At 9.5 years of follow-up the MA.20 trial [24] did not detect any statistically significant difference in OS between patients treated with whole breast plus regional irradiation and those treated with WBI alone (HR, 0.91; 95% CI, 0.72 to 1.13, p=0.38). 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 loco-regional node irradiation (HR, 0.76; 95% CI, 0.61 to 0.94, p=0.01).

The MA.20 trial [24] showed that patients with hormone receptor-negative status may have a better DFS at 10-year follow-up when treated with additional RNI than with WBI alone (ER-: 81.3% vs. 73.9%, HR, 0.69; 95% CI, 0.47 to 1.00, p=0.05, test for interaction: 0.08; PR-: 83.5% vs. 78.9%; HR, 0.76; 95% CI, 0.55 to 1.06, test for interaction: 0.20).

Patients in the RNI group experienced more pneumonitis and radiation dermatitis than patients in the WBI group (1.2% vs. 0.2%, p=0.01, and 49.5% vs. 40.1%, p<0.001, respectively).

No data on loco-regional nodal radiation versus none in patients who only had SLNB are available. We are awaiting results from the ongoing MA-39 trial. Despite all MA-20 patients [24] having had axillary dissection in node-positive patients, benefit was modest (breast cancer-specific mortality at 10 years was 10.3% vs. 12.3%, HR, 0.80; 95% CI, 0.61 to 1.05, p=0.11): There was a 5% improvement in DFS at the cost of a small increase in pneumonitis (1.2% vs. 0.2% p=0.01), and worse grade 2 lymphedema rates for the RNI group (8.4% vs. 4.5%, p=0.001). Therefore, this recommendation is based on our expert opinion.

C) Radiotherapy to the axilla compared with further surgery (ALND)
The OTOASOR [33] and AMAROS [34-36] 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 results of the trials at five years have been presented and data on second cancers are available in two conference abstracts [37,38] that presented the 10-year results of the AMAROS trial [34-36], and showed equivalent local control, and OS, but a small increase in second breast cancers in the regional radiation arm.

The OTOASOR trial has been updated at eight years follow-up [39], and no changes in outcomes have been detected.

While awaiting the full publication of the MA39 (NCT03488693) trial, the recommendation about the use of radiation therapy in combination with surgery, is based on the expert opinion

of Working Group members. At this time, no studies comparing SLNB alone without loco-regional node irradiation have been identified in the mastectomy or lumpectomy setting.

D) Radiotherapy compared with no treatment
In older women, the studies [40,41], that compared radiotherapy of the loco-regional nodes with or without tamoxifen compared with tamoxifen alone, showed a benefit in 20-year recurrence rates (loco-regional recurrence rate: 5.3% radiotherapy + tamoxifen vs. 18.5% tamoxifen, p<0.001; recurrence rate of systemic disease: 40% vs. 50% respectively, p=0.047), with no difference shown in OS. As well, in younger women a benefit for loco-regional recurrence at 20 years (radiotherapy vs. cyclophosphamide: 3.5% vs. 13.9%, p=0.0071) 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 0% to 0.8% (p=0.04), and from 10.5% to 18.4% (p=0.005), respectively in pre- and postmenopausal women. In older women, mortality due to cerebrovascular disease increased from 3.4% to 8.7% with the addition of radiotherapy to hormonal therapy (p=0.015), while in premenopausal women there was no statistically significant difference when radiotherapy was administered with chemotherapy (cumulative cerebrovascular mortality: cyclophosphamide: 0.8% vs. radiotherapy + cyclophosphamide: 1.7%, p=0.52).

Justification and Interpretation of the Evidence for Recommendation 3

Patient Values
A) No further axillary surgery beyond SLNB compared with ALND
Patients highly value reduction in adverse events and quality of life outcomes when ALND is omitted.

B) Radiotherapy of the axilla (loco-regional nodal irradiation) compared with no irradiation to the loco-regional lymph nodes
Patients value the reduction in short-term adverse effects. Patients treated with WBI and additional loco-regional node irradiation experienced more short-term adverse effects than patients treated with WBI only. Patients also value survival, DFS, and local control. One study (MA.20 [24]) did not show a difference in survival, but did show improved DFS with the addition of loco-regional nodal irradiation. However, this came at the cost of an increase in severe short-term adverse events. There is no information about late adverse events, second cancers or quality of life. The addition of loco-regional node radiation may be an option for high-risk patients. Discussion of pros and cons with patients needs 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.

C) Radiotherapy to the axilla (loco-regional nodal irradiation) compared with further surgery (ALND)
Patients value the reduction in short-term adverse effects. Patients treated with axillary irradiation experienced less adverse events in the short term than those treated with ALND, and no evidence is available on second cancers as yet. No statistically significant difference was detected in quality of life at one or five years [34-36]. Even in patients with three or more positive sentinel lymph nodes (25% of patients in the AMAROS trial [34-36]), loco-regional radiotherapy was equivalent to ALND; thus, either treatment strategy is an option. However, radiotherapy has lower lymphedema risk and is, therefore,recommended.

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 loco-regional nodal irradiation of the axilla. At this time, no studies comparing SLNB alone without loco-regional node irradiation have been identified in the mastectomy or lumpectomy setting.

D) Radiotherapy compared with no treatment
Patients highly value a reduction in adverse events. Therefore, we suggest the omission of irradiation for older women. However, studies on which this recommendation is based [40-42] collected data from 1978 to 1985. The cardiac adverse events of radiotherapy that were seen at 25 years follow-up may not be as relevant for patients treated with modern radiotherapy techniques.

OS, DFS, and local control are considered critical outcomes for all comparisons; quality of life and adverse effects are also important outcomes to patients.

Certainty of the Evidence
The overall certainty of this body of evidence is considered to be moderate (see details in Section 4).

Desirable Effects, Undesirable Effects, and Balance of Effects

A) No further axillary surgery beyond SLNB compared with ALND
Benefits outweight harms for patients similar to those included in the trials reviewed for this guideline. The IBCGS 23-01 trial [29,30] examined a subgroup of patients treated by 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, who experienced a very small number of events. We consider this evidence insufficient to be able to generalize to all women who are treated by 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.

B) Radiotherapy of the axilla (loco-regional node irradiation) compared with no irradiation to the loco-regional lymph nodes.
Not all patients will agree on the balance of benefits and harms based on the evidence available to date. No data are available on quality of life, and some groups of patients may benefit more than others.

C) Radiotherapy to the axilla compared with further surgery (ALND)
No statistically significant between-group difference was noted in both the OTOASOR [33] and the AMAROS [34-36] trials for OS, DFS, and recurrence in the axilla. Short-term (i.e., 0 to 11 months) adverse events were not reported. The AMAROS trial [34-36] 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 quality of 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 favour of the radiotherapy treatment.

D) Radiotherapy compared with no treatment
Adding radiotherapy of the loco-regional nodes demonstrated a reduction in recurrence at 20 years, but did not change survival in the studies of older and younger women included here [40,41], and there was a benefit in recurrence at 20 years. The adverse events of radiotherapy with current technologies might be less than what is documented in the trials, but there is no evidence of this as yet.

Acceptability
A) No further axillary surgery beyond SLNB compared with ALND
SLNB is acceptable as it is a less-invasive intervention than ALND.

B) Radiotherapy and surgery (ALND, SLNB) compared with no irradiation to the loco-regional lymph nodes
Some patients, particularly those who undergo 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.

C) Radiotherapy compared with further surgery (ALND) and D) Radiotherapy compared with no treatment
Some patients may consider radiotherapy interventions acceptable, and others less so.

Generalizability
A) No further axillary surgery beyond SLNB compared with ALND
The generalizability of this recommendations is limited to women similar to those in the included trials. For male patients, refer to Generalizability statement in Recommendation 1.

B) Radiotherapy of the axilla (loco-regional node irradiation) compared with no irradiation to the loco-regional lymph nodes.
This recommendation is generalizable to women with fewer than three positive sentinel lymph nodes.

C) Radiotherapy to the axilla compared with further surgery (ALND)
The OTOASOR and AMAROS trials randomized women after SLNB. Therefore, the results are applicable to patients with early-stage breast cancer found in clinical practice.

D) Radiotherapy compared with no treatment
This recommendation is generalizable to women with the same characteristics as those included in the studies that form its evidentiary basis.

Specific objectives 4: to determine what axillary treatment is indicated and what is the best timing of treatment for women with early-stage breast cancer treated with NAC.

Recommendation 4
A) Initially node-negative patients Patients who are initially clinically node negative on physical examination, and those who had clinically suspicious nodes on physical examination but deemed to be pathologically

negative at fine needle aspiration/core needle biopsy, and have been treated with NAC, should have SLNB at the time of surgery as their axillary staging procedure.

B) Initially node-positive patients

1. For patients who were initially clinically and biopsy-proven node positive, and who remained clinically node positive after NAC, we recommend ALND.
2. 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 SLNB, or, in institutions where the use of biopsy clips for nodes is not available, by performing SLNB with dual tracer and excising at least excising three sentinel nodes in order to minimize the false negative rate and optimize accuracy of the procedure. At this time, we also recommend loco-regional radiation for these patients, regardless of pathologic status of sentinel lymph nodes.
3. Post-mastectomy patients who are node positive on surgical pathology after NAC can be offered PMRT after a completion ALND.
4. We recommend loco-regional nodal irradiation for post-mastectomy node positive patients after NAC while awaiting data from ongoing trials (i.e., the MAC19 study).
5. We recommend loco-regional irradiation after ALND for patients clinically and biopsy-proven node positive at breast-conserving surgery who remain pathologically node positive after NAC.
6. Shared decision-making processes should be put in place while we await mature clinical trial data, to enable patient value-based decision making.

C) SLNB Timing: before or after NAC

We recommend against performing lymph node sampling twice, before and after NAC. We recommend that SLNB be performed after NAC and not before in clinically node-negative patients who will receive NAC.

Qualifying Statements for Recommendation 4

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

- To enable patient value-based decision making, shared decision making processes should be put in place, and a decision aid could be developed while we await mature clinical trial data.
- To date, the clinical standards of care for node-positive patients who fail to respond clinically in the axilla to NAC require maximal therapy to the axilla, which includes ALND followed by loco-regional nodal irradiation.

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, therefore, this recommendation is based on clinical expertise.

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

Krug et al. [43] reported that patients who were clinically node-negative at diagnosis, treated with NAC and mastectomy, showed similar results with or without PMRT.

The evidence available at this time for surgical interventions is from a non-randomized, retrospective study [44] that compared 386 patients in five groups. See Section 4 for detailed results.

The currently available evidence for radiotherapy interventions is from a very large (N=15315) retrospective cohort trial with a 39-month follow-up [45], and a retrospective analysis of three randomized trials with a 51.5-month follow-up [43]. In the Rusthovenet et al. trial [45], patients treated with mastectomy and NAC who received PMRT (with or without loco-regional node irradiation) had a significantly better OS compared with patients who did not recive 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=0.014; 80% of patients who were node positive after NAC survived with PMRT compared with 76% without: HR, 0.845; 95% CI, 0.738 to 0.968, p=0.015. In patients treated with breast-conserving surgery, the Rusthoven et al. trial [45] showed that adding loco-regional node irradiation did not provide a statistically significant OS benefit; among patients who were node negative after NAC, 93% survived with breast and loco-regional node irradiation compared to 92% with breast irradiation: HR, 1.028; 95% CI, 0.716 to 1.477, p=0.880; among patients who were node positive after NAC 84% were alive with breast and loco-regional irradiation and 85% survived with just breast irradiation: HR, 0.962; 95% CI, 0.785 to 1.175, p=0.704. The Krug et al. trial [43] included only women treated with mastectomy; in the subgroup of patients with T1-T2 tumours PMRT did not improve loco-regional recurrence (HR, 0.94; 95% CI 0.45 to 1.95, p=0.86).

We are aware of two ongoing randomized trials: the MAC.19 trial (clinicaltrials.gov identifier NCT01901094), that will be completed in 2024, and the RTOG 1304/NSABP B51 trial (NCT01872975), that will be completed in 2028 with first data available in 2023. The MAC.19 trial is comparing ALND with RNI 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 RNI after mastectomy compared with no radiation, or breast irradiation and RNI 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 [46] evaluated timing of SLNB in relation to NAC. Arm B of this trial, that was stopped early, examined SLNB prior to NAC for clinically node-negative patients, and repeated again after NAC. In this cohort, the second SLNB was associated with low overall identification rate (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).

Justification and Interpretation of the Evidence for Recommendation 4

Patient Values

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, 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, as well as the role of clips, remain 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.

Certainty of the Evidence
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 becomes available, the recommendation will be updated as soon as possible (see Section 3 for details). The certainty of this evidence for SLNB compared to ALND in patients who were node positive at diagnosis is low to very low. The certainty of the evidence for radiotherapy interventions compared to no intervention is moderate because of risk of bias, indirectness, and imprecision (see Section 4 for details).

Desirable Effects, Undesirable Effects, and Balance of Effects
The benefits of the recommended course of action outweight 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.

Given the absence of data to guide management, for those patients who are initially clinically and biopsy-proven node positive, we consider loco-regional nodal irradiation the safest approach. In patients who receive NAC and remain node positive, the current standard is to recommend ALND with loco-regional radiotherapy. Data from ongoing studies may change this practice.

The studies that we included in this systematic review do not report data on the adverse effects of ALND, and of radiotherapy. However, the adverse effects of ALND, such as lymphedema, and limitation in range of arm motion are well known. This knowledge prompted us to issue the recommendation for patients who were initially clinically node negative.

With regards to the 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 loco-regional 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 based on this guideline. This is consistent with an evolving clinical practice leading towards loco-regional and systemic management decisions based on residual disease after NAC rather than decisions based soley 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

Acceptability
We consider the proposed intervention acceptable to the majority of the patients.

Generalizability
These recommendations are generalizable to women who are initially node positive or negative. For male patients, refer to Generalizability statement in Recommendation 1.

Specific 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 single sentinel node tracer (e.g., it is not necessary to add blue dye on a regular basis for SLNB if the radiocolloid signal successfully identifies the sentinel node(s) in the axilla).

In cases of non-identification, blue dye can be added. Screening for radiocolloid signal prior to incision is recommended, and, in cases of non-identification, blue dye can be added prior to making the incision.

In patients who receive NAC, we recommend either placing a biopsy clip into the positive node at diagnosis and localizing it at time of surgery, or using dual tracer (radiocolloid plus blue dye).

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

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

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

Qualifying Statements 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 (e.g. low volume centers, surgeons in training/post training).

B) US guided staging versus surgical staging
If a clip is used to identify a biopsied lymph node at diagnosis, the node containing the clip needs to be localized to make sure it is excised. If dual tracer is used, three or more sentinel nodes have to be identified. If three or more sentinel nodes are not identified in a patient who has had NAC according to standard sentinel lymph node techniques, an axillary dissection is recommended.

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. [47] reported an anaphylaxis rate of 0.3%, and a skin tattooing rate of 0.6% with blue dye.

The SENTINA trial [46] reported that, when SLNB was performed before NAC, no difference was observed between identification rate with the combination of radiocolloid and blue dye (dual tracer) and radiocolloid alone (single tracer) (99.5% [399 of 401] vs. 98.8% [573 of 580], p value: not reported*)*. When SLNB was done after NAC, the addition of blue dye was associated with a significant increase in identification rate; 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 identification rate 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 identification rate was 87.8% with dual tracer (144 of 164) versus 77.4% with single tracer (301 of 389), p values: 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=0.046. This study included approximately 6% of patients with stage T3-T4 disease and 14% of patients for whom the clinical size of the tumour was unknown, making this evidence partially indirect.

Tausch et al. [48] reported an identification rate 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. [49] reported no statistically significant difference in identification rate 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=0.180.

In patients who did not receive NAC, Nathanson et al. [50] reported that the identification rate 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<0.0001).

The SENTINA trial [46] reported no statistically significant difference in false negative rate for single versus dual tracer. The American College of Surgeons Oncology Group (ACOSOG) Z1071 trial [51] reported no statistically significant difference in false negative rate for dual tracer (10.8%) compared with single tracer (20.3%), p=0.05. The SN-FNAC trial [52] also reported no statistically significant difference between dual tracer (5.2%) and isotope only (16%), p=0.190.

Hunt et al. [53] showed a statistically significant lower false negative rate with blue dye combined with radiocolloid compared with blue dye alone (OR, 2.61; 95% CI, 0.78 to 8.76, p<0.0001).

Gimbergues et al. [54] reported that factors impacting false negative rate when radiocolloid alone was used were larger tumour size (5.7% for T1-T2 vs. 28.5% for T3 cases, p=0.045) and positive clinical lymph node status before NAC.

B) US-guided staging versus standard guided (dye/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 Verheuvel et al.

population study [55] reported on OS, but the study was considered at critical risk of bias and its results not suitable to support our recommendation. Kramer et al., 2016 [56], Kim et al., 2016 [57], and Cools-Lartigue et al., 2013 [58] reported variable false negative rates. The false negative rate was 6.4% (137 of 2130 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 patient direct outcomes. Stachs et al. [59] 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 false negative rate of axillary US was 23% (87 of 378 patients). Nodal metastases ≤10 mm was an independent predictor for false negative axillary US (OR, 2.66; 95% CI, 1.81 to 3.91, p=0.001).

Justification and Interpretation of Evidence for Recommendation 5

Patient Values
Patients value reduced potentially life-threatening adverse effects, and expect a test with high positive identification rate and low false negative rate.

Certainty of the Evidence
A) Single tracer compared with dual tracer
For outcomes such as survival, disease control, and quality of life the certainty of the evidence can be considered low for this comparison for all patients.

For identification rate and false negative rate the certainty of the evidence for patients treated with NAC can be considered moderate. The studies for these outcomes are at an unclear or high risk of bias. A small portion of the included patients have T3-T4 disease and therefore, the evidence is indirect to a certain extent. The studies generally had a large sample size; however, event rates could be very small (e.g., false negative rate with dual tracer: 5.2% [3 of 58 patients] [52], false negative rate with isotope only: 16.0% [4 of 25 patients]) [46], giving way to imprecision.

The included studies consistently indicated no difference between single and dual tracer. A caveat should be made in regard to confounding factors such as the expertise of the surgeon, with less experienced surgeons reaching a lower identification rate with a single tracer.

The certainty of the evidence for patients who did not receive NAC was moderate to low. The studies included were of high [47,60] or unclear [50] risk of bias. Reported results were inconsistent (e.g., Nathanson et al. [50] reported a higher identification rate for dual compared with single tracer, while Kang et al. [60] 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.

B) US-guided SLNB compared with traditional 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 [55] was considered at critical risk of bias. The other studies [56-58,61] reported on accuracy outcomes, which are an indirect measure. The three studies that reported on false negative rates [57,58,61] had very small sample sizes. We did not pool the results into a meta-analysis because the studies were heterogeneous. False negative rates were higher in studies with smaller sample size. Inconsistencies in the results may be partly

due to different definitions of false negative rate used in the studies. It is not possible to exclude publication bias.

C) US compared with SLNB
The Stachs et al. trial [59] 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 Stachs et al. trial [59] was a single study with 470 patients. Therefore, this body of evidence can be considered imprecise. It is not possible to exclude publication bias.

Desirable Effects, Undesirable Effects, and Balance of Effects
A) Single tracer compared with dual tracer
Blue dye has been linked to anaphylactic reactions, and no statistically significant advantage has been demonstrated in terms of false negative rate by using dual tracer in patients having surgery first before NAC.

Most included studies reported very similar identification rates with single or dual tracer.

When considering all the data, we recommend the use of dual tracer when performing a SLNB after NAC in order to optimize the identification rate, and minimize the false negative rate 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.

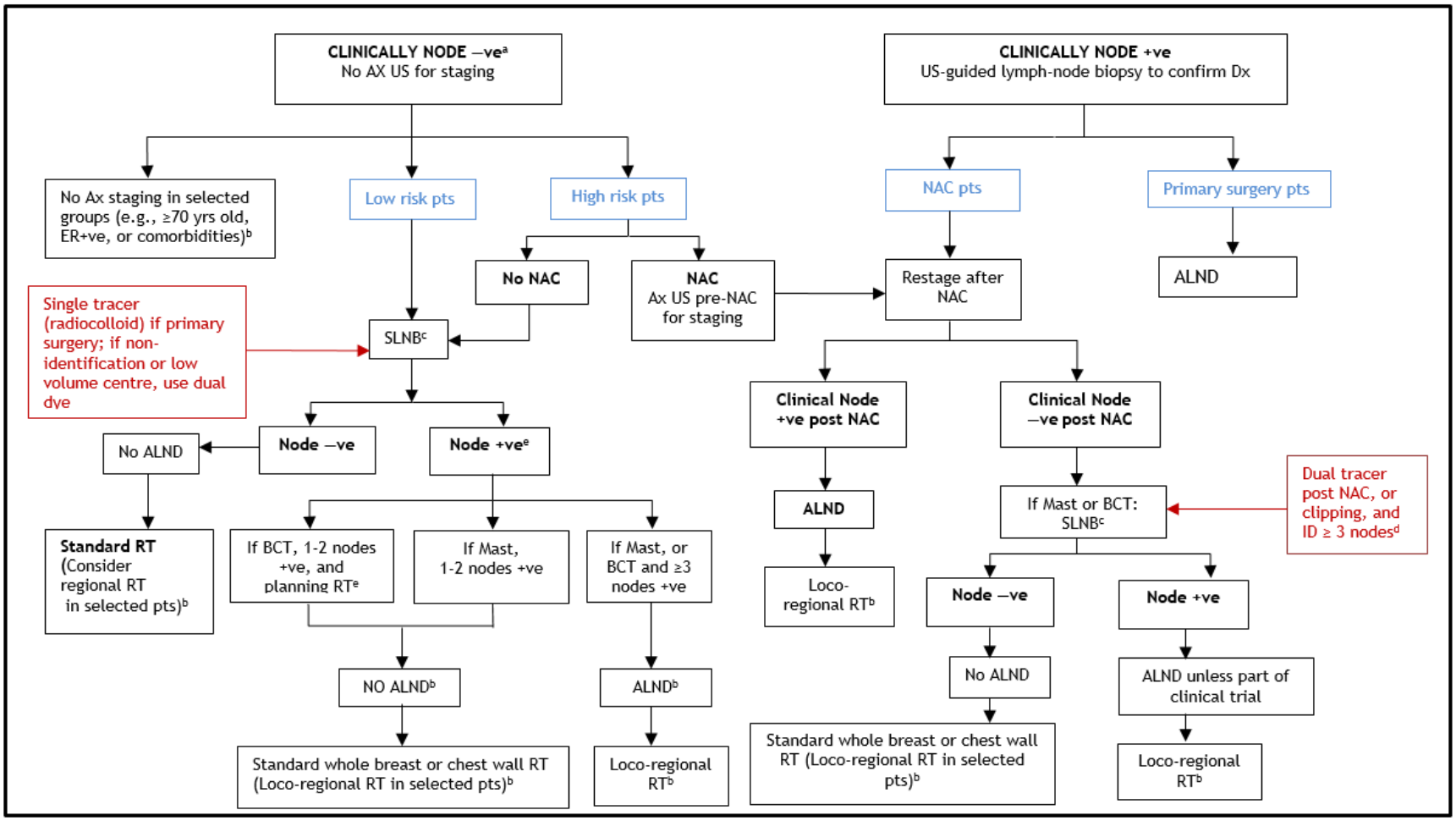
B) US-guided staging versus standard guided (dye/isotope) staging
Axillary US and fine needle biopsy preoperative staging in clinically node-negative patients (especially those with tumours <3 cm) may lead to increased morbidity from more axillary surgery and clinical upstaging to node positive at diagnosis, while these patients might otherwise have been eligible to SLNB alone according to the Z0011 trial [26-28] if the US had not been performed. Therefore, we did not recommend US staging of the axilla in these patients. For patients with stage T3-T4 tumours the likelihood of axillary disease is greater, and recommendations relative to this population are provided in the "Loco-regional therapy of locally advanced breast cancer (LABC), PEBC series 1-19" guideline [1].

C) US staging versus surgical staging
No data are available on patient direct outcomes. The relatively high false negative rate of axillary US, particularly for smaller-size metastases, is the reason for our recommendation.

Acceptability
The Working Group members and the patient representatives consider the proposed interventions acceptable to the majority of the patients.

Generalizability
These recommendations are generalizable to node-positive or negative women, whether they had received treatment with NAC or not. For male patients, refer to Generalizability statement in Recommendation 1.

Figure 2-1. Algorithm for the management of the axilla in patients with early-stage (clinical stage T1,T2, N0,N1 [Stage I to Stage IIB]) breast cancer



a Refers to all patients with no palpable axillary nodes on physical examination, including those who may have had an ultrasound that was equivocal, abnornal, or even biopsy-proven positive.
b Decision making should be made on a case-by-case basis, and include a patient-centred approach; that is, consider and discuss pros and cons of various options in light of patient's specific circumstances, values and preferences.
c Do not recommend SLNB before chemotherapy except in special circumstances after multidisciplinary discussion.
d Evidence supports the use of dual localizing tracer (blue dye and radio-isotopye) and harvesting ≥3 nodes or else do ALND to minimize false negative rate; any clipped positive nodes should be localized for surgery.
e In rare circumstances (e.g., a small T1aN1) it is possible to avoid radiation (see Justification of Recommendation 3D)

+ve = positive; -ve = negative; ALND = axillary lymph node dissection; Ax = axillary; BCT = breast conserving therapy; ER = estrogen receptor; HT = hormonal therapy; Mast = mastectomy; NAC = neo-adjuvant chemotherapy; pts = patients; RT = radiation treatment; SLNB = sentinel lymph node biopsy; US = ultrasound; yrs = years.

IMPLEMENTATION CONSIDERATIONS

Although we did not limit our search to female patients with early-stage breast cancer, all the available evidence at this time includes solely female patients, and no evidence was available for men. Therefore the recommendations presented here are generalizable only to female patients. However, it is clinically reasonable to extend the same recommendations to men as long as their primary breast disease is early stage.

FEASIBILITY

Recommendation 1

Offering SLNB to selected low-risk patients with early-stage breast cancer is feasible to implement as this is the current standard of care. There are no current barriers to implementing SLNB for early-stage, clinically node-negative patients as SLNB is available in all hospitals performing breast surgery.

Recommendation 2

Both radiotherapy and surgical interventions are feasible. SLNB is the standard of care in node-negative patients. Both SLNB and radiotherapy are current clinical standards, and this can be considered an enabler to this recommendation.

Recommendations 3 and 4

The surgical options for all comparisons are feasible. Potential feasibility concerns exists for the delivery of radiotherapy to those patients who may live far away from a radiation centre, and had chosen mastectomy to limit the risk of needing post-operative radiation. In those cases, there is a possibility of patient and physician resistance to the recommendation for adjuvant radiation treatments – especially if the case was at borderline-risk level.

We consider omission of completion ALND, in patients with one or two positive nodes who are planned to undergo radiation, 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. Timing sentinel node biopsy after 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 prior to this guideline. The role of NAC has been well established in breast cancer but the paradigm shift to make surgical and radiation clinical decisions based on 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.

Barriers to implementation of these recommendations may be clinicians in any of the relevant specialties (surgery, radiation, medical oncology) who are accustomed to historical methods of care rather than decision-making based on response to NAC. Clinicians may need to acquaint themselves with the medical literature referenced in this guideline.

Recommendation 5

Methods and timing of SLNB are feasible to implement.

The clarification that dual tracer (radiocolloid and blue dye) should be used after NAC to minimize the false-negative and non-identification rates represents a change to the standard of care.

There are no perceived barriers to implementation of these recommendations.

EQUITY

Recommendations 1 and 2

Application of the recommendation on a case-by-case basis and consideration of comorbidities will reduce risk of increased morbidity, especially in vulnerable, older women. The suggested intervention can be cost-saving, as well as sparing patients the suffering associated with the consequences of a more invasive surgical procedure.

Recommendations 3, 4, and 5

No impact on health equity is expected.

PATIENT CONSIDERATIONS

Recommendations 1 and 2

It is anticipated that most patients would view the recommendations as acceptable, and that the outcomes valued by clinicians align with the outcomes valued by the patients.

Recommendations 3, and 4

It is anticipated that there will be variability in the way patients will view these recommendations as acceptable, and that the outcomes valued by the clinicians will align with the outcomes valued by the patients.

Recommendation 5

It is anticipated that patients and clinicians will view the recommendation as acceptable, and that the outcomes valued by physicians will align with the outcomes valued by patients.

PROVIDER CONSIDERATIONS

Recommendations 1, 2, and 3

We believe that these recommendations will be accepted by most providers for implementation.

These recommendations align with current practice, and with norms within the clinical community.

No additional training is required for providers.

Recommendation 4

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. This recommendation aligns with the norms within the expert breast clinical community. No additional training would be required.

Recommendation 5

This recommendation aligns with current practice and with the norms within the clinical community and does not require additional training.

SYSTEM CONSIDERATIONS

All Recommendations

These recommendations would not require any significant changes in the current system, or its organization. It is anticipated that the implementation of these recommendations will not be costly.

RELATED GUIDELINES

Brackstone M, Fletcher GG, Dayes IS, Madarnas Y, SenGupta SK, Verma S. Loco-regional therapy of locally advanced breast cancer (LABC). Program in Evidence-Based Care Evidence-Based Series No.: 1-19. Toronto, On: Ontario Health (Cancer Care Ontario); 2014 [PMC4381791]. Available from: http://www.current-oncology.com/index.php/oncology/article/download/2316/1689.

Lyman GH, Somerfield MR, Bosserman LD, Perkins CL, Weaver DL, Giuliano AE. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology Clinical practice guideline update. J Clin Oncol. 2017;5(35):561-4 JCO2016710947.

Management of the axilla in early-stage breast cancer

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Ontario Health (Cancer Care Ontario). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of OH (CCO) supported by the Ontario Ministry of Health (OMH). All work produced by the PEBC is editorially independent from the OMH.

JUSTIFICATION FOR GUIDELINE

- There is variation in practice regionally across Ontario. It is possible that the results of the Z0011 study [13], stating that the 10-year OS of women with early-stage breast cancer and one or two positive sentinel lymph nodes treated with SLNB is noninferior to the OS of those treated with ALND, are often applied in practice to women who would have not been included in the original study [62].
- Previous guidelines for practice in Ontario [63,64] are outdated and new studies have been published that could change recommendations.
- Additional guidance is needed on this topic to guide radiology with respect to practice and reporting.
- Additional guidance is needed on this topic for the management of the axilla in the increasing number of patients treated with NAC.
- Experts identified that this topic is subject of discussion at all multidisciplinary disease site rounds across institutions.

GUIDELINE DEVELOPERS

This guideline was developed by the Management of the Axilla in Early Breast Cancer Guideline Developing Group (MAEBCGDG) (Appendix 1), which was convened at the request of the Breast Cancer Advisory Committee.

The project was led by a small Working Group of the MAEBCGDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations and responding to comments received during the document review process. The Working Group had expertise in radiation oncology, surgical oncology, medical oncology, radiology, pathology, and health research methodology. Other members of the MAEBCGDG, with expertise in radiology, radiation oncology, surgical oncology, genetic counselling, medical oncology, and general surgery, served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are

summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

In the planning stage of this guideline, the PEBC and ASCO determined there would be benefit to develop the guideline in collaboration. The PEBC took the lead position, providing methodological resources and support throughout the project and ASCO participated in the PEBC guideline development process. ASCO nominated four additional members to the Expert Panel (all of which agreed to participate) as well as suggested some of the external reviewers. Both the PEBC and ASCO guideline approval panels reviewed the draft guideline (see below). Additional details regarding the Expert Panel and the review process are given in Section 5.

PATIENT AND CAREGIVER-SPECIFIC CONSULTATION GROUP

Eight patient representatives (including one nominated by ASCO) participated as Consultation Group members for the MAEBCGDG. Patient representatives reviewed copies of the project plan and of the draft recommendations, and provided feedback on their comprehensibility, appropriateness and feasibility to the Working Group's Health Research Methodologist (FB). The Health Research Methodologist relayed the feedback to the Working Group for consideration.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [65,66]. This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [67] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence-base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine if an existing guideline could be adapted or endorsed. To this end, the following sources were searched, using relevant guideline search terms combined with breast cancer and axilla related terms, for existing guidelines that addressed any of the research questions: practice guideline databases (i.e., **Inventory of Cancer Guidelines:** https://www.partnershipagainstcancer.ca/tools/cancer-guidelines-database/ **National Guideline Clearing House:** http://www.guideline.gov/**; CMAJ Infobase:** https://www.cma.ca/En/Pages/clinical-practice-guidelines.aspx**),** guideline developer websites (i.e., **NICE (UK)** – NICE Guidance; **SIGN (UK)** – SIGN Guidelines; **ASCO (US)** – ASCO Guidelines; **National Health and Medical Research Council (Aus)** – Cancer Guidelines)**,** and other sources (i.e., electronic databases such as MEDLINE, EMBASE).

Selection of Guidelines

We included guidelines published in English and updated no earlier than three years prior to our initial search conducted in 2017 because we considered guidelines three years old or older out-of-date. The search for existing guidelines yielded 10 guidelines in 11 publications [1,3,4,62,64,68-73].

Assessment of guidelines

Guidelines were considered for endorsement if the Working Group answered yes to the following questions

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

The ASCO guideline [3,4] 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 (FB and NV) with the AGREE II tool [67]. Discrepancies were resolved by discussion and consensus. Table 3-1 presents the results of the quality rating of the ASCO guideline [3,4]. Details of this assessment are reported in Appendix 5A.

Table 3-1. Results of AGREE II Tool [67] quality rating for the included guideline

Guideline	AGREE II Domain Scores					
	Scope and Purpose	Stakeholder Involvement	Rigour of Development	Clarity and Presentation	Applicability	Editorial Independence
ASCO 2014, 2017 [3,4]	92%	89%	95%	100%	52%	96%

ASCO = American Society of Clinical Oncology

DESCRIPTION OF ENDORSED GUIDELINES

The ASCO guideline [3,4] covered a subset of the interventions focus of this guideline (i.e., SLNB and ALND). The ASCO guideline was based on a systematic review [3,4] that went back in time further than this systematic review, and included women who were node negative and positive at diagnosis.

The ASCO authors' [3,4] Clinical Question 1: "Can ALND be avoided in patients who have tumour-free (ie, negative) findings on SNB?" is a subset our Question 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 (i.e., radiation or surgery) indicated?" The ASCO Recommendation 1: "Clinicians should not recommend ALND for women with early-stage breast cancer who do not have nodal metastases" was endorsed for a subset of our Recommendation 2.

The ASCO authors' [3,4] Clinical Question 2: "Is ALND necessary for all patients with metastatic findings on sentinel lymph node biopsy?" is a subset of our Question 3a: "For women with early-stage breast cancer who did not receive NAC and are pathlogically sentinel lymph node positive at diagnosis: a. Which axillary strategy is indicated?" The ASCO recommendation 2.1: "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" was endorsed for a subset of our Recommendation 3.

ENDORSEMENT PROCESS

We agreed to endorse ASCO recommendations 1, and 2.1 for surgical interventions only after it was ascertained that no new evidence was available that would change these

recommendations, and that these recommendations met the values and preferences of patient representatives and clinicians.

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel. As part of the collaboration with ASCO, the ASCO Guideline Review Panel was also required to approve the document before it could be released as a joint PEBC-ASCO guideline. Due to differences in structure of PEBC/OH (CCO) and ASCO guidelines, the ASCO Guideline Review Panel approved a draft document with the same content and recommendations but formatted as an ASCO guideline prepared in accordance with ASCO and *Journal of Clinical Oncology* requirements.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey.

DISSEMINATION AND IMPLEMENTATION

The guideline will be published on the OH (CCO) website and may be submitted for publication to a peer-reviewed journal. The Professional Consultation of the External Review is intended to facilitate the dissemination of the guideline to Ontario practitioners. Section 1 of this guideline is a summary document to support the implementation of the guideline in practice. OH (CCO)-PEBC guidelines are routinely included in several international guideline databases including the CPAC Cancer Guidelines Database, the CMA/Joule CPG Infobase database, NICE Evidence Search (UK), and the Guidelines International Network (GIN) Library. We have added an algorithm to help clinicians to use the recommendations easily.

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- Norma Varela for assessing the ASCO guideline [3,4] with the AGREE II tool [67].
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Management of the axilla in early-stage breast cancer

Section 4: Systematic Review

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 [74], but axillary dissection (full lymph node clearance of the first and second levels of the axilla) was associated with significant morbidity (i.e., lymphedema, dysesthesias). Sentinel lymph node biopsy, which is an excision of the first tier of axillary nodes as a representative sample of the axillary stage, became the standard of care for axillary staging in Canada in 2009 with the Cancer Care Ontario guideline by George et al. [63]. Patients with clinically negative axillae are appropriate for SLNB. Some centres have used axillary US as an adjunctive imaging modality to assess the axilla at diagnosis. Suspicious appearing lymph nodes clinically or sonographically undergo needle biopsy (core needle biopsy or fine needle aspiration biopsy) with image guidance. Over the ensuing decade, the standard of care for patients found to have a pathologically positive sentinel lymph node was to undergo a completion ALND, with the resultant morbidity risks outlined above.

More recently, data emerged to suggest that a completion axillary node dissection for patients with positive nodes from SLNB did not confer an improved survival or regional recurrence benefit [13,36]. Therefore, in a selective cohort of non-high-risk tumours (ER+, no gross extranodal extension, up to two nodes positive, tumour size <3 cm, and planned adjuvant radiation), positive sentinel nodes were no longer being followed by axillary dissection. At the same time a Canadian trial (MA20) [24] found that loco-regional radiation for node positive or high risk node negative after axillary dissection conferred a DFS advantage. Therefore, there has continued to be clinical confusion regarding the benefit of loco-regional radiation, whether it can supplant the completion axillary dissection, and how to synthesize both of these trials. Given the breast cancer population heterogeneity, there are always patients presenting with variations on the theme (slight extranodal extension, high grade, 2 versus 3 positive nodes, etc.), and the indications for avoiding completion axillary dissection is ever expanding without clear data. Additionally, trials are ongoing: the NSABP B51 [75] and the Alliance/MAC19 (NCT01901094) are looking to further de-escalate the axillary surgery for patients who are biopsy proven lymph node positive at diagnosis, who then undergo NAC and are rendered clinically sentinel node negative. Positive nodes are being randomly assigned axillary dissection versus loco-regional radiation, and negative nodes are being randomly assigned to loco-regional radiation versus no treatment.

Given the new mounting evidence around axillary staging, (including improved and novel imaging techniques that might have the sensitivity to supplant SLNB for axillary staging), we, as the Working Group of the Breast Advisory Group, 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 or de-escalating unnecessary treatment but supporting effective or necessary treatment fits the mandate of OH (CCO), which is why we decided to pursue this systematic review and clinical practice guideline. Based on the objectives of this guideline (Section 2), we derived the research questions outlined below. This review has been registered in PROSPERO (https://www.crd.york.ac.uk/prospero/) with the number CRD42017056859.

RESEARCH QUESTIONS

The proposed research questions will help shed light on appropriate treatments. This will support patients in their decision-making process, and guide physician-patients shared decision-making discussions. In this area the evidence base is evolving and oftentimes the risk is overtreatment, particularly when treatment with neoadjuvant/adjuvant chemotherapy is involved. We devised the following five questions to lead the work of this systematic review and guideline.

Q1. Which patients with early-stage breast cancer require axillary staging (i.e., SLNB, ALND, or US)?

Q2. 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 (i.e., radiation, or surgery) indicated?
b. What sentinel node-negative patient subgroups are most likely to benefit from further axillary treatment with radiation therapy?

Q3. 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 either with radiation or with surgery or both?

Q4. For women who were treated with NAC:

a. If the lymph node is negative at diagnosis, what axillary treatment (i.e., radiation or surgery) is indicated after chemotherapy?
b. If the lymph node is positive at diagnosis, what axillary treatment (i.e., radiation or surgery) indicated after chemotherapy?
c. When is the best timing for performing sentinel node excision: prior or following NAC?

Q5. Among patients with early breast cancer appropriate for axillary staging:

a. Is there a better identification rate with single or dual tracer?
b. Is there a better identification rate with US-guided SLNB or traditional SLNB?
c. Is there a better identification rate with US or SLNB?

The Working Group members, in consultation with patient representatives, identified outcomes that are critical to patients. For all questions measures of survival and disease control were considered critical outcomes; quality of life, and adverse events, including surgical complications rate were considered important outcomes.

METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Existing guidelines

Two recommendations for surgical interventions in women who did not receive NAC and were sentinel lymph node negative (Recommendations 2), or positive (Recommendation 3, comparison A) were endorsed from the ASCO guideline [3,4]. A description of content and process is summarized in Section 3.

Search for Systematic Reviews

The full search strategies are reported in Appendix 2A. A search for existing systematic reviews was conducted using the databases MEDLINE, EMBASE, the Cochrane library, EPISTEMONIKOS, and the authors' files for studies published from 2011 to June 9, 2017, and with search strategies dated from 2010 to 2017. Search terms specific to the axilla and breast cancer were combined with terms specific to systematic review design. If more than one systematic review met the inclusion criteria, then one systematic review for each outcome per comparison was selected by the methodologist (FB) based on the age of its search, its quality, and the best match with our study selection criteria reported in Appendix 3, Table 1.

Search for Primary Literature

The primary literature was used to integrate and update evidence from included systematic reviews. For questions where suitable systematic reviews had not been identified (e.g., Question 3), a systematic review of the primary literature was conducted.

Literature Search Strategy

The search strategies of the included systematic reviews were compared with the search strategy we used for the identification of systematic reviews at step 1 of this work, and all the relevant terms were included for the search for primary studies. We searched the electronic databases MEDLINE, EMBASE, and the Cochrane Library for primary studies published from 2007 (year of the first publication of the Z0011 study [27]), to February 18, 2020 for all questions except for Question 4c. For question 4c ("When is the best timing to perform SLNB, before or after NAC?") we examined the literature published after March 2013. In fact, the authors of one of the seminal trials in the area of SLNB timing, the SENTInel-lymph-node biopsy in patients with breast cancer before and after NeoAdjuvant chemotherapy (SENTINA) study [46], conducted a systematic review from January 1997 to March 2013, and were not able to identify any prospective trial with detection rate and false negative rate as end-points in patients who converted during NAC from clinically positive to clinically negative. The ASCO (2016, 2017, 2018, 2019), ASTRO (2016, 2017, 2018, 2019), ESMO (2016, 2017, 2018, 2019), ESTRO (2016, 2017, 2018, 2019) conference proceedings, and the proceedings of the San Antonio Breast Cancer Symposium (2016, 2017, 2018, 2019) were searched on March 26, 2020.

Two separate searches were conducted to identify relevant non-randomized literature addressing Questions 4 and 5 (see Appendix 2: C and D).

For all questions, in addition to the search of electronic databases, the reference lists of the included systematic reviews, guidelines, and primary studies were handsearched.

Study Selection Criteria and Process

Table 1 in Appendix 3 reports the detailed selection criteria and the comparisons for the five questions. In addition, when including comparative, non-randomized studies, we

checked that the studies that met our inclusion criteria, met also a basic quality characteristic: control for confounding. This could be achieved by showing that no statistically significant between-group differences were present at baseline, or by using appropriate statistical analyses (e.g., propensity score-matched or multivariate analyses). If the studies did not control for confounding, we did not include them in our analysis.

The methodologist (FB) reviewed the titles and the abstracts of citations identified by the searches and excluded the most obviously irrelevant. The full text of the remaining articles were retrieved in the library. The methodologist and one of the clinicians (MB, and FP) reviewed each full-text item independently. Discrepancies were resolved by discussion.

Appendix 4 reports the flow diagrams of this study.

Data Extraction and Assessment of Risk of Bias

The methodologist (FB) extracted data and summarized the main characteristics and results of included studies into evidence tables. An independent auditor (SS or DB) audited all extracted data and information.

Risk of bias in relevant systematic reviews was assessed using the ROBIS tool [76] to determine whether existing systematic reviews met a minimum threshold for methodological quality and could be considered for inclusion in the evidence-base. The ROBIS tool comprises three phases: (1) assessement for relevance: identified systematic reviews were evaluated based on their clinical content and relevance; (2) identification of concerns with the review process, and (3) judgement of the risk of bias. The systematic reviews were rated at each phase by answering to signalling questions in the tool. Details of the risk of bias assessment of systematic reviews are reported in Appendix 5B.

If any systematic reviews matched the scope of this review, was of sound methodology, was considered at low risk of bias, and its search was <12 months old, it was considered suitable to be used as the foundation of this work, and its searches updated as necessary. Systematic reviews that contained relevant studies, but did not match the scope or methods of the present review, were used as a source of references for the primary studies portion of this review.

The methodologist (FB) assessed the risk of bias of included, fully published, RCTs with the Cochrane Risk of Bias Tool [77], and of fully published observational studies of treatment with the Cochrane ROBINS-I tool [78], or with the QUADAS 2 [79] for studies of diagnostic outcomes.

Individual patient data meta-analyses were appraised according to the guidance offered by Tierney et al. [80].

The certainty of the evidence, per outcome, for each comparison, taking into account risk of bias, inconsistency, indirectness, imprecision, and publication bias was assessed using the GRADE tool [81].

Synthesizing the Evidence

When clinically homogeneous results from two or more trials were available, a meta-analysis was conducted using the Review Manager software (RevMan 5.3) provided by the Cochrane Collaboration [82]. For time-to-event outcomes, HRs, rather than the number of events at a specific time, are the preferred statistic for meta-analysis, and are used as reported. If the HR and/or its standard error were not reported, they have been derived from other information reported in the study, using the methods described by Parmar et al. [83]. For all outcomes, the generic inverse variance model with random effects, or other appropriate random effects models in RevMan have been used.

Statistical heterogeneity was calculated using the X^2 test for heterogeneity and the I^2 percentage. A probability level for the X^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% was considered indicative of statistical heterogeneity.

Ratios, including HR, were expressed with a ratio <1.0 indicating the evidence favours the control arm (e.g., no staging).

RESULTS

Search and Selection of Existing Systematic Reviews

The search of electronic databases and other sources yielded 7476 citations after duplicates were removed. The full text of 277 articles was reviewed, and 42 systematic reviews [3,7,31,49,84-121], in 53 publications, were initially selected. Three of these reviews [84,88,104] were relevant for more than one question. The study flow chart is presented in Appendix 4A. The reviews that met the inclusion criteria at full text were assessed for relevance and risk of bias with the ROBIS tool [76] (Tables 1 to 7 in Appendix 5B). The reviews that were not considered clinically relevant (Step 1 of the ROBIS tool, Table 1 in Appendix 5B) are not discussed any further. Table 4-1 shows a summary of risk of bias assessment of the reviews that were considered clinically relevant [7,31,49,93,95,96,98,100,101,109,117]. The systematic reviews that were considered at high risk of bias are not discussed any further. Table 4-2 shows the general characteristics and the summary results of the seven systematic reviews that were considered relevant and at low risk of bias [7,31,49,95,98,101,117].

Table 4-1. Risk of bias of included systematic reviews as appraised with the ROBIS tool [76]*

Review	Phase 2				Phase 3
	1. Study eligibility criteria	2. Identification and selection of studies	3. Data collection and study appraisal	4. Synthesis and findings	Risk of bias in the review
Question 1: patients who need staging					
Liang, 2017 [7]	Low	Low	Low	Low	Low
Question 2: patients who are negative at diagnosis					
We included the ASCO 2017 guideline [3,4] that was appraised with the AGREE II (Appendix 5A), and the Early Breast Cancer Collaborative Group [86] that was appraised according to the Tierney et al. guidance [80] (Appendix 5B)					
Question 3: patients who are positive at diagnosis					
We included the ASCO 2017 guideline [3,4] that was appraised with the AGREE II					
Zhao, 2017 [93]	Low	Low	High	Unclear	Unclear
Schmidt-Hansen 2016 [31]	Low	Low	Low	Low	Low
Huang, 2016 [95]	Low	Low	Low	Low	Low
Li, 2015 [98]	Low	Low	Low	Unclear	Low
Budach, 2015 [100]	Unclear	Unclear	High	High	High
Ram, 2014 [101]	Low	Low	Low	Low	Low
Question 4: patients treated with NAC					
El Hage Chehade 2016 [96]	Low	Low	High	Unclear	High
Fontein, 2013 [109] Q4c Timing	Low	High	High	High	High
Question 5: Mapping modalities					
Geng, 2016 [49]	Low	Low	Low	Low	Low
van Wely, 2014 [117]	Low	Low	Low	Unclear	Unclear

*See Appendix 5B for more details.

ALND = axillary lymph node dissection; ASCO = American Society of Clinical Oncology; NAC = neoadjuvant chemotherapy; RT = radiotherapy; SLNB = sentinel lymph node biopsy; US = ultrasound; WBI = whole breast irradiation; yrs = years

Table 4-2. General characteristics and summary results of the relevant systematic reviews

Author, year, Country, Funding	Objectives; Search cut-off; Design	Population	Intervention /Index test	Comparison /Reference standard	Outcomes	Number and design of included studies	Summary results
Question 1: Determining which patients need staging							
Liang, 2017 [7] **Country:** Canada **Funding:** *nr*	**Objectives:** To determine whether, in elderly women with early-stage breast cancer, the omission of axillary staging impacts breast cancer outcomes. **Search cut-off**: August 2014 **Design**: Meta-analysis	2 studies: N = 692 Women with early-stage breast cancer (T1/T2, N0) of age ≥70 yrs	Axillary stging with SLNB, axillary sampling, or ALND	No axillary surgery	Local, regional and distant recurrence, Breast cancer mortality and overall mortality	2 RCTs	*Axillary recurrence:* RR 0.24, 95% CI, 0.06 to 0.95, I^2 = 0%, p=0.04 *In-breast recurrence:* RR 1.20, 95% CI, 0.55 to 2.64, I^2 = 62%, p=0.65 *Distant recurrence:* RR 1.17, 95% CI, 0.75 to 1.82, I^2 = 0%, p=0.48 *Overall morality:* RR 0.99, 95% CI, 0.79 to1.24. I^2 = 0%, p=0.92 *Breast-cancer specific mortality:* RR 1.07, 95% CI, 0.72 to 1.57, I^2 = 0%, p=0.75
Question 2: Patients who are negative at diagnosis							
The ASCO, 2017 guideline [3,4] is discussed in text, and the Early Breast Cancer Collaborative Group [86] individual patient data meta-analysis is reported along with other studies that collected data at the patient level.							
Question 3: Patients who are positive at diagnosis							
No further surgery beyond SLNB vs. ALND							
Schmidt-Hansen 2016 [31] **Country:** UK **Funding:** None declared	**Objectives:** To assess benefits and harms of alternative approaches to axillary surgery including omitting the surgery **Search cut-off**: March 2015 **Design**: meta-analysis for ALND +SLNB vs. SLNB comparison. Narrative synthesis for ALND vs. RT	3 studies: N = 3919 women with operable primary breast cancer with a positive SLN. Pts treated wth ALND + SLNB vs. SLNB alone: N=2020	ALND + SLNB	SLNB	OS DFS Local, regional, and distant recurrence Short-term AE Long-term complications	3 RCTs	<u>ALND + SLNB vs. SLNB (3 trials)</u> *OS:* HR 0.82, 95% CI, 0.58 to 1.15, p=0.25, I^2 =0% *Recurrence:* a) Axillary: RR 0.46, 95% CI, 0.14 to 1.49, p=0.2, I^2=0% b) Local: RR 1.6, 95% CI, 0.86 to 2.97, p=0.14, I^2=0% c) regional: RR 0.34, 95% CI, 0.1 to 1.15, p=0.08, I^2=0% d) distant: RR 1.31, 95% CI, 0.8 to 2.15, p=0.28, I^2=0% DFS: HR 0.81, 95% CI, 0.63-1.04, p=0.1, I^2 =0% BC recurrence in the axilla: Risk ratio (RR): 0.46, 95% CI, 0.14 - 1.49, p=NS Local BC recurrence RR:1.60, 95% CI, 0.86-2.97, p=NS Regional BC recurrence: RR: 0.34, 95% CI, 0.10-1.15, p=NS Distant BC recurrence: RR: 1.31, 95% CI, 0.80-2.15, p=NSCI Adverse events: results were not pooled statistically; when a statistical comparison was made within one trial, adverse events such as lymphoedema, arm

Author, year, Country, Funding	Objectives; Search cut-off; Design	Population	Intervention /Index test	Comparison /Reference standard	Outcomes	Number and design of included studies	Summary results
							circumference increase, were statisticaly significantly worse for pts who received ALND compared with SLNB; no difference was seen in shoulder range of motion.
Huang, 2016 [95] **Country:** Taiwan **Funding:** none declared	**Objectives:** To evaluate the necessity of further ALND in pts with early breast cancer and limited positive axillary SLN metastases **Search cut-off**: February 2016* (included studies published from 2007 to 2013) **Design**: meta-analysis	5 studies N =2057 women with small tumours (<5 cm) and positive SLN	ALND + SLNB	SLNB	OS DFS Recurrence rate Lymphedema and sensory neuropathy	3 RCTs	*Survival (2 trials)* OS: HR 0.82, 95% CI, 0.58 to 1.16, I^2=0%, p=0.25 DFS: HR 0.83, 95% CI, 0.65 to 1.06, I^2=0%, p=0.14 *Recurrence rates (3 trials)* HR 0.88, 95% CI, 0.53 to 1.45, I^2=20%, p=0.61 *Incidence of lymphedema (2 trials)* RR 0.38, 95% CI, 0.17 to 0.85, p=0.02, I^2=74%, p=0.02 *Incidence of sensory neuropathy (2 trials)* RR 0.39, 95% CI, 0.14 to 1.12, I^2=94%, p=0.08
Li, 2015 [98] **Country:** China **Funding:** *nr*	**Objectives:** To compare the safety and efficacy of SLNB alone versus ALND in early breast cancer with sentinel node metastasis **Search cut-off**: February 2014* **Design**: meta-analysis	12 studies: N = 130,575 women with T1/T2, N0,M0 disease and positive SLN	SLNB alone	ALND	OS DFS Loco-regional recurrence AE	12 trials: 5 RCTs, and 7 obs.	*OS (2 RCTs and 5 obs.)* All studies: HR 0.95, 95% CI, 0.85 to 1.06, p=0.35, I^2=0% RCTs: HR 0.87, 95% CI, 0.62 to 1.24, p=0.45, I^2=0% Obs.: HR 0.96, 95% CI, 0.85 to 1.08, p=0.47, I^2=0% *DFS (3 RCTs, and 4 obs.)* All studies: HR 1.00, 95% CI, 0.98 to 1.02, p=0.96, I^2=47% RCTs: HR 1.00, 95% CI, 0.98 to 1.02, p=0.92, I^2=0% Obs.: HR 1.10, 95% CI, 0.94 to 1.29, p=0.23, I^2=62% *Loco-regional recurrence (2 RCTs and 3 obs.)* All Studies: RR 0.92, 95% CI, 0.59 to 1.44, p=0.73, I^2=0% *AE (paresthesia: 2 trials, 1190 pts)* RR 0.26, 95% CI, 0.20 to 0.33, p<0.001, I^2=0% *AE (infections 1 trial):* RR 0.36, 95% CI, 0.18 to 0.70, p=0.003 *AE (axillary seroma 1 trial):* RR 0.40, 95% CI, 0.25 to 0.65, p=0.0002 *AE (lymphedema: 2 trials)* RR 0.28, 95% CI, 0.20 to 0.41, p<0.001, I^2=75% <u>Subgroup (micro-[0.2-2 mm] vs. macro- [>.02 mm] metastases) (2 RCTs and 3 obs.)</u> *OS:* HR 0.94, 95% CI, 0.72 to 1.23, p=0.65, I^2=0% *DFS*: HR 1.00, 95% CI, 0.98 to1.02, p=0.99, I^2=25%
Ram, 2014 [101]	**Objectives:** To ascertain whether SLNB alone was	3 studies: N = *nr*	SLNB alone	ALND	OS DFS	3 RCTs	*OS (2 trials):* HR 0.83 , 95% CI, 0.60 to 1.14, p=0.25, I_2=0% *DFS (3 trials):*

Author, year, Country, Funding	Objectives; Search cut-off; Design	Population	Intervention /Index test	Comparison /Reference standard	Outcomes	Number and design of included studies	Summary results
Country: Multiple countries **Funding:** *nr*	noninferior to ALND in pts with positive SLN **Search cut-off**: *nr** **Design**: meta-analysis	Breast cancer pts with positive SLN					HR 0.94, 95% CI, 0.79 to 1.13, p=0.52, I^2=47%
RT + Surgery vs. No RT of the regional nodes							
No systematic reviews were identified for this comparison							
RT vs. Surgery							
Schmidt-Hansen 2016 [31] **Country:** UK **Funding:** None declared	**Objectives:** To assess benefits and harms of alternative approaches to axillary surgery including omitting the surgery **Search cut-off**: March 2015 **Design**: meta-analysis for ALND +SLNB vs. SLNB comparison. Narrative synthesis for ALND vs. RT	3 studies: N = 1899 women with operable primary breast cancer with a positive SLN	RT	ALND	OS DFS Local, regional, and distant recurrence Short-term AE Long-term complication QOL Disease control in the axilla	5 RCTs	<u>ALND vs. RT (2 trials)</u> **AMAROS trial** [36]: *OS, DFS, Shoulder mobility and QOL:* No statistically significant difference. *Rates of any clinical sign of lymphedema*: At 12 mos: ALND 32/410 vs. Rt 24/410, p=0.332 At 3 yrs: ALND 38/373 vs. Rt 22/341, p=0.08 At 5 yrs: ALND 43/328 vs.16/286, p=0.0009 **OTOASOR trial** [33]: OS, DFS, Axillary recurrence: No statistically significant difference. QOL: *nr*
RT vs. no treatment							
No systematic reviews were identified for this comparison							
Question 4: Patients treated with NAC							
No systematic reviews met inclusion and quality criteria for patients who were initially node negative							
Question 5: Mapping modalities							
Single or dual tracer							
Geng, 2016 [49] **Country:** China **Funding:** Key R &D Program of Shandong Province and the Projects of Medical and Health	**Objectives:** To evaluate the feasibility and accuracy of SLNB **Search cut-off**:November 2015 **Design:** Meta-analysis	16 studies of 1456 pts with initially clinically node – negative BC pts treated with NAC. Stage T1-T4**	SLNB	ALND	IR	13 studies **NOTE:** 3 studies were excluded because different mapping methods were used within a single study	Only blue dye mapping: Pooled IR: (3 studies): 96% (95% CI, 91% to 100%) Only radiocolloid mapping (4 studies): Pooled IR 96% (95% CI, 94% to 99%) Blue dye and radiocolloid (6 studies): pooled IR 97% (95% CI, 96% to 98%) p=0.180

Author, year, Country, Funding	Objectives; Search cut-off; Design	Population	Intervention /Index test	Comparison /Reference standard	Outcomes	Number and design of included studies	Summary results
Technology Development Program in Shandong Province							
US-guided SLNB or traditional SLNB							
van Wely, 2014 [117] **Country:** The Netherlands **Funding:** *nr*	**Objectives:** To determine if US-guided biopsy of suspicious nodes can be a useful tool to identify pts with extensive axillary tumour burden **Search cut-off**: Sept 2013 **Design:** Meta-analysis	115 studies of pts with breast cancer, age and stage *nr*	Index test: Axillary staging with US-guided biopsy	Reference standard: ALND	Number of positive nodes at ALND (1 to 3 nodes)	18 observational studies met the inclusion criteria; the number of studies in meta-analysis is less because data not available	**Number of positive nodes:** *532 US+/biopsy+ vs. 248 US+/biopsy-/SLNB+*: 8 studies 44% vs. 76.2%, RR 0.57, 95% CI, 0.49 to 0.67, p<0.001; I^2=22% Significantly more pts in the US+/biopsy+ group had >3 involved nodes *332 US+/biopsy+ vs. 458 US-/SLNB+*: 6 studies 53.6% vs. 69.7%, RR 0.69, 95% CI, 0.43 to 1.12, p=0.13, I^2=89%. No conclusion can be drawn on whether one group had more positive nodes than the other at ALND. *49 US+/biopsy-/SLNB+ vs. 432 US-/SLNB+* 86% vs. 72%, RR 0.99, 95% CI, 0.89 to 1.10, p=0.84, I^2=0%.
US or SLNB							
No systematic reviews were identified for this comparison							

* Reports only search terms, not complete search strings

** Clinicallly node negative defined as the absence of suspicious or abnormal-appearing lymph nodes on physical examination or ultrasound imaging.

AE = adverse events; ALND = axillary lymph node dissection; AMAROS = After Mapping of the Axilla, Radiotherapy or Surgery; ASCO = American Society of Clinical Oncology; CI = confidence interval; DFS = disease-free survival; FNR = false negative rate; IR = identification rate; mos = months; NAC = neoadjuvant chemotherapy; *nr* = not reported; obs. = observational studies; OS = overall survival; pt(s) = patient(s); QOL = quality of life; RCT = randomized control trial; RR = relative risk; RT = radiotherapy; SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy; US = ultrasound; yrs = years

Literature Search Results for Primary Studies

Question 1: Defining which patients with early-stage breast cancer need axillary staging

The flow diagram for primary studies is reported in Appendix 4B. Table 4-3 shows the evidence that was identified for Question 1. Table 4-4 reports the general characteristics of included primary studies.

The search strategy focused on staging versus no-staging of the axilla in patients of all ages with T1/T2, N0 breast cancer. The Liang et al. [7] systematic review included two randomized controlled trials (RCTs) of women ≥70 years old published from 2006 to 2012 (i.e., Martelli et al. [6], and Rudenstam et al. [5]). We searched for RCTs of women of all ages published from 2007 to 2018. The Liang et al. [7] review's outcomes did not include quality of life, adverse events, and complication rates, although one of the studies included in the review [5] reported on quality of life measures such as pain and arm movement.

Our systematic review identified two additional, fully published, unique RCTs [8,122]. The AXIL95 group study [122], similarly to the Liang et al. [7] review, included older patients, while the INT09/98 trial [8] included adult women of all ages. We identified the full-text publication of the ongoing SOUND, and BOOG 2013-08 trials [9,10,123], and the abstract publications of the ongoing Tucker et al. [11] and INSEMA [124] trials. These studies are expected to be completed in 2021 [9,11], 2024 [124], and 2027 [10].

Women included in the studies had node-negative disease [5,6], or both node negative and positive, or micrometastases [8]. Staging in all included studies was performed by ALND. All four included fully published studies [5,6,8,122] compared ALND with no dissection for staging of the axilla in adult women with early-stage breast cancer. In the arms treated with axillary dissection, 28% [5,8], 23% [6], and 14% [122], of patients were found to have metastases in at least one lymph node. All of the four studies [5,6,8,122] reported on OS; three studies [5,8,122] reported on DFS or event-free survival (EFS); three studies [6,8,122] reported on recurrence; one study [5] reported on quality of life; and one study [122] reported on functional outcomes. None of the included studies reported on surgeons' experience.

Table 4-3. Literature search results for Question 1

Comparison in Question 1		Endorsed guidelines	Included, high quality SRs	Included RCTs	Included Observational comparative trials	Ongoing trials
Intervention	Control					
Axillary staging (by surgery or imaging)	No staging	NA	Liang, 2017 [7]	Avril, 2011 [122]; Agresti, 2014 [8]; Martelli, 2012 [6]*, Rudenstam, 2006 [5]*	NA	Gentilini, 2012 SOUND trial [9]; van Roozendaal, 2017 [10], Reimer, 2017 [12]; Tucker, 2014 [11]

*These studies were included also in the Liang et al. systematic review [7]
NA = not applicable; RCTs = randomized controlled trials; SRs = systematic reviews

Companion studies

We identified four companion publications [125-128] of two of the the included unique studies [6,9]. These publications reported on long-term follow-up of the studies [126,129], on the incidence of tumour-positive sentinel lymph nodes after exclusion of micrometastasis [125]; evaluated the impact of different types of surgery [128]; and compared in- and off-study patients [127]. None of the companion publications reported on surgeon experience. Table 4-5 presents their objectives and summary results of these studies.

Ongoing, Unpublished, or Incomplete Studies

We identified the protocols of two studies: the SOUND (Sentinel node vs. Observation after axillary UltrasouND) trial [9], expected to be completed at the end of 2021; and the BOOG 2013-08 trial [10] due for completion in 2027. As well, we identified two abstract publications of interim analyses of ongoing trials: The Intergroup-Sentinel-Mamma (INSEMA) trial [12], the Italian trial [130], trial NCT01821768 [11], and the IEO S637/311 (NCT02167490) trial. Unlike the included studies mentioned above, that examined staging by ALND, these studies explored the option of abandoning staging by SLNB in patients with early-stage breast cancer treated with breast-conserving surgery or mastectomy.

Table 4-4. Question 1: Axillary staging vs. no staging (by surgery or imaging). General characteristics of included primary studies

Study, date, country, study name, Funding	Design, Accrual period, Aim Follow-up	Population	Sample size calculation	Comparison	Outcome(s)	Adjuvant treatment
*Agresti, 2014 [8] **Country:** Italy INT09/98 trial **Funding:** No specific funding declared	Single centre noninferiority RCT **Accrual Period:** Jun 1998 - Jun 2003 **Aim:** To determine whether axillary surgery is necessary in the management of the axilla either as treatment or as a guide to adjuvant treatment in pts with T1N0 disease. **Follow-up** (median (range): 127.5 mos (IQR, 112.5 - 141.1 mos)	565 women aged 30 to 65; 517 in analysis **Age** (mean ± SD): 52.6 ± 7.7 yrs **Stage**: T1N0	Approximately 600 pts were required in order to achieve 80% power with 1-sided alpha. Clinical noninferiority was defined as the QUAD arm had a 5 yr OS of ≤4%	245 QUAD vs. 272 QUAD + ALND	**Primary outcome:** OS **Secondary outcomes:** DFS Incidence and time of axillary lymph node disease occurrence in the no axillary surgery arm (QUAD arm)	**Adjuvant treatment** All pts: RT to the residual breast (not to the axilla); chemotherapy; and tamoxifen 20 mg/d for 5 yrs. Pts with favourable prognostic factors (i.e., node -ve, and/or ER+ve, Grade I-II) did not receive adjuvant chemotherapy; pts with unfavourable prognostic factors (i.e., node +ve, and/or ER-ve and/or Grade III) received adjuvant treatment
Martelli 2012 [6], **Country: Italy **Funding:** Italian Association for Cancer Research	Single centre RCT **Accrual Period:** Jan 1996 – Jun 2000 **Aim** To assess the efficacy of ALND in older BC pts with clinically negative axilla **Follow-up**: median (range): 150 (125-175) mos in the ALND arm 149 (124-174) mos in the no ALND arm	238 women (219 in analysis) 65-80 yrs of age with early BC and clinically negative axilla **Age** (median): 70 yrs **Stage**: T1N0 ≤2 cm diameter	642 pts were needed to reach a power of 94% in excluding a 10% increase in distant metastases in the CG. Stopped early for slow accrual at 4.5 yrs.	109 ALND vs. 110 no ALND	**Primary outcome:** OS, BC mortality **Secondary outcomes:** AE (breast) (ipsilateral BC, contralateral BC, and distant metastases) Overt axillary disease for pts who did not receive AD	**Adjuvant treatment** All pts: Breast-conserving surgery; RT to the residual breast, and tamoxifen 20 mg/d for 5 yrs
Avril, 2011 [122] **Country:** France AXIL95 or Institute Bergonié Trial **Funding:** French Ligue Contre le Cancer	Multicentre RCT phase 3 equivalence, pragmatic trial. **Accrual Period:** Oct 1995 - Oct 2005 **Aim:** 1. To compare survival outcomes with and without ALND 2. Examine the 2 groups functional impairements 3. Examine the rates of axillary nodes events in the no-ALND group **Follow-up:** median (range): OS and EFS 60 mos	625 post-menopausal women with early, invasive BC and clinically negative axilla after loco-regional treatment **Age** (median): No-ALND: 62.6 yrs (range 50-81 yrs) ALND: 61.6 yrs (range 50-87 yrs) **Stage**: tumours ≤10 mm	105 events and 1612 pts were required to obtain 90% power with a 2-sided 0.10-level test. The equivalence margin was set at 3% (i.e., equivalence will be admitted if HR inferior to 1.6 or OS in the no ALND group is ≥92%). †Terminated early, at first interim analysis, because of lack of equivalence and low accrual	297 no ALND vs. 310 ALND	**Primary outcome:** OS **Secondary outcomes:** EFS Functional outcomes	**Adjuvant treatment** Either radical modified mastectomy or lumpectomy. Rt was given to all lumpectomy pts and most mastectomy pts. Tamoxifen 20 mg/d for pts with estrogen- or progesterone-positive or unknown status (for 3 or 5 yrs, depending on the randomization date). For negative receptor pts adjuvant chemotherapy

Study, date, country, study name, Funding	Design, Accrual period, Aim Follow-up	Population	Sample size calculation	Comparison	Outcome(s)	Adjuvant treatment
Rudenstam, 2006 [5] **Country: Multiple International Breast Cancer Study Group Trial 10-93 IBCSGT 10-93 **Funding:** public funding from various countries	Multicentre RCT **Accrual Period:** May 1993 - Dec 200224 **Aim** To determine the effect of ALND on QOL, survival and recurrence **Follow-up** median: 79.2 mos	473 pts aged ≥60 yrs with clinically node negagive, unilateral operable BC **Age** median (range): 74 yrs, (60–91) **Stage**: T1a, T1b, T2a, T2b, T3, N0, or M0. 80% estrogen receptor-positive	473 pts were needed to reach a 80% power to detect a decrease of 13% in the percentage of pts bothered by hand, arm, shoulder, or chest for pts not receiving axillary clearance	234 surgery + ALND vs. 239 surgery	**Primary outcome:** QOL **Secondary outcomes:** OS, DFS, BC-specific mortality Axillary recurrence	**Adjuvant treatment** All pts received tamoxifen 20 mg/d for 5 yrs
ONGOING TRIALS						
Gentilini, 2012 [9] Nadeem, 2015 [125] (protocol, feasibility study) **Country:** Italy SOUND (Sentinel node vs. Obs. after axillary UltrasouND) trial **Funding:** Fondazione Umberto Veronesi and Fondazione Istituto Europeo di Oncologia	Multicenter noninferiority RCT **Accrual Period:** Jan 2012 - Dec 2021 **Aim** To determine the usefulness of SLNB compared with no axillary surgical staging in pts with small BC and negative preoperative US. To compare imaging methods with surgical methods for staging **Follow-up** (median (range): 12 mos	Pts with BC ≤2 cm and negative pre-op axilla US or negative FNAC of a single doubtful axillary LN Has results only for AE outcome on the first 180 pts (176 in analysis) **Age**: median, (range) yrs SLNB group: 62 (52-69) yrs; Obs.: 60 (51-69) yrs **Stage**: T1	1560 women (780 per arm) to be enrolled to decide whether the group without treatment of the axilla is no worse than the reference group, given a margin delta of non-inferiority of 2.5% (maximum tolerable 5-yrs DDFS = 94%) with power of 80% and α=0.05. The study was designed to detect a difference between the QuickDASH (Disability of the Arm, Shoulder and Hand) scores of 15% after surgery.	SLNB vs. Obs.	**Primary outcome:** DDFS **Secondary outcomes:** Cumulative incidence of axillary recurrences, DFS, and OS. QOL, and evaluation of type of adjuvant treatment administered; physical function and symptoms of the upper limb as measured with the Quick DASH questionnaire	**Adjuvant treatment** *nr*
Van Roozendaal, 2017 [10] **Country:** The Netherlands BOOG 2013-08 **Funding:** Dutch Cancer Society, Central Health Insurance, Netherlands Organization for Health Research and Development	Multicentre noninferiority RCT **Accrual Period:** 2014 - 2027 NCT02271828 **Aim** To investigate whether SLNB of the axilla can be omitted in SLN negative pts treated with BCT **Follow-up:** NA	Pts with early BC treated with mastectomy and with ≤3 positive LNs **Age**: ≥18 yrs **Stage**: T1-2 N0	1644 pts	ALND vs. no treatment. Staging is done with US.	**Primary outcome:** Regional recurrence rate at 5 and 10 yrs **Secondary outcomes:** Distant DFS OS QOL Local recurrence rate Contralateral BC Administration of adjuvant radiation therapy Delayed axillary treatment	**Adjuvant treatment** BCT (lumpectomy and WBI)
Reimer, 2017 [12]	Multicentre RCT	Pts with operable BC with tumours ≤5 cm; clinically	7095 pts planned for enrolment; per-protocol	First randomization	**Primary outcome:** Invasive DFS	**Adjuvant treatment**

Study, date, country, study name, Funding	Design, Accrual period, Aim Follow-up	Population	Sample size calculation	Comparison	Outcome(s)	Adjuvant treatment
Country: Germany, Austira INSEMA trial **Funding:***nr*	**Accrual Period:** 2015 completion due in 2024 NCT02466737 **Aim** To show noninferiority of reduced extent axillary surgerycompared with axillary dissection **Follow-up** (median (range) mos: NA	negative (undefined) prior to core biopsy **Age**: ≥35 yrs **Stage**: M0	analyses: 6,740 (5,940 German and 800 Austrian patients) Noninferiority trial	in clinically negative pts: No SLNB (n=201) vs. SLNB (n=800) (Q1) Second randomization in pts with SLNB positive: (Q4): SLNB alone (n=49) vs. ALND (n=48))	**Secondary outcomes:** OS Local and axillary recurrence Rates and determination of actual applied RT dose at each axillary level. QOL	Breast-conserving surgery and post operative whole breast irradiation
Tinterri, 2017 ABS [130] **Italian Trial** **Country:** Italy **Funding:** *nr*	Multicentre RCT **Accrual Period:** Jan 2016 Jan 2019 **Aim** To confirm that performing only SLNB does not affect survival or relapse risk in patients with 1-2 positive SN. **Follow-up** (median (range): 36 mos	2000 with SN macrometastases A total of 396 pts evaluated **Age** *(*median): age 61 years (30-90 yrs) **Stage**: T1-T2, N0	*nr*	ALND (Standard treatment) vs. SLNB	**Primary outcome:** *nr* **Secondary outcomes:** *nr*	**Adjuvant treatment** *nr* **Authors'conclusions** NA
Tucker, 2014 ABS [11] **Country:** *nr* **Funding:** *nr*	Noninferiority RCT **Accrual Period:** 2013 completion due in 2021 NCT01821768 **Aim** To determine the utility of axillary US for pre-operative staging **Follow-up** (median (range) mos: NA	460 clinically node negative (undefined) axillary US women **Age**: ≥18 yrs **Stage**: T1-T2, N0 M0	Assuming a noninferiority limit of 2% difference, the sample size will allow 80% power at 1-sided 0.1 significance level to assure non inferiority. N=*nr*	No SLNB vs. SLNB	**Primary outcome:** Axillary recurrence **Secondary outcomes:** DSF OS	**Adjuvant treatment** NA

* This trial was a subsequent study to the Martelli et al., 2012 [6]. The authors were from the same group, but the population was different.
** The star indicates the two studies that were included in Liang et al. [7]. As part of the Liang et al. review [7]., the Rudenstam, et al. study is represented in the evidence tables, even though it was published prior to our cut-off date.
† The AXIL95 study [122] was stopped after the first 15 pt deaths because of lack of equivalence of outcomes, and changes in adjuvant and surgical (SLNB instead of ALND) therapy.

AD = axillary dissection; AE = adverse events; ALND = axillary lymph node dissection; BC = breast cancer; BCT = breast-conserving therapy; CG = control group; D = day; DDFS = distant disease-free survival; DFS = disease-free survival; EFS = event-free survival; ER+ = estrogen receptor-positive; ER- = estrogen receptor-negative; FNAC = fine needle aspiration cytology; HR = hazard ratio; IQR = interquartile range; LN = lymph node; mos = months; NA = not applicable; *nr* = not reported; Obs = observation; OS = overall survival; pts = patients ; QOL = quality of life; QU = quandrantectomy without axillary lymph node dissection; QUAD = quandrantectomy with axillary lymph node dissection; pts = patients; RCT = randomized controlled trial; RT = radiotherapy; SD = standard deviation; SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy; US = ultrasound; WBI =whole breast irradiation; yrs = years

Table 4-5. Axillary staging vs. no staging (by surgery or imaging). Corollary studies of included trials for Question 1.

Main study; Comparison; Objectives	Companion publications; Objectives	Summary results of the companion publication
Martelli, 2012 [6] (also included in the Liang et al. review) ALND vs. no ALND **Objectives:** To assess the role of axillary dissection in old BC pts with a clinically clear axilla.	Martelli, 2014 [127] **Objectives:** Compared in-trial with out-of-trial pts of the main study	After 15 yrs follow-up BC mortality was not different between ALND and no ALND group in the trial and out-of-trial cohorts. 15-yr cumulative incidence of axillary disease was 6% (95% CI, 0% to 12.6%) in the no ALND arm and 0 in the ALND arm.
	Martelli, 2011 [126] **Objectives:** 15 yrs follow up for safety in a retrospective cohort of treated pts	After 15 yrs (range 14 - 17 yrs) no statistically significant difference was noted between the treated and untreated groups. Cumulative incidence in the no-ALND group was: 3.7% in pT1 pts.
Gentilini, 2012 [9] (protocolof an ongoing trial SLNB vs. obs SOUND trial (sentinel node vs. obs after axillary ultrasound) **Objectives:** To compare SLNB with no axillary surgical staging in pts with small BC and negative pre-op US. Is the information obtained by SLNB useful? Can we use imaging methods for staging instead of surgical methods?	Gentilini, 2016 [128] **Objectives:** In the first 180 pts (94 Surgery + SLNB±ALND vs. 82 obs.) evaluated the impact of different types of surgery on post-operative physical function and symptoms of the ipsilateral upper limb as measured with the *QuickDASH* questionnaire	Pre-surgery score values were 3.0% and 2.7% in the SLNB and obs arms, respectively (p=0.730). One wk after surgery, the score increased to 24% in the SLNB arm and 10.6% in the obs. arm (p<0.001). After 6 and 12 mos, the score decreased in both arms to values similar to baseline values. The overall trend in time of the score was significantly different between the two arms (p<0.001), even after the exclusion of five pts who received ALND in the SLNB arm (p<0.001).
	Nadeem, 2015 [125] **Objectives:** To identify a group of pts in whom SLNB is no longer required	A total of 194 pts met the inclusion criteria; incidence of SLNs metastasis, further non-SLNs metastasis after ALND, and a total number of tumour positive ALNs of ≥4 varied between different groups and was 9.3–15.5%, 0–35% and 0–2.65%, respectively. However, the incidence of tumour positive SLNs after exclusion of micrometastasis in SLNs only varied between 4.6% and 13.4%. Pts with T1b, grade 1-2 tumours had <5% risk of ALNs macrometastasis.

ALN(s) = axillary lymph node(s); ALND = axillary lymph node dissection; BC = breast cancer; CI = confidence interval; mos = months; obs = observation; pts = patients; pre-op = pre-operatively; SNL(s) = sentinel ymph node(s); SLNB sentinel node excision; US = ultrasound; wk = week; yrs = years

Study Design, Risk of Bias, and Certainty of the Evidence

The fully published studies comprised a noninferiority RCT [8], a multicentre equivalence RCT [122]; a multicentre RCT [5], and a single-centre RCT [6]. Four of the ongoing trials are noninferiority RCTs [9-11,123], and two [124,130] are multicentre RCTs.

The risk of bias by outcome was not serious for OS (three trials [5,6,8]), and for DFS (two trials [5,8]). The risk of bias was serious for local and distant recurrence (two trials [6,122]). The Institute Bergonié trial [122] was at high overall risk of bias; all other trials were at moderate to low risk of bias (Figures 4-1A, and B). None of the studies reported whether outcome assessors were blinded, or described the surgeons' expertise.

We did not pool the Institute Bergonié trial [122] in meta-analysis because we considered it at high risk of bias. This pragmatic, unblinded study was stopped early at less than half the planned population, and less than one-fourth of the planned number of events for OS.

We considered the overall certainty of the existing body of evidence moderate to high for staging performed by ALND compared with no ALND. Table 4-6 presents the assessment of the certainty of the evidence available according to the GRADE method [81] for OS, DFS, and recurrence.

The certainty of the evidence was high for OS, and DFS. For recurrence the certainty of the evidence was moderate because one of the trials [122] was at high risk of bias. For incidence of breast cancer events the certainty of the evidence was moderate because of imprecision; only one study [6], which was stopped early, represented the body of evidence for this outcome.

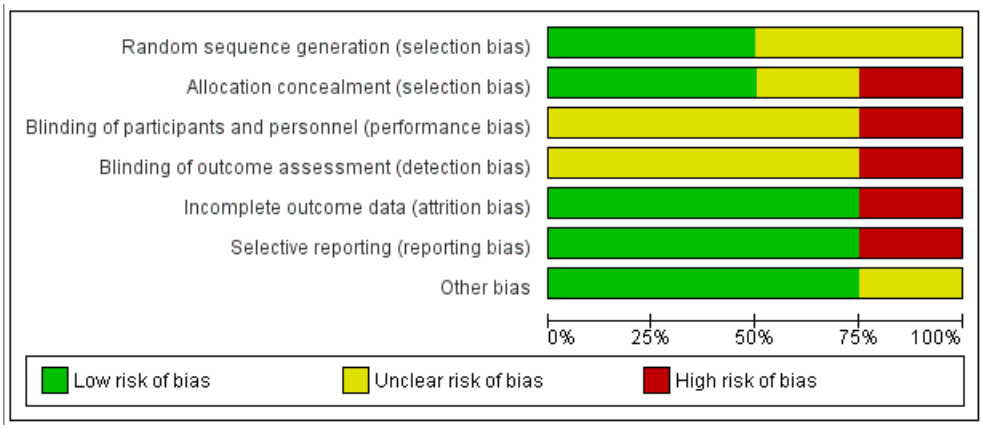

Figure 4-1A. Risk of bias graph for studies included for question 1: review authors' judgements about each risk of bias item presented as percentages across all included studies

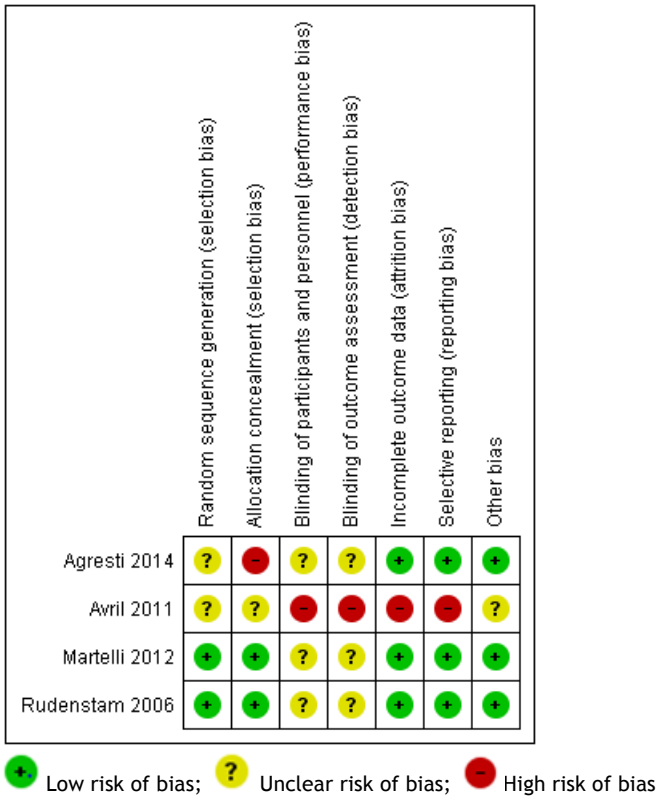

Figure 4-1B. Risk of bias summary for studies included for question 1: review authors' judgements about each risk of bias item for each included study across all outcomes

Outcomes

Table 4-7 reports the results of the completed trials.

Overall Survival

The Liang et al. [7] meta-analysis of two studies of older patients [5,6] concluded that the omission of axillary staging by ALND in women over 65 years of age with clinically negative axilla did not impact overall, and breast-specific mortality (RR, 0.99; 95% CI, 0.79 to 1.24, I^2=0%, p=0.92; RR, 1.07; 95% CI, 0.72 to 1.57, I^2=0%, p=0.75 respectively).

We updated the Liang et al. [7] meta-analysis and we included three studies for OS [5,6,8] (1257 patients). Figure 4-2A shows the statistical pooling of the results for OS. For women assigned to no staging compared with those assigned to axillary staging (by ALND) in our update meta-analysis, there was no statistically significant difference in OS: HR, 1.09; 95% CI, 0.85 to 1.39, with I^2=0%. No results are available for the studies that are still ongoing that compared axillary staging by SLNB versus no staging [9-11,123,124].

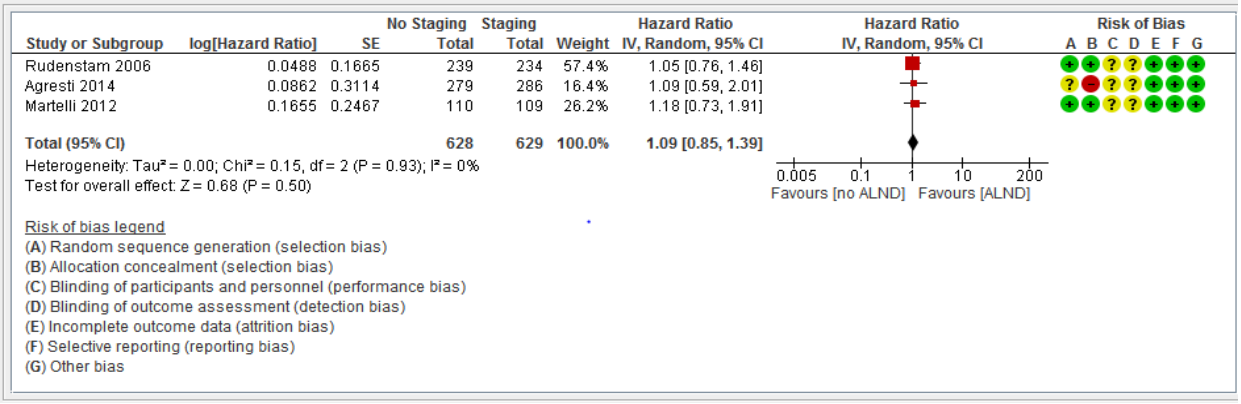

Figure 4-2A. Overall survival for no staging by ALND versus staging by ALND: meta-analysis of three studies [5,6,8]

DFS

Our meta-analysis of 1038 patients (2 studies) showed no statistically significant difference for DFS (HR 1.06, 95% CI, 0.81 to 1.38, I^2=0%) for women assigned to no staging compared with axillary staging (Figure 4-2B).

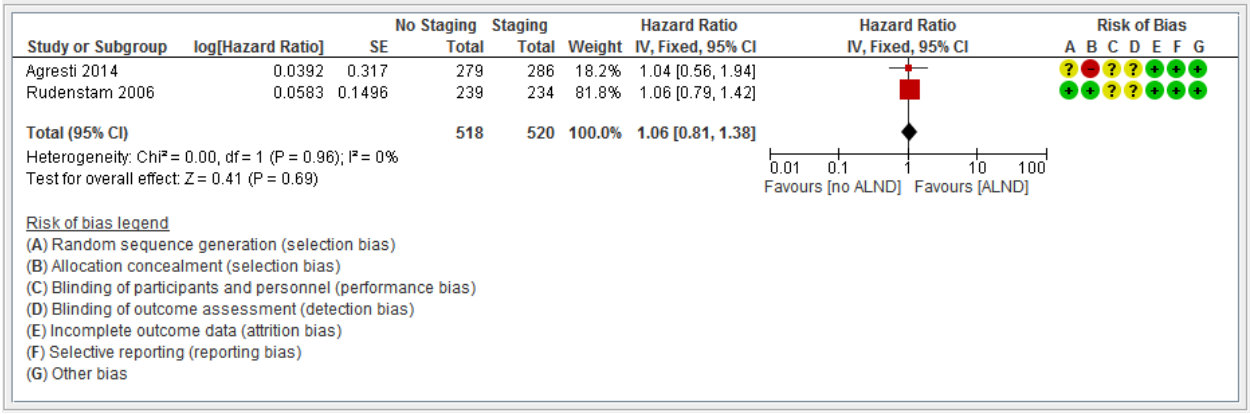

Figure 4-2B. Disease-free survival for no staging by ALND versus staging by ALND: meta-analysis of two studies [5,8].

Recurrence

The Liang et al. [7] meta-analysis of 692 patients (2 studies [5,6]) reported no statistically significant differences for in-breast recurrence (RR, 1.20; 95% CI, 0.55 to 2.64, I^2=62%, p=0.65), or distant recurrence (RR, 1.17; 95% CI, 0.75 to 1.82, I^2=0%, p=0.48) between patients who received axillary staging and those who did not. However, patients in the axillary staging group experienced less axillary recurrence than the no surgery group (RR, 0.24; 95% CI, 0.06 to 0.95, I^2=0%, p=0.04).

Our systematic review identified one additional study, the INT09/98 trial [8], that reported on recurrence outcomes. The INT09/98 trial [8] did not define recurrence outcomes in the same way, and did not report data in a consistent way as Liang et al. [7], therefore we were not able to update the meta-analysis [7] for this outcome. The INT09/98 study [8] reported no statistically significant difference in local (4.6% vs. 5.2%, p=0.839) or contralateral breast cancer recurrence (5.7% vs. 4.8%, p=0.695).

Quality of life

One of the four included studies [5] reported on quality of life. Quality of life was measured by physician's assessment and by patient experience (self-assessed) of restricted ipsilateral arm movement and/or pain. By physician assessment, at one month after surgery, the authors found a significant increase in restriction of movement in the group who received ALND compared with no ALND: 39% vs. 15%, p=0.000001. Physicians reported that 23% of patients who received ALND compared with 7% in the no ALND group experienced pain, p=0.00006. Arm circumference and activity of daily living were found to be similar by physician assessment (values not reported). After the first postoperative period physician-reported quality of life outcomes, as well as lymphedema rate were not statistically different between groups. As well, patients in the ALND arm reported more restricted arm movement (p<0.0001), and more severe postsurgery numbness (p=0.04) at the first assessment.

The ongoing SOUND [9] trial is planning to provide data on quality of life.

Adverse events and surgical complication rate

None of the included trials reported on surgical complication rates. One of the included studies [122] reported on functional outcomes on a subset of patients; detailed results are shown in Table 4-7.

Ability to map and procedure completion rate

None of the included trials reported on these outcomes.

Table 4-6. Question 1: Axillary staging vs. no staging (by surgery or imaging). Assessment of the certainty of the evidence for included studies.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Staging	No Staging	Relative (95% CI)	Absolute (95% CI)		
Overall Survival (absolute risk is the risk of staying alive) (assessed with: HR)												
3	RCTs [5,6,8]	not serious	not serious	not serious	not serious	none	370/629 (58.8%)	361/628 (57.5%)	**HR 1.05** (0.84 to 1.32)	**18 more per 1,000** (from 62 fewer to 102 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Disease-free survival												
2	RCTs [5,8]	not serious	not serious	not serious	not serious	none	356/520 (68.5%)	336/518 (64.9%)	**HR 0.96** (0.77 to 1.18)	**15 fewer per 1,000** (from 60 more to 96 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Recurrence breast (assessed with: Risk ratio [Liang et al. [7])												
2	RCTs [6,122]	serious	not serious	not serious	not serious	none	13/343 (3.8%)	11/349 (3.2%)	**RR 1.20** (0.55 to 2.64)	**6 more per 1,000** (from 14 fewer to 52 more)	⊕⊕⊕ MODERATE	CRITICAL
Recurrence distant (assessed with: Risk ratio [Liang et al. [7])												
2	RCTs [6,122]	serious	not serious	not serious	not serious	none	38/343 (11.1%)	33/349 (9.5%)	**RR 0.99** (0.79 to 1.24)	**1 fewer per 1,000** (from 20 fewer to 23 more)	⊕⊕⊕ MODERATE	CRITICAL
Recurrence axilla (assessed with: Risk ratio [Liang et al. [7])												
2	RCTs [6,122]	serious	not serious	not serious	not serious	none	2/343 (0.6%)	10/349 (2.9%)	**RR 0.24** (0.06 to 0.95)	**22 fewer per 1,000** (from 1 fewer to 27 fewer)	⊕⊕⊕ MODERATE	CRITICAL
Incidence of breast cancer events (invasive relapse at any site or contralateral breast cancer)												
1	RCT [6]	not serious	not serious	not serious	serious[a]	none	50.112/464 (10.8%)	49.502/467 (10.6%)	**HR 0.97** (0.65 to 1.46)	**3 fewer per 1,000** (from 36 fewer to 45 more)	⊕⊕⊕ MODERATE	CRITICAL
Local recurrence												
1	RCT [8]	not serious	not serious	not serious	Serious[b]	none	13/272 (4.8%)	11.27/245 (4.6%)	**p=0.839**	5.2% vs. 4.6% (95% CI *nr)*	⊕⊕⊕ MODERATE	CRITICAL

[a] one study – stopped early; [b] one study

CI =confidence interval; HR = hazard ratio; nr = not reported; RCTs = randomized controlled trials; RR = relative risk

Table 4-7. Question 1: Axillary staging (by surgery or imaging) vs. no staging. Summary results of included studies with patient-level data. Primary outcome reported in bold font.

Study, date, study name	Comparison	OS	DFS	Recurrence	Adverse events / Surgical complications
Agresti, 2014 [8] INT09/98 trial	ALND[a] vs. obs	**OS rate at 10 yrs:** obs: 91.5% (95% CI, 87.0%-94.4%) vs. ALND: 93.3% (95% CI,89.4%-95.8%) Adjusted HR for obs. vs. ALND: 1.09 (95% CI, 0.59 to 2.00; p=0.783) The 90% CI of the HR was (90% CI, 0.65 to 1.81), the right boundary being below the noninferiority margin (degree of difference, 1.9) noninferiority p=0.037	DFS rate at 10 yrs: Obs.: 91.3% (95% CI, 86.7% to 94.3%) vs. ALND: 92.4% (95% CI, 88.5% to 95.1%) Adjusted HR for Obs. vs. ALND: 1.04 (95% CI, 0.56-1.94; p=0.898) The 90% CI of the HR was 0.62 to 1.76; noninferiority p=0.029	**Axillary recurrence:** *nr* (only favourable and unfavourable subgroups in the observation group were compared) **Local recurrence:** 5.2% vs.4.6%, p=0.839	*nr*
*Martelli 2012 [6]	ALND vs. no ALND	**OS:** NS **BC mortality:** 15-yr crude cumulative incidence of BC death: 7.6% (95% CI, 2.5 to 12.7) vs.9.2% (95% CI, 3.7 to 14.6). Crude cumulative incidence curves for BC mortality and distant metastases p=0.64 and p=0.95 respectively. HR of death: 1.18 (95% CI, 0.73 to 1.92)	*nr*	Axillary disease: 15-yr crude cumulative incidence: 0% vs. 6% (95% CI, 0 to 12.6). Ipsilateral breast disease: 15-yr cumulative incidence: 4% (95% CI, 0.1 to 7.8) vs. 8.3% (95% CI, 2.1 to 14.5). Distant metastases: 15-yr crude cumulative incidence: 8.6% (95% CI, 3.2 to 13.9) vs. 9.6% (95% CI, 3.3 to 15.9)	*nr*
Avril, 2011 [122]	Surgery + ALND vs. surgery with no ALND	OS at 5 yrs: 98% vs. 94%; HR 2.91 (95% CI, 1.33 to 6.36) (ITT analysis) Equivalence is not demonstrated due to a higher than expected OS in the no ALND group (expected 95%), and lack of statistical power.	EFS at 5 yrs: 96% vs. 90%; HR 2.26 (95% CI, 1.32 to 3.86) (per protocol analysis, ITT analysis *nr*)	At 5 yrs: Axillary metastases: 0 vs. 1.3% (p value *nr*) Breast/chest wall metastases: 1.3% vs. 1.7% Metastatic event: 0.3% vs. 1.3% Contralateral breast cancer: 0.3% vs. 0.7% BC death: 0.3% vs. 1.7% (All of the above per protocol analysis)	Functional outcomes (on 543 of 625 pts): Null vs. moderate and/or major: Arm fatigue: 254/4 vs. 249/24, p=0.0002 Shoulder mobility: 252/5 vs. 250/21, p=0.0005 Parestesia: 252/6 vs. 233/41, p<0.0001 Lymphedema: 255/3 vs. 246/29, p<0.0001 Other functional impairments: 251/12 vs. 260/16, p=0.252 Number of pts with functional impairment: 242/8 vs. 200/15, p=0.0005
*Rudenstam, 2006 [5] International Breast Cancer Study Group Trial 10-93	Surgery + axillary clearance vs. surgery alone	OS: 75% vs. 73%, HR 1. 05; 95% CI, 0.76 to 1.46; p=0.77	DFS: 67% vs. 66%, HR 1. 06; 95% CI, 0.79 to 1.42; p=0.69	Total BC events: 18% vs. 16%: p=NS including: Deaths because of recurrence: 31% vs. 30% p=*nr* Local recurrence: 4% vs. 2% Contralateral recurrence: 1% vs. 2% Axillary recurrence[b]: 1% vs. 3% Distant recurrence: 12% vs. 10%	*nr*

* included in Liang et al. review [7]
[a] 3 Berg levels axillary dissection
[b]Axillary recurrence in Rudenstam et al. [5] includes both axillary recurrence among patients with axillary dissection, and reappearance of tumour in undissected axilla

ALND = axillary lymph node dissection; BC = breast cancer; CI = confidence interval; DFS = disease-free survival; EFS = event-free survival; HR = hazard ratio; ITT = intention-to-treat; *nr* = not reported; NS = not significant; obs = observation; OS = overall survival; pts = patients; SLNB = sentinel lymph node biopsy; yr = year

Literature Search Results for Primary Studies

Question 2: Further axillary treatment for women who did not receive NAC and were sentinel lymph node negative at diagnosis

The flow diagram for primary studies is reported in Appendix 4. Table 4-8 shows the evidence that was identified for Question 2. Table 4-9 reports the general characteristics of the included primary studies. Table 4-10 presents summary results. We identified studies that examined the effects of two types of further axillary treatment: surgery intended as ALND, and radiotherapy of the axilla.

Surgery trials

The Lyman et al. guideline and systematic review [3,4] included seven studies: the National Surgical Adjuvant Breast and Bowel Project (NSABP) B32 trial, from which we captured three publications [15-17]; the Sentinella/Gruppo Interdisciplinare Veneto di Oncologia Mammaria (GIVOM) [18], the Canavese et al. trial [19]; the Royal Australasian College of Surgeons/Sentinel Node Versus Axillary Clearance (RACS/SNAC) [20,21]; and the Veronesi et al. (NCT00970983) trial [22]. The Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial, and the Cambridge/East Anglia Study Group, which were published prior our cut-off date of 2007, were also included in the Lyman et al. guideline [3,4].

The participants of included studies had breast cancer of stage II or lower. The intervention in all studies was ALND in combination with SLNB compared with SLNB alone.

Outcomes reported included OS and death rate [15-19,22], DFS [15,18,22], and loco-regional or distant recurrence [15,18,19,22]. Quality of life outcomes were reported by the SNAC trial [20], by the Sentinella/GIVOM trial [18], and by a companion study [131] of the NSABP-B-32 trial [15]. The NSABP-B-32 trial [15] reported on surgery-related adverse events, while the SNAC trial [20] reported on arm volume and function, and the Sentinella/GIVOM trial [18] reported on lymphedema, movement restrictions, pain and numbness.

Two companion trials of the NSABP B-32 reported on accuracy of SLNB and allergic reactions rates to blue dye [16], and on the effect of occult metastases on survival [17].

Two of the included trials reported information on the surgeon's experience: Veronesi et al. [22] reported that all patients were treated at a single centre by an experienced breast team, and the SNAC trial [20] reported that each participating surgeon was required to have completed 20 consecutive cases of SLNB followed by axillary clearance with a >90% success rate in detection of the sentinel node.

Our search of the literature, as well as the ASCO 2017 update [3] did not uncover any new evidence that would change the 2014 ASCO recommendations [4].

Radiotherapy trials

For radiotherapy interventions, we included the Early Breast Cancer Collaborative Group [86] individual patient data meta-analysis, and we supplemented this evidence with three primary studies [23,25,132]. In addition, 10% of participants in the MA.20 trial [24] (Table 4-13) had high-risk node negative disease with primary tumours of size ≥5 cm, or tumours >2 cm with fewer than 10 lymph nodes removed, and at least one of the following: grade III histology, lymphovascular invasion, or ER negativity.

The participants in these studies had early-stage breast cancer, and a clinically negative axilla at diagnosis. The Early Breast Cancer Trialists' Collaborative Group [86] individual patient data meta-analysis included women with node-positive and -negative disease, and presented separate results for them. The studies in which these women participated started recruitment before the year 2000. For this reason, the irradiation treatment that they received is not comparable with radiation treatment that is currently given. We, therefore, did not use this study as the base for our recommendation. Zurrida et al. [132] was an unplanned analysis of a

previous study [14] published before 2007, the cut-off date of this systematic review. Wang et al. [25] included women with triple-negative breast cancer.

The intervention in the included studies was described as irradiation of the axilla [132], or of the chest wall and regional nodes [23,25,86], and it was compared with no irradiation. None of the included studies reported on the expertise of the operators who administered the radiotherapy intervention.

The four included studies reported on recurrence [23,25,86,132], OS [23,132], or mortality rates [86], DFS [23,132], and adverse events [23].

Table 4-8. Literature search results for Question 2

Comparison for Question 2		Endorsed guidelines	Included, high quality SRs	Included RCTs	Included Observational comparative trials	Ongoing trials
Intervention	Control					
Further axillary treatment (e.g., with radiation therapy)	No further axillary treatment	**Surgical interventions**				
		ASCO 2017 guideline [3,4]	NA	All identified studies [15,18-20,22] were also included in the endorsed guideline	NA	NCT02651142
		Radiotherapy interventions				
		NA	EBCTCG [86] IPD meta-analysis	EORTC 22922/10925 [23] MA.20, 2015 [24][a] Wang, 2011 [25]	Zurrida, 2013 [132] (subgroup of GRISO 053 RCT [14])	PMRT-NNBC 1602 (NCT02992574) TAILOR RT trial (NCT03488693)

[a] Ten percent of the population in the MA.20 were high-risk node negative

ASCO = American Society of Clinical Oncology; IPD = individual patient data; NA = not applicable; PMRT-NNBC = Post-Mastectomy Radiation Therapy in High Risk, Node Negative Women With Early Breast Cancer (PMRT-NNBC) 1602 trial; RCT = randomized controlled trial; SRs = systematic reviews

Companion studies

We identified 14 corollary studies [16,131,133-144] of the included trials (Table 4-11). Among these trials one examined patient-reported outcomes for morbidity [131], two examined lymphedema rates [135,137], and two reported on long-term follow-up [138,139]. The other publications examined false negative rate [133,140], accuracy [16] of SLNB, and surgeon preparation [136], which were not outcomes of interest for question 2.

Ongoing Unpublished, or Incomplete Studies

The search for ongoing trials (Appendix 8, Table 1) identified three RCTs that are still recruiting participants. The PMRT-NNBC 1602 trial (CTRI/2016/12/007532 NCT02992574) that is expected to be completed at the end of 2028, examines PMRT in node-negative women with high-risk, early-stage breast cancer; the NCT02651142 trial, expected to be completed in January 2025 examines SLNB with or without parasentinel lymph node dissection; the TAILOR RT trial (NCT03488693) examines regional radiotherapy in women with low-risk node-positive breast cancer, and it was expected for completion at the end of 2027.

Subgroups

Among the included radiotherapy studies Zurrida et al. [132] examined the subgroup of patients with high (≥14%) Ki67 of the GRISO53 trial [14].

Table 4-9. Question 2: Further axillary treatment in patients with negative lymph nodes who did not receive NAC. General characteristics of included studies with patient-level data

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Sample size calculation	Comparison	Outcome(s)	Adjuvant treatment
Surgery (i.e., ALND) trials						
Veronesi, 2010 [22] **Country:** Italy **Funding:** Associazione Italiana per la Ricerca Sul Cancro and The American-Italian Cancer Foundation	Single-centre equivalence RCT 10 yrs follow-up **Accrual Period:** Mar 1998 to Dec 1999 **Aim:** To compare outcomes of pN0 pts who were given ALND vs. no ALND **Follow-up, median:** 102 mos (range 1 to 120 mos)	532 pts with tumour of the breast ≤2 cm, 516 pts in the per protocol analysis. Age: Median (range): ALND arm: 56 yrs (40 to 75); SLNB arm: 55 yra (40 to 75) Stage: Tumour size: Tumour size ≤2 cm	The sample size was calculated initially only for pathologically negative pts: 490 pts were needed to show equivalence (a ≤5% between-group difference) with 90% power and α at 0.05. With 516 pts enrolled, 30% of whom were node positive, the study had 84% power.	SLNB + ALND vs. SLNB alone (+ ALND only if positive at SLNB)	**Primary outcome:** Number of axillary metastases in the SLNB arm and negative nodes during follow-up **Secondary outcomes:** DFS OS	All pts received breast-conserving surgery
Krag, 2010 [15] **Country:** US and Canada **National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32** **Funding:** US Public Health Service, National Cancer Institute, and Department of Health and Human Services	Multicentre (80 centres) RCT phase III **Accrual Period:** May 1999 to Feb 2004 **Aim:** To establish whether SLNB achieves the same survival and regional control as ALND, but with fewer side-effects **Follow-up, median:** 95.6 months (range 70.1 to 126.7 mos)	5611 pts with clinically negative axilla (as assessed by physical examination but not specified), operable BC Age: ≤49 yrs: 24.5% ≥50 yrs: 75.5% Stage: Tumour size: ≤2 cm: 83.8% 2.1-4.0: cm 14.7% ≥4.1: cm 1.5%	To detect a difference of 2% in OS at 5 yrs 300 deaths were needed with an α at 0.05	2807 SLNB + ALND vs. 2804 SLNB alone (and subsequent ALND if SN positive).	**Primary outcome:** OS **Secondary outcomes:** DFS (including local, regional or distant metastases) Regional control Death Morbidity	Surgery, systemic adjuvant treatment, RT
Gill, 2009 [20] **Country:** Australia, New Zealand **SNAC Trial** **Funding:** Australian National Health and Medical Research Council, the National Breast Cancer Foundation, the Australlian Department of Health and Ageing, Medical Benefit Fund Australia, the	Multicentre RCT **Accrual Period:** May 2001 to May 2005 **Aim:** To determine whether management of the axilla by SLNB for negative nodes with ALND if nodes were positive was better than routine ALND in terms of morbidity and cancer-related outcomes. **Follow-up, median:** 12 mos	1088 women with unifocal, clinically node-negative early BC ≤3 cm (1028 in analysis) Age: SLNB vs. ALND: 30-49 yrs: 21% vs 22% 50-69 yrs: 65% vs. 66% ≥70 years: 13% vs 12% Stage: Tumour size: SLNB vs. ALND ≤1 cm: 27% vs. 27% 1-2 cm: 45% vs. 46% 2-3 cm: 19% vs. 19% >3 cm: 9% vs. 8%	The sample size of 1,100 women was calculated to give: over 80% power to detect a 6% absolute difference in the rates of significant arm swelling between RAC and SNBM (15% vs. 9%) with a two-sided p value of 0.05, over 90% power to detect a difference of this magnitude on a continuous scale with a two-sided p value of 0.01, and over 90% power to detect one-point difference on the SSSS for arm symptoms, functions, and disabilities, with a two-sided p value of 0.01	544 SLNB (+ ALND if node + or not detected) vs. 544 ALND	**Primary outcome:** Increase in arm volume from baseline to the average at 6 and 12 mos **Secondary outcomes:** Proportions of women with ≥15% increase in arm volume, and early axillary morbidity. Average scores for arm symptoms, dysfunctions, and disabilities at 6 and 12 mos	Postoperative adjuvant therapies

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Sample size calculation	Comparison	Outcome(s)	Adjuvant treatment
Scottwood Trust (New Zealand)						
Canavese, 2009 [19] **Country:** Italy **Funding:** *nr*	Single-centre noninferiority RCT. Stopped early for benefit **Accrual Period:** Nov 1998 to Oct 2001 **Aim:** To test the efficacy of SLNB on survival and regional control **Follow-up, median:** 66±16.8 mos	248 women with early BC ≤3 cm, clinically negative (undefined) axilla. (225 pts included in analysis) Age: median 59 Stage: pTis: 0.9% pT1mic: 0.9% pT1a: 9.3% pT1b: 18.7% pT1c: 51.5% pT2: 18.7%	2570 pts were needed to obtain a power at 90% for a one-sided α = 0.025 and considering both accrual and follow-up periods of 5 years, with an estimated annual lost-to-follow-up rate of 2%	124 SLNB + routine ALND (110 evaluable) vs. 124 SLNB + ALND only if node + (115 evaluable)	**Primary outcome:** EFS at 5 yrs **Secondary outcomes:** OS at 5 yrs; Frequency of axillary recurrencies; Sensitivity and predictive value of SLNB for the presence of axillary metastases	Mastectomy of quadranctectomy + RT of the breast, and adjuvant or hormone therapy according to prognostic factors
Zavagno, 2008 [18] **Country:** Italy **Sentinella/ GIVOM** **Funding:** Istituto Oncologico Veneto, fondazione della Cassa di Risparmio di Padova e Rovigo	Multicentre (18) noninferiority RCT **Accrual Period:** May 1999 to December 2004 **Aim** To assess the efficacy and safety of SLNB compared with ALND **Follow-up, median:** 56 mos (IQR 42.4 to 63.1) mos	749 pts with BC ≤3 cm, and a clinically negative axilla (697 pts in analysis) Age (**mean [SD]):** ALND: 58.2 [10.6] yrs SLNB: 57.6 [10.4] yrs **Stage:** T1a: ALND: 2% SLNB: 3.5% T1b: ALND: 20.4%; SLNB: 19.5% T1c: ALND: 59.1% SLNB: 57.6% T2 ≤3 cm: ALND: 17.9% SLNB: 17.9% T4: ALND: 0 SLNB: 0.9% NA: ALND: 0.6% SLNB: 0.6%	1498 were required to show with 80% power, at 5 yrs, that DFS for SLNB was noninferior to ALND by >6% inabsolute difference with 2-sided α = 0.05	SLNB + routine ALND vs. SLNB + ALND only if node+	**Primary outcome:** DFS **Secondary outcomes:** OS Physical Morbidity Side effects QOL (measured with the SF 36, and the Psychological General Well Being Index) Loco-regional recurrence	All pts who underwent breast-conserving surgery received RT of the breast. Pts with unfavourable prognostic features received adjuvant chemo-and/or hormonal therapy
Schem, 2011 ABS [145] **Country:** Germany **KISS** **Funding:** *nr*	RTC phase III, multicentre (33) **Accrual Period:** *Nr* **Aim** To provide long term data on the results of the SLNB approach **Follow-up, median:** 115 mos	1182 pts with operable, clinically node negative (undefined) invasive BC Age: *nr* Stage: *nr*	*nr*	594 ALND (independent of the SLNB outcome) vs. 588 ALND only if SLNB positive or failure of SLNB detection, and observation only if SLNB negative	**Primary outcome:** RFS OS **Secondary outcomes:** *nr*	*nr*
Radiotherapy trials						

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Sample size calculation	Comparison	Outcome(s)	Adjuvant treatment
Poortmans, 2015 [23] **Country:** Multiple (13) **EORTC trial 22922/10925** **Funding:** Fonds Cancer	Multicentre, RCT **Accrual Period:** Jul 1996 to Jan 2004 **Aim** To study the effect of internal mammary and medial supraclavicular lymph-node irradiation (regional node irradiation) plus whole-breast irradiation or thoracic wall irradiation after surgery **Follow-up, median:** 130.8 mos	4004 women with early-stage breast cancer with centrally or medially located adenocarcinoma. 3866 pts included in analysis of long-term side effects Age: median 54 yrs (range 19 to 75) yrs Stage: T1: 60.1%, T2: 35.7%, or T3[a]: 3.5%; pN0: 44.4% pN1a: 43.1% pN2a:9.9% pN3a: 2.6%	4000 pts, and 791 deaths were needed to detect a difference of 4 percentage points (79% vs. 75%) in 10-yr OS with 80% power at a two-sided α at 0.05	2002 regional + whole breast or thoracic wall irradiation vs. 2002 whole breast or thoracic wall alone Regional irradiation dose: 50 Gy in 25 fractions	**Primary outcome:** OS **Secondary outcomes:** DFS rates DDFS Death from breast cancer AE at 3 yrs (3866 pts) [146]	Breast surgery (mastectomy, breast-conserving surgery and ALND)[b], and adjuvant systemic treatment
Early Breast Cancer Trialists' Collaborative Group, 2014 [86] **Country:** UK **Funding:** Cancer Research UK, British Heart Foundation, UK Medical Research Council	IPD meta-analysis **Accrual Period:** 1964 to 1986 **Aim:** To assess the effect of radiotherapy in pts who received mastectomy and axillary dissection **Follow-up, median:** 112.8 mos per woman (IQR 44.4 to 207.6 mos) 120 mos for recurrence 240 mos for mortality	8135 women from 22 trials with 1 to 3 positive lymph nodes. Of these, 1594 women had node negative disease, and are relevant for this Question Age: *nr* Stage: I, II and III Has separate results for stage pN0	NA	347 ALND pts and 425 axillary sampling pts: Surgery + RT of the chest wall, internal mammary chain, and supraclavicular and/or axillary lymph nodes vs. 353 ALND pts and 445 axillary sampling pts Surgery alone 24 pts had unknown extent of axillary surgery	**Primary outcome:** Recurrence **Secondary outcomes:** BC mortality	Mastectomy and ALND (700 pts) or mastectomy and axillary sampling (870 pts) or axillary surgery unknown (24 pts) Axillary RT vs. no RT and chemo- and hormonal therapy
Zurrida, 2013 [132] **Country:** Italy **GRISO053[c] unplanned subset analysis** **Funding:** *nr*	Case series: subset analysis of a multicentre RCT **Accrual Period:** Feb 1995 to Jul 1998 **Aim:** To assess the prognostic importance of tumour biological factors (i.e., ER, PgR, HER2, Ki67, and molecular subtype) from a subset of the GRISO053 study which compared axillary RT vs. no RT in pts not given axillary dissection	285 (66% of the 435 pts in the original study) with clinically negative (undefined) axilla of age >45 yrs, with tumours ≤1.4 cm, who were not given ALND Age: median 57 yrs (IQR 51-63) Stage: pT1a: 14.7%; pT1b: 54.4%; pT1c: 30.9%; ER+: 89.5%; low (<14%) Ki67: 60.7% Surgeon experience: *nr*	NA, this was a subgroup analysis of a larger study	145 Axillary RT vs. 140 no axillary RT RT was given with X-rays by two opposed tangential fields at a dose of 50 Gys in 25 fractions plus a boost to the tumour bed	**Primary outcome:** DFS **Secondary outcomes:** OS Cumulative incidence of loco-regional recurrence Cumulative incidence of distant recurrence	ER+ pts: hormonal therapy for 5 yrs; Ki67>20% pts: adjuvant chemotherapy for 6 mos

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Sample size calculation	Comparison	Outcome(s)	Adjuvant treatment
	Follow-up, median: 133.2 mos, (IQR 121.2 –146.4) mos					
Wang, 2011 [25] **Country**: China **Funding**: Health Fund for Breast Carcinoma Research from Shanxi Province Health Ministry	Multicentre RCT **Accrual Period:** Feb 2001 to Feb 2006 **Aim:** to evaluate whether the combination of chemotherapy and radiotherapy could significantly increase survival outcomes in triple negative BC women after mastectomy **Follow-up, median:** 63 mos	681 women who had received mastectomy for with triple negative BC Age: RT group: ≤50 yrs: 62% >50 yrs: 38% Control group: ≤50 yrs: 61.9% >50 yrs: 38.1% Stage: I or II; 86.1% were node negative	*nr*	[c] 145 Axillary RT vs. 140 no axillary RT RT was given with X-rays by two opposed tangential fields at a dose of 50 Gys in 25 fractions plus a boost to the tumour bed	**Primary outcome:** Treatment compliance Acute toxicities **Secondary outcomes:** Recurrence-free survival OS Cumulative incidence of loco-regional recurrence Cumulative incidence of distant recurrence	Chemotherapy with radiotherapy 2–3 weeks after the sixth cycle of chemotherapy or chemotherapy alone. ER+ pts: hormonal therapy for 5 yrs; Ki67>20% pts: adjuvant chemotherapy for 6 months

[a]In 95.8% of patients the primary tumour was ≤5 cm; in 87.5% no axillary nodes or one to three involved axillary nodes.
[b]76.1% of the patients had breast-conserving surgery followed by whole-breast radiation; in 85.1% of these patients, this radiation therapy was followed by boost irradiation to the primary tumour bed.
[c] The Authors reported that regional nodal irradiation was added as clinically indicated, mostly for patients with more than 2 positive axillary nodes.

α = alpha; ABS = abstract; AE = adverse events; ALND = axillary lymph node dissection; AR = absolute reduction; BC = breast cancer; CG = control group; CMF = cyclophosphamide, methotrexate, 5 fluorouracil (also known as 5FU); D = day; Dec = December; DDFS = distant disease-free survival; DFS = disease-free survival; EFS = event-free survival; ER = estrogen receptor; FN = false negative; FNAC = fine needle aspiration cytology; Gy = gray (unit); HER2 = Human epidermal growth factor receptor 2; IPD = individual patient data; IQR = inter quartile range; Ki67 = tumour proliferation index antigen Ki-67; mos = months; NA = not applicable; NAC = neo-=adjuvant chemotherapy; *nr* = not reported; OS = overall survival; PgR = progesterone receptor; pN0; no regional lymph node metastasis; pts = patients; QOL = quality of life; RAC = routine axillary clearance; RCT = randomized controlled trial; RFS = relapse-free survival (i.e., DFS); RT = radiotherapy; SD = standard deviation; SF-36 = 36 Item Short Form Survey; SLN = sentinel lymph node; SNBM = sentinel node-based management; SLNB = sentinel lymph node biopsy; SSSS = SNAC study specific scale; US = ultrasound; yrs = years

Table 4-10. Question 2: Further axillary treatment in patients with negative lymph nodes who did not receive NAC. Summary results of included studies with patient-level data. Primary outcome results in bold font.

Study, date, (Reference) study name	Comparison	OS / Mortality	DFS	QOL	Recurrence	Adverse events / Surgical complications
Surgery Trials						
Veronesi, 2010 [22]	SLNB + ALND vs. SLNB alone	OS at 10 yrs: 89.7% (95% CI, 85.5 to 93.8) vs. 93.5% (95% CI, 90.3% to 96.8%) Death rate: 8.9% vs. 5.8%, p=0.15	BC-related event rates: 88.8% (95% CI, 84.6%-92.9%) vs. 89.9% (95% CI, 85.9%-93.9%), p=0.52	*nr*	Local, regional and distant metastases rates: 10.1% vs. 8.9%, p=0.52 Distant metastases rates: 7.8% vs. 6.6%, p=0.5 Carcinoma rates: 3.9% vs. 3.5%, p=0.71 Rates of primary tumours in other organs: 4.7% vs. 2.3%. p=0.13	*nr*
Krag, 2010 [15] **National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32**	SLNB + ALND vs. SLNB alone	**OS at 5 yrs:** 96.4% (95% CI, 95.6 to 97.2) vs. 95.0% (95% CI, 94.0 to 96.0), HR 1.19 (95% CI, 0.95 to 1.49), p=0.13	DFS: 89.0% (95% CI, 87.6 to 90.4) vs. 88.6% (95% CI, 87.2 to 90.0) HR 1.07 (95% CI, 0.90-1.22), p=0.57	From companion study [131]: Arm symptoms measured as patient-reported outcomes: SLNB+ALND vs. SLNB alone: At 6 mos: mean 4.8 vs. 3.0, p<0.001; At 12 mos: 3.6 vs. 2.5, p=0.006	Local recurrence rate: 2.7% vs. 2.4% Regional node recurrence rate: 0.4% vs. 0.7% (p=0.22) Distant metastases rate: 2.8% vs. 3.2% (p value *nr)*	≥grade 3 surgery-related AE: 0.5% vs. 0.4% (p values *nr)*
Gill, 2009 [20] **SNAC Trial**	SLNB (+ ALND if node + or not detected) vs. ALND	*nr*	*nr*	[b]**Changes in pt self-ratings in the SSSS (between-group difference):** Overall summary score: 4.4 vs. 7.0, difference 2.6% (95% CI, 1.3 to 3.9), p<0.001; Arm symptoms: 5.5 vs. 9.7 difference: 4.2% (95% CI, 2.8 to 5.7), p<0.001; Arm swelling: 3.4 vs. 7.3 difference: 4.0% (95% CI, 2.3 to 5.5), p<0.001; Arm dysfunctions: 3.6 vs. 5.5, difference: 1.9% (95% CI, 0.3 to 3.5), p=0.02 Arm disabilities: 2.9 vs. 3.4, difference 0.5% (95% CI, -0.1 to 2.1), p=0.5 Percentage changes in clincian's ratings from baseline to the average between 6 and 12 months: Increase in arm volume: 2.8% vs. 4.2%, difference: 1.4 (95% CI, 0.6 to 2.3), p=0.002 Decrease in lateral abduction: 2.5% vs. 4.4%, difference 1.9 (95% CI, 0.3 to 3.5), p=0.02	*nr*	**Arm volume and function: Increase in arm volume**: (per protocol 519 vs. 509): 2.8% vs. 4.2%; difference 1.4% (95% CI, 0.6 to 2.3%), p=0.002 Number with an increase in arm volume ≥15%: 4.2% vs. 6.9%; difference: 2.7% (95% CI,-0.1 to 5.5), p=0.06. Decrease in lateral abduction: 2.5% vs. 4.4%; difference 1.9% (95% CI, 0.3 to 3.5), p=0.02
Canavese, 2009 [19]	SLNB + ALND only if node+ vs. SLNB + routine ALND	OS rate: 97.2% (95% CI, 95.4 to 98.9) vs. 97.2% (95% CI, 95.4 to 98.9), p=0.697	**EFS at 5 yrs:** 89.8% (95% CI, 86.9% to 92.7%) vs. 94.5% (95% CI, 90.9% to 98.1%), p=0.715	*nr*	Recurrence of any type: RR 0.87 (95% CI, 0.38 to 2.01), p=0.741	*nr*

Study, date, (Reference) study name	Comparison	OS / Mortality	DFS	QOL	Recurrence	Adverse events / Surgical complications
Zavagno, 2008 [18] **Sentinella/GIVOM**	SLNB + routine ALND vs. SLNB + ALND only if node+	OS estimate rate at 5 yrs: 95.5% (95% CI, 92.2 to 97.5) vs. 94.8% (95% CI, 91.6 to 96.8) Death rate due to BC: 2.3% vs. 2.9% p value *nr*	**DFS rate at 5 yrs**: 89.9% (95% CI, 85.3 to 93.1) vs. 87.6% (95% CI, 83.3 to 90.9); difference 2.3% (95% CI, -3.1% to 7.6%,), p=0.7692. The upper bound is more than the set boundary for noninferiority of 6%, therefore the possibility that DFS is worse with SLNB could not be excluded.	SF 36: NS in all domains Psychological Well Being Index Questionnaire: better anxiety profile (p=0.013), and in the general index (p=0.015) in the the SLNB group than in the ALND group	Distant metastases: 4.6% vs. 3.2%, p value *nr*	[c]Lymphedema: OR 0.48 (95% CI,0.3 to 0.8), p=0.01 [c]Movement restrictions: OR 0.55 (95% CI, 0.3 to 0.9), p=0.016 [c]Pain: OR 0.74 (95% CI, 0.5 to 1.1), p=0.11 [c]Numbness: OR 0.51 (95% CI, 0.4 to 0.7), p<0.0001
Schem, 2011 ABS [145]	ALND (independent of the SLNB outcome) vs. ALND only if SLNB positive or failure of SLNB detection, and observation only if SLNB negative	**OS** HR 1.53 (95% CI, 0.88 to 2.66) p=0.13	**RFS** HR 1.44 (95% CI, 0.95 to 2.18) p=0.084	*nr*	*nr*	*nr*
Radiotherapy Trials						
Poortmans, 2015 [23] **EORTC 22922/10925 trial**	Regional + whole breast or thoracic wall irradiation vs. whole breast or thoracic wall irradiation alone	**OS at 10 yrs:** 82.3% (95% CI, 80.4 to 83.9) vs. 80.7% (95% CI, 78.8 to 82.5), HR 0.87 (95% CI, 0.76 to 1.0) p=0.06 Death rate from BC at 10 yrs: 12.5% (95% CI, 11.0 to 14.0) vs. 14.4% (95% CI, 12.8 to 16.0) HR 0.82, 95% CI, 0.70 to 0.97, p=0.02).	72.1% vs. 69.1% (HR for disease progression or death 0.89 (95% CI, 0.80 to 1.00), p=0.04 Distant DFS: 78% (95% CI, 76.1 to 79.8) vs. 75% (95% CI, 73 to 77), p=0.02	*nr*	Rate of first recurrence at 10 yrs: 19.4% (95% CI, 17.6 to 21.1) vs. 22.9% (95% CI, 21.0 to 24.8), p=0.02	At 10 yrs follow-up: Pulmonary fibrosis: 4.4% vs. 1.7%, p<0.001 Cardiac disease: 6.5% vs. 5.6%, p=0.25 Cardiac fibrosis: 1.2% vs. 0.6%, p=0.06
Early Breast Cancer Trialists' Collaborative Group, 2014 [86]	Surgery + RT of the chest wall, internal mammary chain, and supraclavicular and/or axillary lymph nodes vs. Surgery alone	**ALND pts :** BC mortality at 20 yrs: 28.8% vs. 26.6% RR 1.18 (95% CI, 0.89 to1.55, 2 sided p>0.1) Overall mortality at 20 yrs: 47.6% vs. 41.6%, RR 1.23 (95% CI,1.02 to 1.49, 2 sided p=0.03)	*nr*	*nr*	<u>ALND pts :</u> **Loco-regional recurrence rate:** 3.0% vs. 1.6% RR 1.81 (95% CI, 0.6 to 5.17, 2 sided p>0.1) **Overall recurrence:** 22.4% vs. 21.1% RR 1.06 (95% CI, 0.76 to 1.48, 2 sided p>0.1) <u>Axillary sampling pts:</u> **Loco-regional recurrence rate:**	*nr*

Study, date, (Reference) study name	Comparison	OS / Mortality	DFS	QOL	Recurrence	Adverse events / Surgical complications
		Axillary sampling pts: BC mortality: 32.0% vs. 35.8%, RR 0.97 (95% CI, 0.77 to 1.22, 2sided p>0·1) Overall mortality: 46.1% vs. 49.9%, RR 1.00 (95% CI, 0.84 to 1.18, 2sided p>0.1)			3.7% vs. 17.8% RR 0.25 (95% CI, 0.16 to 0.38, 2 sided p<0.00001) **Overall recurrence rate:** 22.1% vs. 34.2%, RR 0.61 (95% CI, 0.47 to 0.80, 2 sided p=0.0003)	
Zurrida, 2013 [132] **Unplanned subset analysis of the GRISO053 trial**	Axillary RT vs. no axillary RT	OS at 10 yrs follow-up: 96% (95% CI, 90% to 98%) vs. 90% (95% CI, 84% to 94%), p=0.078 [a]HR 0.39 (95% CI, 0.14 to 1.05), p=0.062	**DFS At 10 yrs follow-up:** 94% (95% CI, 88% to 97%) vs. 89% (95% CI, 82–93%), p=0.077 [a]HR 0.50 (95% CI, 0.24 to 1.04), p=0.065 [a]Subgroups: Ki67 ≤14%: 93% (95% CI, 88% to 99%) vs. 95% (95% CI, 90% to 100%), HR 1.26 (95% CI, 0.43 to 3.64), p=0.91 Ki67 ≥14%: 95% (95% CI, 89% to 100%) vs. 79% (95% CI, 69% to 92%), HR 0.23 (95% CI, 0.08 to 0.67), p=0.005	*nr*	At 10 yrs follow-up: Loco-regional recurrence rate: 5% (95% CI. 2% to 10%) vs. 4% (95% CI, 2% to 9%), p=0.66 [a]Cause-specific hazard for loco-regional failure: HR 0.71 (95% CI, 0.28 to 1.79), p=0.470 Distant recurrence rate: 1% (95% CI, 0% to 6%) vs. 7% (95% CI, 4% to13%), p=0.037 [a]Cause-specific hazard for distant metastases: HR 0.25 (95% CI, 0.07 to 0.92), p=0.037	*nr*
Wang, 2011 [25] Country: China Funding: Health Fund for Breast Carcinoma Research from Shanxi Province Health Ministry	Chemotherapy + RT vs. Chemotherapy	OS at 5 yrs: 90.4% vs. 78.7%, HR 0.79 (95% CI, 0.74 0.97), p=0.03	*nr*	*nr*	RFS at 5 yrs: 88.3% vs. 74.6%, HR 0.77 (95% CI, 0.72 to 0.98), p=0.02 Distant metastases: 1-2 metastases: 24.2% vs. 38.5%, p<0.05	**Neutropenia and nausea/emesis:** 38% and 14.8%, vs. 37.1% and 13.0%, p>0.05 for both.

[a]Multivariate analysis
[b]As measured with the SNAC Study Specific Scales (SSSS), average of 6 and 12 months scorees
[c]Mean of evaluations at 6, 12, 18, and 24 months
AE = adverse events; ALND = axillary lymph node dissection; BC = breast cancer; CI = confidence interval; DFS = disease-free survival; ; EFS = event-free survival; HR = hazard ratio; NAC = neoadjuvant chemotherapy; *nr* = not reported; NS = not significant; OR = odds ratio; OS = overall survival; pts = patients; QOL = quality of life; RFS = recurrence-free survival; RR = relative risk; RT = radiotherapy; SLNB = sentinel lymph node biopsy; yrs = years

Table 4-11. Companion publications of unique studies identified for Question 2

Main study; Comparison; Objectives	Companion publications; Objectives	Summary results of the companion publication
Surgery trials		
Krag 2010 [15] **National Surgical Adjuvant Breast and Bowel Project** **NSABP B-32** SLNB + ALND vs ALND **Objectives:** To establish whether SLNB achieves the same survival and regional control as ALND, but with fewer side-effects	Mamounas, 2011 ABS [133] **Objectives:** To evaluate SLN paraffin tissue blocks from negative SLNs for occult metastases deeper in the blocks to examine FNR of SLNB	FNR of SLNB in B-32 was reduced to 6.4% (49 of 763 cases), p<0.001. In the B-32 trial, more detailed assessment of the SLNs would have significantly reduced the FNR of SLNB by about one-third. However, this reduction would have come at the expense of a 16% increase in the rate of axillary dissection by taking occult metastases into account.
	Land, 2010 [131] **Objectives:** Pre-planned subgroup analysis RCT phase III to present pt-reported outcomes of morbidity of the main study	At 6 and 12 mos follow-up arm symptoms were significantly more bothersome to pts for ALND than for SLNB (mean 4.8 vs. 3.0, p<0.001, and 3.6 vs. 2.5, p=0.006 respectively) . Pts who received ALND were more likely to experience arm and breast symptoms restriced work and social activity, and impared QOL (p≤0.002)
	Krag, 2007 [16] **Objectives:** To present technical aspects of main study including accuracy of SLNB, and allergic reaction rates to BD	Data available for 5536 of 5611 pts; SLNs were successfully removed in 97.2% of pts (5379 of 5536). Identification of a preincision hot-spot was associated with greater SLN removal (98.9% [5072 of 5128]). Only 1.4% (189 of 13171) of SLN specimens were outside of axillary levels I and II. 65.1% (8571 of 13171) of SLN specimens were both radioactive and blue; a small percentage was identified by palpation only (3.9% [515 of 13 171]). The overall accuracy of SLN resection in pts in group 1 was 97.1% (2544 of 2619; 95% CI, 96.4 to 97.7), with a FNR of 9.8% (75 of 766; 95% CI, 7.8 to 12.2). Differences in tumour location, type of biopsy, and number of SLNs removed significantly affected the FNR. Allergic reactions to BD occurred in 0.7% (37 of 5588) of pts with data on toxic effects. Surgeon experience: All surgeons did a minimum of 1-5 prequalifying cases of SLN resection for breast cancer.
	Ashikaga, 2010 [134] **Objectives:** To compare 3-yr post-surgical morbidity levels between pts with negative SLNB alone with those with negative SLNB and negative ALND	Shoulder abduction deficits ≥10% peaked at 1 week for the ALND (75%) and SLNB (41%) groups. At 36 mos arm volume differences ≥10% were evident for the ALND (14%) and SLNB (8%) groups. Numbness and tingling peaked at 6 mos for the ALND (49%, 23%) and SLNB (15%, 10%) groups. Over a 4-yr follow-up period SLNB was shown to be superior to ALND for post-surgical morbidity.
	McCloskey, 2014 [135] **Objectives:** Secondary data analysis to assess the impact of RT on lymphedema risk among women for SLNB vs. ALND	Baseline objective and subjective lymphedema were available for 3916 and 735 pts, respectively. 82% of those with lymphedema assessments received RT with 2.2% receiving regional nodal RT. There was no significant impact of RT on long-term (6-36 mos) lymphedema (p>0.8).
	Krag, 2009 [136] **Objectives:** To evaluate the relationship of surgeon trial preparation, protocol compliance audit, and technical outcomes.	Overall SLNB success rate 96.9% (95% CI, 96.4% to 97.4%) Overall FNR 9.5% (95% CI, 7.4% to 12.0%), p=NS between training methods. **Surgeon experience:** Training categories included surgeons who submitted material on five prerandomization surgeries and were trained by a core trainer (category 1) or by a site trainer (category 2). An expedited group (category 3) included surgeons with extensive experience who submitted material on one prerandomization surgery
	Wetzig, 2017 [144] **Objectives:** To determine whether the benefits of sentinel node-based management (SNBM) over routine axillary clearance (RAC) persisted to 5 yrs	Limb volume increased progressively in the operated and nonoperated arms for 2 yrs and persisted unchanged to year 5, accompanied by weight gain. Correction by change in the nonoperated arm showed a mean volume increase of 70 mL in the RAC group and 26 mL in the SNBM group (p<0.001) at 5 yrs. Only 28 pts (3.3%) had a corrected increase [15% from baseline (RAC 5.0% vs. SNBM 1.7%). Significant predictors were surgery type (RAC vs. SNBM), obesity, diabetes, palpable tumour, and weight gain exceeding 10% of baseline value.

Main study; Comparison; Objectives	Companion publications; Objectives	Summary results of the companion publication
	Goodwin, 2011 ABS [137] **Objectives:** To review lymphedema rates and loco-regional recurrence (single institution) in a subgroup (Group 1) of 71 pts	Lymphedema rate: 11.3% vs. 0%, p=0.007. Median time to lymphedema: 12 mos. Recurrence: Breast tumour recurrence: 5.6% vs. 3.2%,p=0.69 Regional recurrence: 2.8% vs. 1.6%, p=0.71)
	Weaver, 2011 ABS [143] **Objectives:** To ascertain whether OM are a prognostic factor for disease recurrence and survival	OM were detected in 15.9% (95% CI, 14.7% to 17.1%) of the 3887 cases. A statistically significant difference between OM-positive and -negative pts for OS; p=0.03, adjusted HR 1.31 (95%CI, 1.07 to 1.60), DFS; p=0.02, HR 1.40 (95% CI, 1.05 to 1.86), and DDFI; p=0.04, HR 1.30 CI, 1.02 to 1.66). Five year Kaplan-Meier estimates for OS for pts with and without OM detected were 94.6% and 95.8%, respectively. In a subset analysis by OM categorical size, HRs for isolated tumour cell clusters (ITC) and micrometastases were 1.29 and 1.66 (OS), 1.19 and 1.41 (DFS), 1.19 and 1.42 (DDFI), and, for survival without BC death, 1.38 (CI, 1.02 to 1.87) and 1.91 (CI, 1.41 to 2.59), compared to no metastases having been detected. Five year Kaplan-Meier estimates of survival without BC death are 98.4%, 97.8%, and 96.0% when no metastases, ITCs, or micro/macrometastases are detected.
	Weaver, 2011 [17] **Objectives:** To prospectively examine the effct of OM on survival in node-negative BC pts	A statistically significant difference was detected between pts with or without OM for OS; HR for death 1.40 (95% CI, 1.05 to 1.86), p=0.02; DFS; HR for any outcome event 1.31 [95% CI, 1.07 to 1.66]), p=0.009; and distant-free metastases HR for distant disease 1.30 (95% CI, 1.02 to 1.66), p=0.03.
	Julian, 2011 [141] **Objectives:** To evaluate group outcomes for OM	316 (16.4%) of 1924 pts had OM in SLNB+ALND group and 300 (15.3%) of 1960 in SLNB alone group. Non-SN status was available in 312/316 pts in the SLNB alone group; 23 (7.4%) had positive non-SN. In pts with OM, no statistically significant between groups differences were detected in OS or DFS (SLNB alone vs. vs. SLNB + ALND OS HR: 0.89, p=0.62; DFS HR: 0.79, p=0.16). No statistically significant differences in OS or DFS between the groups in pts who were negative for OM were detected (SLNB alone vs. SLNB + ALND: OS HR:1.25, p=0.07; DFS HR: 1.11, p=0.22).
Gill, 2009 [20] SLNB (+ ALND if node + or not detected) vs. ALND **Objectives:** To determine whether management of the axilla by SLNB for negative nodes, with ALND if nodes were positive, was better than routine ALND for morbidity and cancer-related outcomes.	Gill, 2010 ABS [138] **Objectives:** To determine at 3-yr follow-up: a) whether the early reduced morbidity of SN based SLNB compared with routine ALND was sustained, and b) what are the predictors of lymphedema	SLNB significantly reduced the rate of arm swelling compared with ALND, and the benefits at 3 yrs exceeded those seen at 12 mos. The incidence of lymphedema increased after 12 mos but plateaued after 2 yrs. Significant reduction in arm swelling was restricted to those women who were SN negative (p values *nr)*; women who were SN positive and required a second operation had identical lymphedema outcomes to those in the ALND arm. Arm swelling occurred in both the operated and non operated arms and was associated with progressive weight gain over 3 yrs. Multivariate analyses revealed significant predictors of lymphedema (objective measure) were type of surgery, age, presence of a palpable primary cancer, and an extensive in situ component. Similar analysis showed that significant predictors of self-rated swelling were type of surgery, body mass index, side of tumour and lymphatic invasion.
	Smith, 2009 [21] **Objectives:** To compare pts and clinicians assessment of outcome	Pts' ratings on single items were 3-5 times more efficient than clinicians' measurements.
	Wetzig, 2017 [144] **Objectives:** To determine whether the benefits of SLNB management over routine ALND persisted at 5 yrs follow-up	Limb volume increased progressively in the ALND and no-ALND arms for 2 yrs and persisted unchanged to yr 5, accompanied by weight gain. Correction by change in the nonoperated arm showed a mean volume increase of 70 mL in the ALND group and 26 mL in the SLNB group (p<0.001) at 5 yrs. Significant predictors were surgery type (ALND vs. SLNB), obesity, diabetes, palpable tumour, and weight gain exceeding 10% of baseline value.
Canavese, 2009 [19] ALND vs. SLNB **Objectives:** To test the efficacy of SLNB on survival and regional control	Canavese, 2016 [139] **Objectives:** To update the results at 15-yrs follow-up	The ALND and SLNB arms included 115 and 110 pts, respectively. At 14.3 yrs median follow-up: Recurrences (primary BC): 22 (19 %) vs. 17 (16 %) (p=0.519). Axillary relapse: 2 vs. 0, p values *nr* OS (82.0 vs. 78.8 %), p = 0.502 EFS (72.8 vs.72.9 %) p=0.953

Main study; Comparison; Objectives	Companion publications; Objectives	Summary results of the companion publication
Zavagno [18] **Sentinella/GIVOM** **Country:** Italy ALND vs. SLNB **Objectives:** To assess the efficacy and safety of SLNB compared with ALND	Zavagno, 2008 [140] **Objectives:** To assess the FNR of SLNB and its correlation with unfavorable pathological factors; To investigate the impact of false negative results on the choice of adjuvant treatment and on axillary nodal recurrence	FNR: 16.7%. (Defined as the percentage of patients with negative SLN who were found to have other metastatic nodes in the ALND specimen among all patients with positive nodes). Tumour size ≤2 cm and presence of a single metastatic axillary node were significantly associated with a risk of false negative (p=0.033 and p=0.018, respectively). The false negative SLNB would have led to different adjuvant therapy indications in 12/18 cases. Clinically evident axillary nodal recurrences at 56 mos: 0 vs. 1 case.
Radiotherapy trials		
Veronesi, 2005 [14] **GRISO053**[a] Axillary RT vs no RT **Objectives:** To assess the role of axillary RT in reducing axillary metastases in patients with early breast cancer who did not receive axillary dissection.	Zurrida, 2013 [132] **Objectives:** To assess the prognostic importance of tumour biological factors (i.e., ER, PgR, HER2, Ki67, and molecular subtype) from a subset of the GRISO053 study which compared axillary RT vs. no RT in pts not given ALND	N=285 (66% of the 435 pts in the original study) with clinically negative (undefined) axilla who were not given ALND; age >45 yrs; tumours ≤1.4 cm, Age: median 57 yrs (IQR 51-63) Stage: pT1a: 14.7%; pT1b: 54.4%; pT1c: 30.9%; ER+: 89.5%; low (<14%) Ki67: 60.7% 145 Axillary RT vs. 140 no axillary RT RT was given with X-rays by two opposed tangential fields at a dose of 50 Gys in 25 fractions plus a boost to the tumour bed. OUTCOMES: DFS, OS, Cumulative incidence of loco-regional recurrence Cumulative incidence of distant recurrence. Centralized randomization Adjuvant treatment: ER+ pts: hormonal therapy for 5 yrs; Ki67>20% pts: adjuvant chemotherapy for 6 months

ABS = abstract; ALND = axillary lymph node dissection; BC = breast cancer; BD = blue dye; CI = confidence interval; DDFI = distant disease-free interval; DFS = disease-free survival; EFS = event-free survival; ER = estrogen receptor; FNR = false negative rate; GRISO 053 = Italian Oncological Senology Group 053 trial; Gys = grays; HER2 =human epidermal growth factor receptor 2; HR = hazard ratio; IQR = inter quartile range; Ki67 = Antigen KI-67; mos = months; *nr* = not reported; NS = not significant; OM = occult metastases; OS = overall survival; PgR = progesterone receptor; pT = pathological T stage; pts = patients; QOL = quality of life; RCT = randomized controlled trial; RT = radiotherapy; SLN = sentinel lymph node; SN = sentinel node; SLNB = sentinel lymph node biopsy; yr(s) = year(s)

Study Design, Risk of Bias, and Certainty of the Evidence

Surgery trials

The ASCO update guideline [3,4], as evaluated with the AGREE II instrument (Appendix 5A), was of high quality. Both methodologists (FB and NV) agreed that its recommendation for surgical interventions could be endorsed.

Of the five trials [15,18-20,22] included in the Lyman et al. guideline and systematic review [3,4], one was a single-centre equivalence trial [22], two were multicentre trials [15,20], one was a single-centre noninferiority trial [19], and one was a multicentre noninferiority trial [18]. The overall risk of bias of this body of evidence was considered moderate (Figures 4-3A and 4-3B).

For outcomes such as OS, and death rates at five- or 10-year follow-up, the certainty of the evidence was moderate to high. The risk of bias was moderate for this set of outcomes. The Canavese et al. trial [19] was terminated early for benefit after 22 events, and the Veronesi et al. study [22] reported only per protocol analysis. We could not detect imprecision, or indirectness. The four studies that reported on OS [15,18,19,22] had generally large samples, and populations of women with stage T1 or T2, and tumours ≤2 cm in diameter; the results were consistent across studies.

For outcomes such as DFS and EFS the certainty of the evidence was moderate. The risk of bias for the trials [15,18,19,22] that reported on this set of outcomes was moderate. We could not detect imprecision or indirectness and the results were consistent across studies.

For disease control (local, regional, distant recurrence/metastases), the certainty of the evidence was moderate. The risk of bias for the trials [15,18,19,22] that reported on this outcome was moderate. We could not detect imprecision, or indirectness, and the results were consistent across studies.

For quality of life, the certainty of the evidence was low. Two of the included studies [18,20] and a substudy [131] of the NSABP B-32 [15] reported on this outcome. Risk of bias was high. The Land et al. trial [131] had 46% missing data; the Zavagno et al. study [18] used two generic, somewhat overlapping instruments to measure quality of life. There were inconsistencies on what aspects of quality of life were measured.

For adverse events the certainty of the evidence was moderate. The risk of bias in the studies that reported on this outcome [15,18,20] was moderate. One of the three studies [20] blinded participants to treatment assignment. There were inconsistencies in the results because each study defined the outcomes differently (e.g., arm volume vs. lymphedema).

Radiotherapy trials

We included four studies: an individual patient data meta-analysis [86]; a parallel group RCT [23]; an unplanned subgroup analysis [132] of an RCT [14] published prior to 2007, and a trial of women with triple negative breast cancer [25].

The overall risk of bias of this body of evidence was moderate. The individual patient data meta-analysis [86] was at low risk of bias (Table 1, Appendix 5B); however, the data were collected when radiotherapy were so different than what is currently in use that results are no longer applicable. The risk of bias of the Poortmans et al. [23] trial, was moderate. The Wang et al. trial [25] was at high risk of bias; it was not clear whether allocation was concealed (sealed envelopes were used, but it was not reported whether they were opaque); no intention-to-treat analysis was conducted; and results for one of the primary outcomes were not reported (Figures 4-3A and B). We did not evaluate the risk of bias of the Zurrida et al. study [132], because it was not a unique study.

For outcomes such as OS, overall mortality, breast cancer mortality, and death rate, the certainty of the evidence was moderate. Two RCTs [23,132], with a 10-year follow-up, and an individual patient data [86], with a 20-year follow-up for survival outcomes, comprise this

body of evidence, including a large number of patients and events. The body of evidence was at low risk of bias, and did not present serious imprecision for this set of outcomes. Some indirectness was present: the included trials collected data from 1964 to 1986 [23], and from 1996 and 2004 [86]. Radiotherapy technologies have evolved since then, and more recent technologies may cause less damage to surrounding tissues, and less adverse events. It is also possible that some radiotherapy adverse events require a follow-up longer than 10 years to be detectable. Furthermore, the EORTC 22922/10925 trial [23], included a small percentage (3.4%) of participants with stage T3 disease. All the women in the EORTC 22922/10925 trial [23] were treated with breast surgery (breast-conserving surgery or mastectomy), and ALND; while some of the women in the individual patient data meta-analysis received breast surgery and ALND, others had a less involved surgery (i.e., axillary sampling), and the authors presented results for these subgroups. Survival outcomes were measured in different ways. There were some inconsistencies between studies for the group of women who received ALND (see Table 4-10). The Wang et al. trial [25] provided indirect evidence for the subgroup of triple-negative patients because 14% of the patients were node positive, and results were not reported separately for the two groups; additionally the intervention was radiotherapy to the chest wall, and not to the axillary lymph nodes.

For outcomes such as DFS, disease progression or death, or distant DFS, the certainty of the evidence was moderate to low. The body of evidence was at moderate to high risk of bias, and presented some marginal indirectness. The EORTC 22922/10925 trial [23], and the Zurrida et al. analysis [132] of a previously published trial comprise the body of evidence available. The EORTC 22922/10925 trial [23], included a small percentage (3.4%) of participants with stage T3 disease, making the evidence from this trial marginally indirect; neither of the studies blinded patients, clinicians, or outcome assessors, and the Zurrida et al. trial [132] was an unplanned subset analysis.

For recurrence (i.e., recurrence rate at 10 years, loco-regional recurrence rate, overall and distant recurrence rates), the certainty of the body of evidence was moderate. Multiple studies [23,86,132] comprise the body of evidence for this outcome. The body of evidence was at moderate risk of bias because none of the studies blinded participants, clinicians or the outcome assessors. The EORTC 22922/10925 trial [23], included a small percentage (3.4%) of participants with stage T3 disease, making the evidence from this trial marginally indirect.

For adverse events, the certainty of the body of evidence was low. This body of evidence was at high risk of bias, imprecise, and partially indirect. One study [23] that included a small percentage of patients with stage 3 breast cancer reported on pulmonary fibrosis and cardiac outcomes. The study was not blinded, and the 10-year follow-up might have been too short to detect adverse effects of radiotherapy.

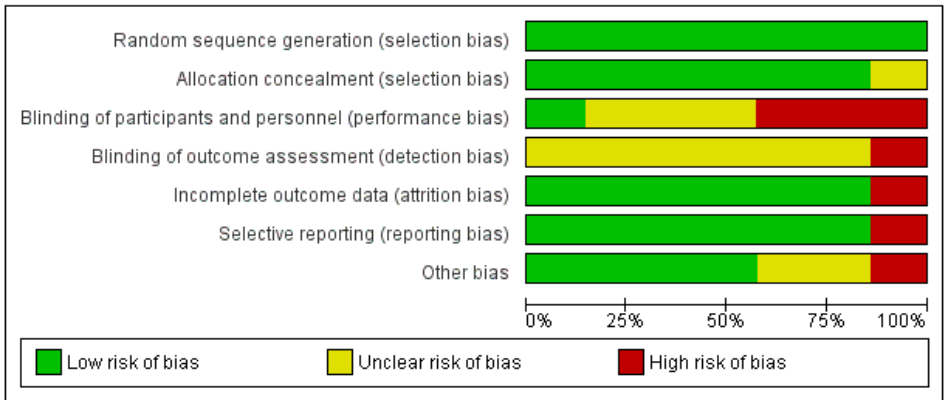

Figure 4-3A. Risk of bias graph for studies of further treatment in patients with negative axilla: review authors' judgements about each risk of bias item presented as percentages across all included studies.

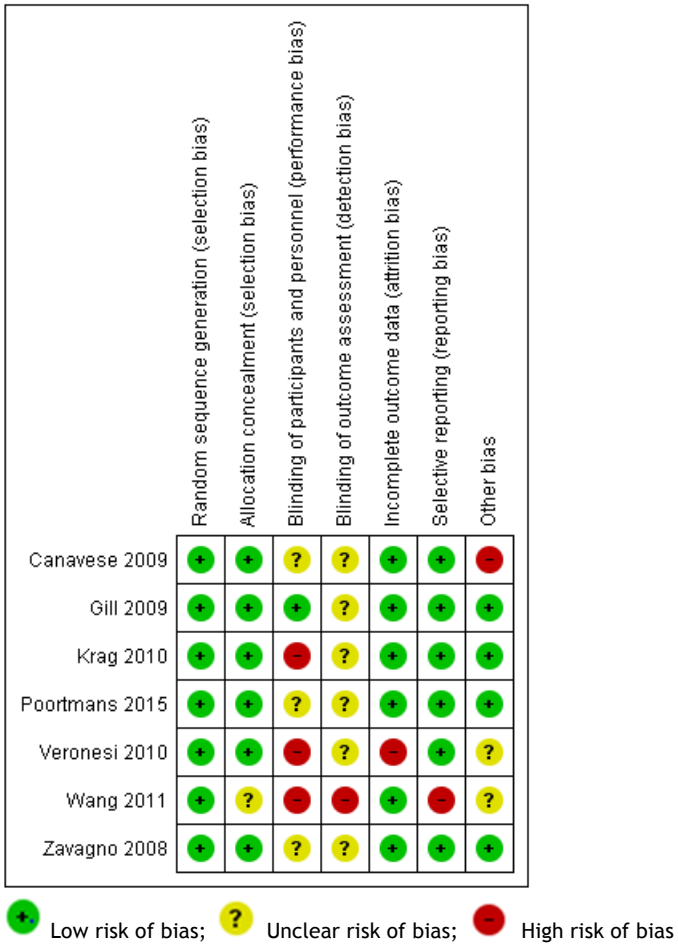

Figure 4-3B. Risk of bias summary for studies of further treatment in patients with negative axilla: review authors' judgements about each risk of bias item for each included study.

Outcomes

Table 4-10 reports the results of the completed trials.

Surgery trials

We endorsed Recommendation 1 of the Lyman et al. ASCO 2017 guideline [3,4] for our Recommendation 2: surgical interventions in women with early breast cancer who do not have nodal metastases.

OS and Death Rates

In patients allocated to SLNB plus ALND versus SLNB alone, Veronesi et al. [22] reported no statistically significant difference in death rate (p=0.15), and no statistically significant difference in OS at 10-year follow-up; the NSABP-B-32 [15], the Canavese et al. study [19], and the Sentinella/GIVOM [18] trials reported no statistically significant between-group differences at five-year follow-up (Table 4-10).

DFS and EFS

Veronesi et al. [22] showed no statistically significant differences in breast cancer-related events (log rank p=0.52) between patients allocated to SLNB alone or SLNB and ALND. As well, the NSABP-B-32 study [15] reported no statistically significant between-group difference in DFS (p=0.57), while the Sentinella/GIVOM trial [18] failed to demonstrate noninferiority of SLNB alone compared to SLNB plus ALND (Table 4-10).

Canavese et al. [19] found no between-group difference in EFS at five years (89.8% vs. 94.5%, p=0.715).

Recurrence

For patients who received ALND compared with SLNB Veronesi et al. [22] reported no between-group statistically significant better local, regional, and distant metastases rates combined, distant metastases rates, carcinoma rates and rates of primary tumours in other organs (Table 4-10). Canavese et al. [19] reported a similar result for recurrence of any type.

Quality of Life

Quality of life was measured with different tools. Land et al. [131] in a pre-planned subgroup analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 [15] adapted items from previous studies, and from the Disability of Arm, Shoulder, and Hand scale [147] to examine arm symptoms, arm-use avoidance, activity limitations, and quality of life between patients who received SLNB or ALND. Arm symptoms were significantly more bothersome for patients who had received ALND at six and 12 months compared with patients who received SLNB (4.8 vs. 3.0, p<0.001, and 3.6 vs. 2.5, p=0.006, respectively). Patients in the ALND group experienced arm and breast symptoms, restricted work and social activity and impaired quality of life (all p≤0.002).

Gill et al. [20] in the Sentinel Node biopsy versus Axillary Clearance (SNAC) trial assessed arm morbidity as subjectively reported by patients, physicians, as well as with the quality of life SNAC Study-Specific Scale that measures arm symptoms, swelling, dysfunctions, and disability. The authors found that the SLNB group experienced statistically significantly better quality of life, than the ALND group. When arm symptoms were measured by physician ratings, a statistically significant difference from baseline to the average of six and 12 months was also found in favour of the SLNB group (see Table 4-10 for numerical results).

The Sentinella/GIVOM trial [18] found that when quality of life was measured with a generic instrument (36-Item Short Form Survey [148]), there was no between-group statistically significant difference in all domains. When measured with the Psychological Well-Being Index

Questionnaire [149], patients in the SLNB group scored more favourably in the anxiety and in the general index profiles than patients in the ALND group (see Table 4-10 for numerical results).

Adverse events

The SNAC trial [20] reported a reduced increase in arm volume (p=0.002), and a reduced decrease in lateral abduction (p=0.02) in patients who had SLNB as compared with patients who received ALND (see Table 4-10 for numerical results).

Subgroups

Ashikaga et al. [134] in a subgroup analysis of the NSABP B-32 trial [15] explored the three-year post-surgical morbidity in 3983 patients who had negative SLNB alone and those who had negative SLNB and negative ALND. Statistically significant between-group differences in shoulder abduction deficit appeared at week 1 (ALND vs. SLNB: 75.3% vs. 40.8%, p<0.001) and persisted at week 2, week 3 (55.7% vs. 20.5%, p<0.001), and month 6 (9.0% vs. 5.7%, p<0.001). Between-group differences in arm volume were statistically significant at six months (12.6% vs. 9.0%, p<0.001), and persisted consistently at 36 months (14.3% vs. 7.5%, p<0.001). The authors showed a statistically significant between-group difference at 36 months follow-up in residual shoulder abduction deficit (19% vs. 13.2%, OR estimate 0.64; 95% CI, 0.53 to 0.79, p<0.001), in residual arm volume difference (27.6% vs. 16.7%, OR estimate 0.52; 95% CI, 0.43 to 0.65, p<0.001), in residual arm numbness (30.5% vs. 7.5%, OR estimate 0.19; 95% CI, 0.15 to 0.23, p<0.001), and in residual arm tingling (13.2% vs. 6.7%, OR estimate 0.47; 95% CI, 0.36 to 0.62, p<0.001).

Radiotherapy trials

The included studies were clinically heterogeneous, with different populations, interventions, and designs; therefore, we did not pool the results in meta-analysis.

Overall survival

At 10-year follow-up, the EORTC 22922/10925 trial [23] reported no statistically significant difference in OS (82.3% vs. 80.7%, HR, 0.87; 95% CI, 0.76 to 1.0, p=0.06), in patients treated with ALND, and loco-regional radiation in addition to whole breast and thoracic wall irradiation, compared with those who received whole breast or thoracic irradiation alone. The same authors showed a statistically significant difference in death rate from breast cancer in favour of the loco-regional irradiation group: 12.5% vs. 14.4%, HR, 0.82; 95% CI, 0.70 to 0.97, p=0.02. In contrast, at 20-year follow-up, the IPD meta-analysis [86] reported, in patients treated with ALND compared with those treated with radiotherapy, no difference in breast cancer mortality (RR, 1.18; 95% CI, 0.89 to 1.55, p=0.1), but a worse overall mortality for those who had received radiotherapy treatment (RR, 1.23; 95% CI, 1.02 to 1.49, p=0.03) (Table 4-10). In the same study, for women treated with breast surgery and axillary sampling (less-invasive surgery), the authors did not detect any statistically significant difference in overall or breast cancer mortality.

DFS

The EORTC 22922/10925 trial [23] reported a better DFS (HR for disease progression 0.89; 95% CI, 0.80 to 1.00, p=0.04), and distant DFS rate (78% vs. 75%, p=0.02) at 10-year follow-up for patients who had loco-regional node irradiation compared with those who did not.

Recurrence

The EORTC 22922/10925 trial [23] reported a statistically significant lower 10-year rate of first recurrence for patients treated with loco-regional irradiation compared with patients who had ALND (19.4% vs. 22.9%, p=0.02). The EBCTCG [86] found no statistically significant difference in overall recurrence (see Table 4-10 for numerical results) between patients who were treated with loco-regional node irradiation and those who were not. The same authors [86] showed no statistically significant difference in recurrence rate for patients treated with loco-regional irradiation compared with those who did not received irradiation (RR, 1.06; 95% CI, 0.76 to 1.48, 2-sided p>0.1). Conversely, patients who had received less-invasive surgery (i.e., axillary sampling) showed a statistically significant advantage for loco-regional recurrence (3.7% vs. 17.8% RR, 0.25; 95% CI, 0.16 to 0.38, 2-sided p<0.00001), and overall recurrence (22.1% vs. 34.2%, RR, 0.61; 95% CI, 0.47 to 0.80, 2-sided p=0.0003) if treated with loco-regional irradiation compared with those who received surgery alone (Table 4-10).

Quality of life

None of the included radiotherapy trials reported on quality of life.

Adverse events

In the EORTC 22922/10925 trial [23], at 10-year follow-up, patients who received loco-regional irradiation experienced more pulmonary fibrosis (4.4% vs. 1.7%, p<0.001) than patients who received thoracic wall and whole breast irradiation. No statistically significant difference was detected for cardiac disease or fibrosis (Table 4-10).

Subgroups

Zurrida et al. [132], in an unplanned subgroup analysis of the GRISO053 study [14] showed that patients with high Ki67 (≥14%) who received ALND had better DFS if given axillary radiotherapy compared with those who did not at 10-year follow-up: DFS, 95% (95% CI, 89% to 100%) vs. 79% (95% CI, 69% to 92%), p=0.005. No between group difference was found for OS, 96% (95% CI, 90% to 98%) vs. 90% (95% CI, 84% to 94%), p=0.078; and HR, 0.39 (95% CI, 0.14 to 1.05), p=0.062.

The Wang et al. trial [25] provided some information on the subgroup of triple negative patients treated with axillary irradiation compared with no irradiation; 80.6% of patients were node negative in the arm receiving chemo-radiation therapy. The irradiated patients experienced better OS at five years (90.4% vs. 78.7%; HR, 0.79; 95% CI, 0.74 0.97, p=0.03), less distant metastases (24.2% vs. 38.5%, p<0.05, for those with 1–2 distant metastases; 75.8% vs. 61.5% for those with >2 metastase, p<0.05), and better relapse-free survival (88.3% vs. 74.6%; HR, 0.77; 95% CI, 0.72 to 0.98), with no statistically significant difference in neutropenia, nausea, and emesis.

The MA.20 trial [24] (data reported in Table 4-5) showed that loco-regional nodal irradiation in all patients, those with positive nodes, and those with negative nodes and high-risk features, such as negative receptor status, was associated with improved DFS at 10 years (ER status negative: 61.6% vs. 76.2; HR, 0.56; 95% CI, 0.39 to 0.81; PR status negative: 70.5% vs. 81.9%; HR, 0.57; 95% CI, 0.41 to 0.80; p value for interaction: p=0.04) and distant disease-free survival (HR, 0.76; 95% CI, 0.60 to 0.97).

Literature Search Results for Primary Studies
Question 3: Axillary strategies for women who did not receive NAC and were sentinel lymph node positive at diagnosis

The flow diagram for primary studies is reported in Appendix 4B. Table 4-12 shows the evidence that was identified for Question 3. Table 4-13 reports the general characteristics of included primary studies. Table 1 in Appendix 7 shows a list of all studies' inclusion and exclusion criteria. Table 2 in Appendix 7 shows a comparison of the selection criteria and patient characteristics for the three studies [26-30,32] included in the Schmidt-Hansen et al. systematic review [31].

We endorsed Recommendation 2.1 from the ASCO 2017 guideline [3,4] for comparison A): No further axillary surgery beyond SLNB compared with ALND. The systematic review by Schmidt-Hansen et al. [31] covered comparison C): Radiotherapy versus further surgery (ALND). The Schmidt-Hansen et al. [31] search was updated with primary studies published after this review search cut-off (March 2015). For the remaining comparisons (i.e., B): radiotherapy plus surgery vs. no radiotherapy to the regional lymph nodes, and D): radiotherapy vs. no treatment) a systematic review of primary studies published from 2007 to February 18, 2020 was conducted.

Table 4-12. Literature search results for Question 3

Comparisons in Question 3		Endorsed guidelines	Included, high quality SRs	Included RCTs	Included Observational comparative trials	Ongoing trials
Intervention	Control					
A) No further axillary surgery beyond SLNB	ALND	ASCO 2014, 2017 [3,4]	Schmidt-Hansen, 2016 [31]	ATTRM-048-13-2000, 2013 [32]*; IBCSG-23-01 2011, 2013 [29,30,150]*; ACOSOG Z0011 [26-28]*	NA	SENOMAC (NCT02240472, NCT03083314, NCT01468883) [151] INSEMA (NCT02466737); SERC [152] (NCT01717131)
B) RT + ALND	No RT to the regional lymph nodes	NA	NA	MA.20 trial [24]	NA	POSNOC [153,154] (NCT02401685)
C) RT	ALND	NA	Schmidt-Hansen, 2016 [31]	OTOASOR [33] AMAROS [34-36] EBCTC, 2014 [86]	NA	MA39 (NCT03488693, NCT00005957) HypoG01 (NCT03127995)
D) RT	No treatment	NA	NA	Killander, 2007, 2009 [40,41]	NA	OPTIMAL (NCT02335957)

*These studies were included in Schmidt-Hansen, 2016 [31]
ALND = axillary lymph node dissection; ASCO = American Society of Clinical Oncology; NA = not appllicable; RT = radiation therapy; RCTs = randomized controlled trials; SLNB = sentinel lymph node biopsy; SRs = systematic reviews

Companion studies

Table 4-14 reports the objectives of the original and companion studies, and the summary results of the corollary studies. For comparison A) we identified five companion publications [27,155-158] of the ACOSOG Z0011 trial [13], and two follow-up publications [129,150] of the IBCSG 23-01 trial [30]. An interim analysis of the SERC ongoing trial was identified [159]. No companion studies were identified for comparison B). For comparison C), we identified two companion publications [37,38] of the AMAROS trial [36], and four

companion publications [39,160-162] of the OTOASOR trial [33]. For comparison D, we identified a companion publication [42] of the Killander et al. trials [40,41].

Ongoing, Unpublished, or Incomplete Studies

We identified the published protocols of the SENOMAC (NCT02240472) [151], and of the UK-ANZ POSNOC (NCT02401685) trials [153,154]. In patients with up to two axillary macrometastases, the SENOMAC trial [151] plans to compare SLNB and ALND with SLNB alone (our comparison A), and the UK-ANZ POSNOC trial [153] plans to compare ALND or radiotherapy and systemic therapy with systemic therapy alone in 1900 positive sentinel node patients (our comparison B). These studies are expected to be completed in 2029,and in 2023.

For Comparison C (Radiotherapy of the axilla vs. further surgery), we identified an ongoing trial: the Canadian Cancer Trial Group MA39 study (NCT03488693).

Additionally, a search of clinicaltrials.gov captured the following ongoing randomized trials for comparison A): the INSEMA trial (NCT02466737), that compares SLNB with no axillary surgery in 5505 patients treated with breast-conserving surgery and it is expected to be completed in the Fall 2024; the SERC trial (NCT01717131), that compares ALND with no ALND in 3000 sentinel node-positive patients and is due for completion in the summer of 2028. Two more trials exploring radiotherapy interventions: the OPTIMAL (NCT02335957), and the HypoG01 (NCT03127995) are due to complete in 2021 and 2029 respectively. See Table 1 in Appendix 8 for more details on the ongoing trials.

Comparison A: No further surgery beyond SLNB compared with ALND

The ASCO 2017 guideline [3,4], based on the IBCSG 23-01 trial [29,30], and on the Z0011 [26-28] trials, issued a recommendation for women who have one or two positive nodes at SLNB. The ASCO 2017 updated search [3] did not identify any additional evidence that could change the recommendation. We included the Schmidt-Hansen systematic review [31], which included the above trials, and an additional smaller study [32], which did not change the recommendation. Our update search identified a follow-up of the IBCGS 23-01 [150] for this comparison, which, however, did not change the recommendation.

Study Design, Risk of Bias, and Certainty of the Evidence

The ASCO guideline [3,4] is considered of high quality (Appendix 5A).

The Schmidt-Hansen et al. [31] is a high-quality systematic review, and its methodology aligns with ours. The authors [31] searched MEDLINE, PreMEDLINE, The Cochrane Library and the Specialized Register of the Cochrane Breast Cancer group, EMBASE, WHO International Trials Registry Portal, ClinicalTrials.gov, and conference proceedings from ASCO and San Antonio Breast Cancer meetings on March 16, 2015 for approaches less invasive than ALND in patients with pathologically confirmed positive sentinel lymph nodes.

Schmidt-Hansen et al. [31] considered the ATTRM-048-13-2000 [32] at high risk for patient selection, and detection bias. Furthermore, this study did not report on adverse events and it was considered at high risk of reporting bias for this outcome. The IBCSG-23-01 [29,30] study was considered at high risk for detection bias because outcome assessors were not masked. In the ACOSOG Z0011 trial [26-28], it was not clear whether outcome assessors were masked; 30-days short-term adverse events data were not reported for all patients, and outcome data were progressively missing for larger proportions of participants over time, particularly in the SLNB group.

Figures 4-4A and B present graphically our risk of bias judgement of the studies included in the Schmidt-Hansen et al. review [31].

The overall certainty of the evidence for this comparison was moderate to high.

For outcomes such as OS (2 studies), we considered the certainty of this evidence high. For other outcomes, such as DFS (3 studies), adverse effects (2 studies), and recurrence (2 studies), we considered the certainty of this evidence moderate. For patients that met the inclusion criteria of the included studies, benefits outweighed harms. The included studies may suffer from selection bias because no blinding was implemented. Recruitment bias might have been present because patients were randomized after the results of SLNB were known. Consequently, results are applicable only to patients that meet the inclusion criteria of these studies, and that are perceived to be at low risk. However, we could not detect any inconsistency (all of the studies results point in the same direction), indirectness, or imprecision.

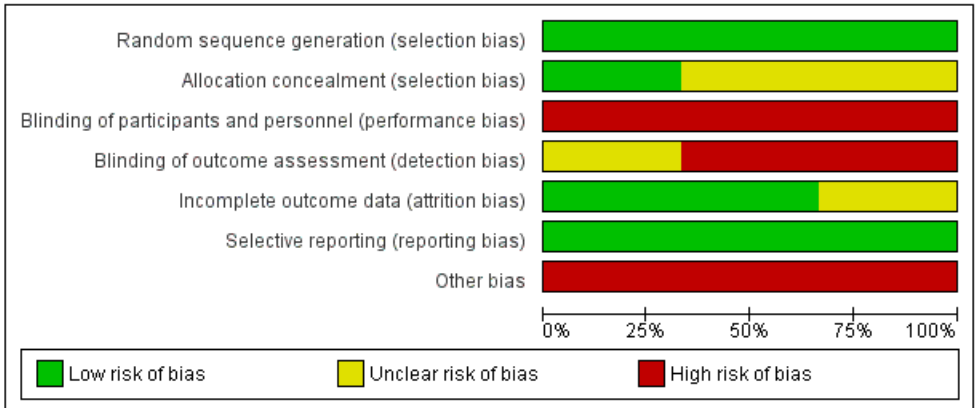

Figure 4-4A. Risk of bias graph for the studies included in the Schmidt-Hansen review [31]: our judgements about each risk of bias item presented as percentages across all included studies.

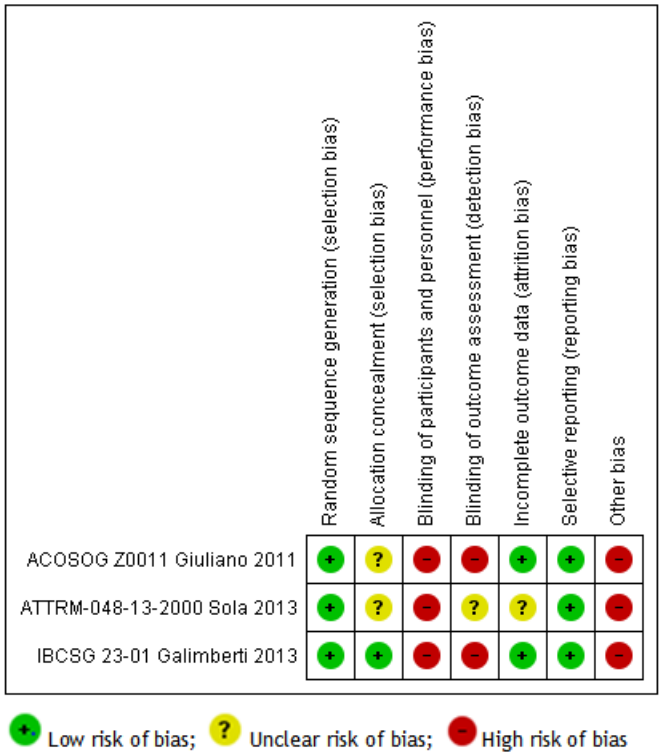

Figure 4-4B. Risk of bias summary of the studies included in the Schmidt-Hanssen review [31]: our judgements about each risk of bias item for each included study. Other bias refers to possible recruitment bias because the patients were randomized after the results of SLNB were known.

Comparison B: Radiotherapy and ALND compared with no RT of the loco-regional nodes

The MA.20 trial [24] tested whether the addition of loco-regional nodal irradiation to WBI and surgery in women with early-stage breast cancer could improve outcomes. The MA.20 [24] was a parallel group RCT that enrolled almost 2000 women with node-positive or high-risk node negative (i.e., primary tumour measuring ≥5 cm, or ≥2 cm with <10 axillary nodes removed and at least one of: grade III histologic categorization, ER negativity, or lymphovascular invasion) early-stage breast cancer treated with breast conserving surgery and SLNB or ALND. Women in the control group were assigned to receive WBI alone; women in the intervention group received nodal irradiation (i.e., ipsilateral internal mammary lymph nodes in the upper three intercostal spaces, along with the supraclavicular and axillary lymph nodes). OS was the primary outcome, and DFS, isolated loco-regional DFS, distant DFS, and toxicity were secondary outcomes.

Study Design, Risk of Bias, and Certainty of the Evidence

We considered the MA.20 Trial [24] to be at moderate risk of bias overall (Figure 4-5). The sequence was generated in a random manner, allocation was concealed, and the authors conducted an intention-to-treat analysis. The authors, however, did not state whether patients, clinicians, or outcome assessors were blinded. Results for some of the outcomes mentioned in the protocol and methods section, such as quality of life and cosmetic and arm function outcomes, were not reported, potentially exposing a selective reporting bias. Finally, we believe that a follow-up of 9.5 years may be too short to detect some of the long-term adverse effects of radiotherapy.

We considered this body of evidence to be of moderate certainty. The MA.20 trial [24] was a study with no serious risk of bias for all outcomes. We did not detect any indirectness. For this comparison, the MA.20 [24] had a relatively large number of events (323 events), and we consider imprecision to be not important.

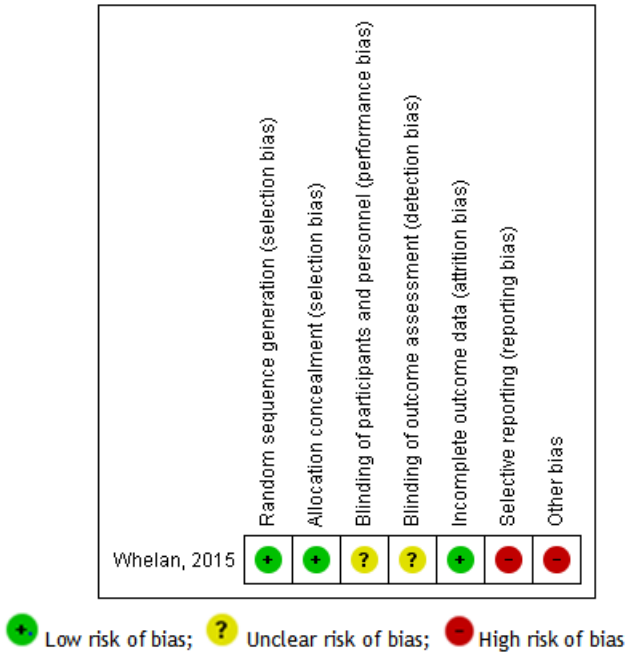

Figure 4-5. Risk of bias summary: review authors' judgements about the risk of bias item for the included study.

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

The Schmidt-Hansen et al. systematic review and meta-analysis [31] included two studies for this comparison, the EORTC 10981 After Mapping of the Axilla: Radiotherapy or Surgery? (AMAROS) trial [34-36], and the Optimal Treatment Of the Axilla - Surgery Or Radiotherapy (OTOASOR) trial [33], and did not pool the results in meta-analysis. Women were treated with either breast-conserving surgery or mastectomy, and irradiation of the axilla was compared with ALND. General characteristics of the trials are reported in Table 4-13, and details of the studies inclusion and exclusion criteria are in Table 4, Appendix 7. The trials presented results at five years, and data on the 10-year update results of the AMAROS trial [34-36] on second cancers are available in a conference abstract [37] (Table 4-14). The outcomes reported were OS, DFS, quality of life, and adverse effects.

Our search identified an individual patient data meta-analysis of 22 trials [86] that collected data from 1964 to 2009. Radiotherapy and surgery were compared with surgery alone in women treated with mastectomy and axillary surgery (i.e., ALND or a less-invasive surgery called axillary sampling). A subset of node-positive patients in this meta-analysis met the inclusion criteria for our study (patients with early-stage breast cancer: stage I, IIA, IIB; prognostic groups T1, T2, N0, N1mi, N1, M0). Table 4-13 reports the general characteristics of this IPD meta-analysis for women with positive SLNB [86].

Study Design, Risk of Bias, and Certainty of the Evidence

Schmidt-Hansen et al. systematic review [31] is a high-quality review and it forms the evidentiary basis for this comparison. Schmidt-Hansen et al. [31] considered the OTOASOR trials [33] at risk for reporting bias for morbidity outcomes, and at risk for selection and detection bias for all outcomes, because very little information was reported about patient selection, allocation, and blinding. It was also noted that at baseline, significantly more patients in the ALND arm had pathological stage T2-3 than patients in the radiotherapy arm. The AMAROS trial was open label, and did not report long-term complications, other than lymphedema and

shoulder mobility for which a progressively larger or unclear number of data were missing. Therefore, Schmidt-Hansen et al. [31] concluded that the results of this study [34-36] are to be considered at high risk of detection bias (for all outcomes but survival), attrition bias (for lymphedema and shoulder mobility) and reporting bias (for short-term complications). Both the AMAROS [34-36], and the OTOASOR trials [33] randomized patients before SLNB. Therefore, the populations are representative of patients seen in clinical practice. Schmidt-Hansen et al. [31] concluded that, given the shortcomings of the included studies, more studies on this topic are warranted, and for the time being in current practice the results should be applied to patients that strictly meet the inclusion criteria of the studies, and considered on a case-by-case basis.

According to Tierney et al. guidelines [80] (see Table 1, Appendix 5B), we considered the individual patient data meta-analysis [86] a well conducted study. However, radiotherapy techniques have improved since the time when the included studies were conducted, and the subgroup of node-positive patients of this study included patients with N1, along with patients with N2 disease, and the results were not separated, making this evidence indirect.

We can consider the overall certainty of this body of evidence as moderate.

The certainty of the evidence for this comparison is high for OS, and low for DFS and recurrence, because the studies did not apply masking. The certainty was very low for adverse events because one of the studies [33] did not report this outcome and the other [34-36] had increasingly higher amounts of missing data. The AMAROS [34-36] and OTOASOR [33] studies were at serious risk of bias for adverse events, and at moderate risk of bias for recurrence and DFS. There was inconsistency between the results of the AMAROS [34-36] and OTOASOR [33] studies.

Comparison D: Radiotherapy compared with no treatment to the axilla

We did not identify any systematic review for this comparison.

Our search identified two trials of women with invasive early-stage breast cancer treated with mastectomy and chemotherapy (pre-menopausal women) [41], or mastectomy and hormonal therapy (post-menopausal women) [40]. Women were randomized to three groups: radiotherapy of the chest and regional nodes alone; combination radiotherapy and chemotherapy or hormonal therapy; and no further treatment. Outcomes reported were OS and recurrence.

We also identified a 25-year follow-up of these trials combined [42] that reported on adverse events. The combination treatment was compared with chemo- or hormonal therapy, or radiotherapy alone. The outcomes reported were time to recurrence, type of recurrence, and OS. General characteristics and results of the studies are reported in Tables 4-13, and 4-15, and details of the studies inclusion and exclusion criteria are in Tables 1, and 5, Appendix 7. General characteristics of the companion trial and its summary results are reported in Table 4-14.

Study Design, Risk of Bias, and Certainty of the Evidence

Both of the identified trials [40,41] were randomized, phase III trials. We considered these trials to be at high risk of selection and performance bias because random sequence generation and allocation concealment were not blinded. Block randomization was not by permuted blocks, and allocation was done using closed envelopes that were not described as opaque. The trials did not report whether clinicians, patients, or outcome assessors were blinded. The trials were at low risk for attrition and reporting bias. The follow-up allowed for an evaluation of adverse effect of irradiation past the second decade post-intervention. However, the radiotherapy interventions that were used during the accrual period were not the same of what is available to date.

We considered the body of this evidence of moderate to low certainty. The results were consistent, and can be considered precise since the number of patients (and events) is large. Both included trials were at high risk of bias, and the evidence provided was indirect because radiotherapy interventions have changed since the data were collected in the mid seventies and eighties, and therefore the results may not be generalizable.

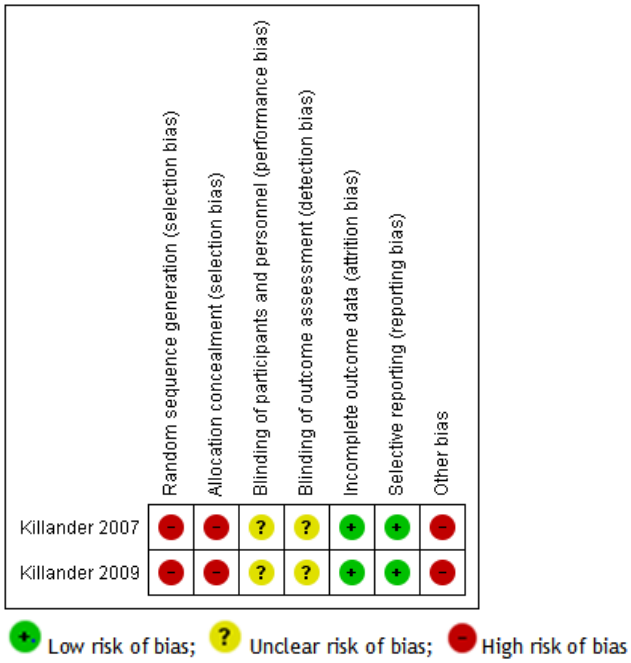

Figure 4-6. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Table 4-13. Question 3: patients with positive lymph nodes who did not receive NAC. General characteristics of included studies with patient-level data

Study, date, country, study name, Funding	Design Accrual period Aim Follow-up	Population	Sample size calculation	Comparison	Outcome(s)	Adjuvant treatment
Comparison A: SLNB vs. ALND						
Galimberti, 2013, [29,30,150] **Country:** multiple countries IBCSG 23-01 **Funding:** International Breast Cancer Study Group	Multicentre noninferiority RCT, phase III, open label; stopped early because of low event rate. **Accrual Period:** Apr 2001 – Feb 2010 **Aim** To determine whether ALND is necessary in pts with minimal SN involvement **Follow-up (median, range):** 9.7 yrs (IQR 7.8-12.7) [150]	934 pts with early BC, tumours ≤5 cm, clinically negative (undefined) in the axilla, who had ≥1 micro-metastases (≤2 mm) and isolated tumour cells. 931 in analysis. (931 pts in efficacy analysis, 900 pts in safety analysis) **Age** median (range): 54 (26-81) yrs **Stage**: *nr*	1960 pts (558 events) would have provided 90% power to detect noninferiority of no axillary dissection with α=0.10 assuming that 5-yr DFS with ALND was 70%; noninferiority HR <1.25 for no ALND vs. ALND	NO ALND: 469 vs. ALND: 465	**Primary Outcome:** DFS **Secondary outcome(s):** OS Site of recurrence, ALND surgical complications	All pts received SLNB; mastectomy or BCT
Solà, 2013 [32] **Country:** Spain **ATTRM-048-13-2000** **Funding:** Catalan Agency for Health Information, Assessment, and Quality	Multicentre RCT (18 centres) **Accrual Period:** Jan 2001 to Dec 2008 **Aim** To determine whether without ALND prognostic information stays the same, and pt outcomes are maintained. **Follow-up (median, range):** 62.4 mos (24 – 106.92 mos)	247 pts with micrometastases in the SN nodes (233 in analysis) **Age** (median, range): SLNB + ALND: 55.3 yrs (29 to 75 yrs), SLNB + observation: 53.2 yrs (33 to 75 yrs) **Stage**: T<3.5 cm, clinical N0, M0	352 pts were required to detect a maximum difference of 15% in survival with α=0.05 and 80% power	SLNB + ALND (n=123, 112 in analysis) vs. SLNB + observation (n=124, 121 in analysis)	**Primary Outcome:** DFS **Secondary outcome(s):** Recurrence	Breast-conserving surgery (92.3%), or mastectomy + whole breast radiotherapy (89.7%) and post-operative adjuvant chemotherapy
Giuliano, 2011 [13] **Country:** US **American College of Surgeons Oncology Group (ACOSOG) Z0011** **Funding**: National Cancer Institute grant U10 CA 76001 to the ACOSOG	Multicentre noninferiority RCT phase III, stopped early for low event rate **Accrual Period:** May 1999 to Dec 2004 **Aim** To determine the effect of ALND on survival of BC pts with positive sentinel lymph nodes **Follow-up (median, range):** 75.6 mos, (IQR 62.4-92.4 mos)	891 pts with macroscopic but limited axillary involvement, clinically negative (undefined), and 1-2 involved nodes. 813 pts who received treatment were include in the analysis **Age** median (range): ALND vs. SLNB 56 yrs (24-92 yrs) vs. 54 yrs (25-90 yrs) **Stage**: T1-T2	Assuming survival of 80% at 5 yrs 1900 pts were required with 1-sided alpha of 0.05. The boundary of noninferirority was HR <1.3.	446 SLNB (436 in analysis) vs. 445 (420 in analysis) SLNB+ALND	**Primary Outcomes:** OS Surgical morbidities (short term) **Secondary outcome(s):** DFS Loco-regional recurrence Distant metastases	96% of pts received chemotherapy, hormonal therapy or both, and tangential field whole breast RT

Study, date, country, study name, Funding	Design Accrual period Aim Follow-up	Population	Sample size calculation	Comparison	Outcome(s)	Adjuvant treatment
Comparison B: RT axilla (regional) vs. whole breast irradiation						
Whelan, 2015 [24] **Country:** Canada **NCIC Clinical Trial Group MA.20 Trial** **Funding:** Canadian Cancer Society Research Insitute, The Canadian Breast Cancer Research Initiative, the US National Cancer Institute, and the Cancer Council of Victoria, New South Wales, Queensland, and South Australia	RCT prarallel group **Accrual Period:** Mar 2000 to Feb 2007 **Aim** To compare whole-breast irradiation plus regional nodes irradiation with whole-breast irradiation alone **Follow-up (median, range):** 114 mos	1832 women with invasive carcinoma (N1) of the breast with positive or negative axillary nodes with high-risk features[a] **Age** (median): WBI: 53 yrs; WBI + RNI: 54 yrs **Stage**: 99% of pts T1 or T2	To detect a HR of 0.73 for OS with 80% power, 312 deaths in a 3-year follow-up period, among 1832 pts were needed, with two-sided α=0.05	916 WBI + RNI vs. 916 WBI alone Dose and schedule: 50 Gy in 25 fractions to the whole breast. For pts in the nodal irradiation group a modified wide-tangent technique and a technique involving a separate internal-mammary-node field plus tangents.	**Primary outcome:** OS **Secondary outcomes:** DFS DDFS Isolated loco-regional DFS AE QOL Cosmetic and arm function outcomes	Breast conserving surgery, ALND (96%) or SLNB, and adjuvant systemic therapy (with chemo- or hormonal therapy)
Comparison C: RT vs. Surgery						
We included the Schmidt-Hansen et al. systematic review and meta-analysis [31] described in Table 4-2; additional description in text.This review included the AMAROS trial [36], and the OTOASOR trial [33] for this comparison.						
Savolt, 2013 [33,39] **OTOASOR** **Country:** Hungary **Funding:** Hungarian National Institute of Oncology	**Design:** RCT equivalence trial **Accrual period**: Aug 2002 to Jun 2009 **Aim**: To study whether the result of ALND influenced the recommendation for adjuvant treatment in pts with SLN positive BC **Follow-up (median, range):** Median: *nr* Range: 41.88 – 42.36 mos	474 women with positive SLN **Age**: Mean ALND 54.7 yrs (range 26 to 74) vs. RNI 55.2 yrs (range 27 to 74) **Stage**: tumours <3 cm	*nr*	244 ALND vs. 230 RNI (all three levels of the axilla and supraclavicular fossa: 50 Gy in 25 fractions of 2 Gy) ALND: Postoperative RT to the regional nodes when ≥4 positive nodes (pN2a-3a) or 1-3 positive nodes (pN1a) with other high-risk characteristics. 232 pts received RT to the breast/chest wall, 76 pts received RT to the axillary/ supraclavicular	**Primary outcome:** *nr* **Secondary outcomes:** OS, DFS QOL	BCT or mastectomy. ALND (level I and II lymph, at least 6 nodes) Chemotherapy: 190 ALND; 159 aRT Hormone therapy: 213 ALND; 204 aRT

Study, date, country, study name, Funding	Design Accrual period Aim Follow-up	Population	Sample size calculation	Comparison	Outcome(s)	Adjuvant treatment
				nodes. aRT: 208 patients received RT to the breast/chest wall, 230 pts received RT to the axillary/supraclavicular nodes.		
Straver, 2010, Donker, 2014 [34-36]* **AMAROS** **Country**: Europe **Funding**: US National Cancer Institute	**Design:** Multicentre (9 centres) RCT equivalence trial **Accrual period**: Feb 2001 to Apr 2010 **Aim**: To assess whether aRT provides comparable regional control with fewer side-effects than ALND **Follow-up (median, range):** 73.2 mos (IQR 49.2 – 96)	1425 women with operable unifocal invasive BC and clinically negative (undefined) LN **Age**: median: 57 yrs (IQR 24-87) ALND: 56 yrs (IQR 48–64); aRT: 55 yrs (IQR 48–63) **Stage**: Tumour size: 5 to 30 mm up to Feb 2008. Afterwards size up to 50 mm, or multifocal disease were included for tumours localized in one quadrant.	52 events were needed to ensure a power of 80% with a one-sided log-rank test for the hazard ratio (HR) for non-inferiority (non-inferiority margin of 2) with α=0.05. Because of low event rate, the timing of the final analysis was anticipated, with a data cutoff of Oct 31, 2012, leaving the primary non-inferiority test underpowered.	744 ALND vs. 681 aRT	**Primary outcome:** 5-yrs recurrence **Secondary outcomes:** AE DFS OS Shoulder mobility, Lymphedema, QOL EORTC quality-of-life questionnaire (EORTC-QLQ-C30; version 3) and breast cancer module (QLQ-BR23) [b]	BCT, including whole-breast RT or mastectomy with/without RT to the chest wall) + ALND (level I and II; at least 10 nodes)
Early Breast Cancer Trialists' Collaborative Group, 2014 [86] **Country:** UK **Funding:** Cancer Research UK, British Heart Foundation, UK Medical Research Council	IPD meta-analysis **Accrual period**: 1964 to 1986 **Aim** To assess the effect of radiotherapy in pts who received mastectomy and axillary dissection **Follow-up (median, range):** 112.8 mos per woman (IQR 44.4 - 207.6) 120 mos for recurrence 240 mos for mortality	8135 women with node positive invasive early BC from 22 trials. **Age**: *nr* **Stage**: I, II and III Has separate results for stage pN0.	NA	ALND or axillary sampling + RT of the chest wall, internal mammary chain, and supraclavicular and/or axillary LN vs. Surgery alone (i.e., 353 ALND pts and 445 axillary sampling pts) 24 pts had unknown extent of axillary surgery	**Primary outcome:** Recurrence **Secondary outcome:** BC mortality	Mastectomy and ALND followed by chemo- and hormonal therapy
Comparison D: RT vs. No treatment						
Killander, 2009 [41]	RCT **Accrual Period:** 1978 to 1985	395 Pre-menopausal women with stage II BC (367 pts fully evaluable)	150 pts were needed in each treatment arm in	1) (n=134) RT 2) (n=125) RT+ C 3) (n=136) C alone	Time to recurrence, type of recurrence and OS.	Radical mastectomy and ALND

Study, date, country, study name, Funding	Design Accrual period Aim Follow-up	Population	Sample size calculation	Comparison	Outcome(s)	Adjuvant treatment
Country: Sweden **Funding:** Swedish Cancer Society, University Hospital of Lund Research Foundation, Skane County Research Foundation and Governmental funding of research within the National Health Service	**Aim** To study long term loco-regional and distant recurrence rate and survival **Follow-up (median):** 288 mos	**Age**: (median) 47 yrs **Stage**: Stage II **RT RT+C C** pN0 33% 32% 34% pN1-3 46% 46% 40% pN≥4 19% 20% 21%	order to detect a between-arm difference of 10% with α=0.05		No disctinction was made between primary and secondary outcome	
Killander, 2007 [40] **Country:** Sweden **Funding:** Swedish Cancer Society	RCT phase III **Accrual Period:** 1978 to 1985 **Aim** To evaluate long term effects of radiotherapy and tamoxifen **Follow-up (median, range):** 276 mos	724 post-menopausal women (668 fully evaluable in analysis) **Age**: (median) 63 yrs **Stage**: *nr* Tumour size (median) 25 mm	*nr*	1) (n=239, 221 in analysis) RT 50 Gy/25 fractions to chest wall and regional LNs 2) (n=234, 214 in analysis) RT + Tam 30 mg/d for one yr 3) (n=251, 233 in analysis) Tam alone	Time to recurrence Type of recurrence OS	Modified radical mastectomy
ONGOING TRIALS						
de Boniface, 2017 [151] **Country:** multiple **SENOMAC trial** **Funding:** Swedish Research Council, Swedish Cancer Foundation, Swedish Society of Medicine, Swedish Breast Cancer Association (BRO) and Swedish Society for Medical Research	RCT multicentre noninferiority **Accrual Period:** Jan 2015 to 2029 **Aim** To evaluate whether it is safe to omit ALND in BC pts with SN macrometastasis (i.e., tumours larger than 5 cm) **Follow-up (median, range):** 72 mos	(Planned) 3700 clinically node-negative BC pts with up to two macrometastases at SLNB **Age**: *nr* **Stage**: T1-T3	225 BC deaths and 700 pts are needed for a 5-yr BC-specific survival of 89.5% in the intervention group vs. 92% in the control (i.e., standard of care) group using a one-sided α= 10% and a power of 80%. In other words, the upper one-sided 90% CI for the HR: Intervention/Standard of care falls below 1.33.	Completion ALND vs. no further axillary surgery	**Primary outcome:** Cancer-specific survival at 5-yrs foloow-up **Secondary outcomes:** Loco-regional recurrence, DFS, OS, arm morbidity[c], health economic outcome QOL.	*nr*

Study, date, country, study name, Funding	Design Accrual period Aim Follow-up	Population	Sample size calculation	Comparison	Outcome(s)	Adjuvant treatment
Goyal, 2015 ABS [153] **Country:**UK UK-ANZ POSNOC Trial NCT02401685 **Funding:**	Pragmatic RCT, multicenter, noninferiority trial. **Accrual Period:** May 2014 to 2024 **Aim** To define the role of axillary treatment in pts with 1 or 2 SNs with macrometastases **Follow-up (median, range):** 60 mos	Women with unifocal or multifocal invasive BC ≤5 cm who had breast-conserving surgery or mastectomy, clinical and US nodenegative, who have 1 or 2 nodes with macrometastases at SLNB and no extranodal extension.	1900	Control group: adjuvant therapy plus ALND or axillary RT Intervention group: systemic adjuvant therapy alone	**Primary outcome:** axillary recurrence at 5 yrs. **Secondary outcomes:** Arm morbidity, QOL, anxiety, loco-regional recurrence, distant metastasis, time to axillary recurrence, axillary RFS, DFS, OS, contralateral BC, non-breast malignancy and economic evaluation	Systemic adjuvant therapy

*Data from Schmidt-Hansen et al. [31], except for sample size calculation, primary, secondary outcomes, and randomization method

[a]High-risk features: primary tumour measuring 5 cm or more, or 2 cm or more with fewer than 10 axillary nodes removed and at least one of the following: grade 3 histologic categorization, estrogen-receptor negativity, or lymphovascular invasion.

[b]QOL was assessed using the EORTC quality-of-life questionnaire (EORTC-QLQ-C30; version 3) and breast cancer module (QLQ-BR23). The selected scales were pain, body image, and arm symptoms. The arm symptoms scale was composed of three items: pain in arm or shoulder, swollen arm or hand, and dificulties moving arm. Questionnaires were completed at baseline and at years 1, 2, 3, 5, and 10.

[c]Arm morbidity as measured with Lymphedema Functioning, Disability and Health Questionnaire (Lymph-ICF) [163], the EQ-5D-5 L utility scores [164] QOL measured with EORTC's well-validated QLQ-30 [165,166] and BR-23 [167]

Abbreviations:

α = alpha; AE = adverse events; ALND = axillary lymph node dissection; aRT = axillary radiotherapy; BC = breast cancer; BCT: breast-conserving therapy; C = cyclophosphamide; CI = confidence interval; d = day; DDFS = distant disease-free survival; DFS = disease-free survival; Gy = gray (unit); HR = hazard ratio; IPD = individual patient data; LN = lymph nodes; mos = months; *nr* = not reported; IQR = interquartile range; NAC = neo-adjuvant chemotherapy; OS = overall survival; PMRT = postmastectomy radiation therapy; pt(s) = patient(s); QOL = quality of life; RCT = randomized controlled trial; RFS = recurrence-free survival; RNI = regional nodal irradiation; RT = radiotherapy; SLN = sentinel lymph node; SN = sentinel node; SLNB = sentinel lymph node biopsy; Tam = tamoxifen; US = ultrasound; WBI = whole breast irradiation; yrs = years

Table 4-14. Companion publications of unique studies identified for Question 3

Main study; Comparison; Objectives	Companion publications; Objecives	Summary results of the companion publication
Comparison A: No further axillary intervention beyond SLNB vs. ALND		
Giuliano, 2011 [13] American College of Surgeons Oncology Group (ACOSOG) Z0011 **Objectives:** To determine the effects of complete ALND on survival of pts with SLN BC metastasis	Giuliano, 2017 [155] **Objectives:** To determine whether the 10-yr OS of pts with SLN metastases treated with BCT and SLNB alone without ALND is noninferior to that of pts treated with ALND	856 (96%) of 891 women randomized (median age, 55 yrs), completed the trial (446 SLNB alone, and 445 ALND). At a median follow-up of 9.3 yrs (IQR, 6.93-10.34 yrs), the 10-yr OS was 86.3% in the SLNB group and 83.6% in the ALND group (HR, 0.85 [1-sided 95% CI, 0 - 1.16]; noninferiority p=0.02). 10-yr DDFS: 80.2% in the SLNB group and 78.2% in the ALND group (HR, 0.85; 95% CI, 0.62-1.17; p=0.32). Between yr 5 and yr 10, 1 regional recurrence was seen in the SLNB group vs. none in the ALND group. 10-yr regional recurrence did not differ significantly between the 2 groups.
	Jagsi, 2014 [156] **Objectives:** To ascertain RT coverage of the regional nodes in the Z0011 trial	89% of 605 pts with completed case report forms in the Z0011 trial, received WBI. Of these, 89 (15%) were recorded as also receiving treatment to the supraclavicular region. Detailed RT records were obtained for 228 pts, of whom 185 (81.1%) received tangent-only treatment. Among 142 with sufficient records to evaluate tangent height, high tangents (cranial tangent border ≤2 cm from humeral head) were used in 50% of pts (33 of 66) randomly assigned to ALND and 52.6% (40 of 76) randomly assigned to SLNB. Of the 228 pts with records reviewed, 43 (18.9%) received directed regional nodal RT using ≤3 fields: 22 in the ALND arm and 21 in the SLNB arm. Those receiving directed nodal RT had greater nodal involvement (p<0.001) than those who did not.
	Giuliano, 2016 [157] **Objectives:** To report long-term loco-regional recurrence results.	N=891 pts randomized (SLNB=446, SLNB+ ALND=445). Pts randomized to ALND had a median of 17 axillary nodes removed compared with a median of only 2 SLNs removed with SLNB alone (p<0.001). ALNDalso removed more positive LNS (p<0.001). At a median follow-up of 9.25 yrs, there was no statistically significant difference in local RFS (p=0.13). The cumulative incidence of nodal recurrences at 10 yrs was 0.5% for ALND and 1.5% for SLNB alone arm (p=0.28). 10-yr cumulative loco-regional recurrence rate was 6.2% with ALND and 5.3% with SLNB alone (p=0.36).
	Giuliano, 2011 [158] **Objectives:** To determine the association between survival and metastases detected by immunochemical staining of SLNs and bone marrow specimens from pts with early-stage BC	Of 5119 SLN specimens (98.3%), 3904 (76.3%) were tumour-negative by hematoxylin-eosin staining. Of 3326 SLN specimens examined by immunohistochemistry, 349 (10.5%) were positive for tumour. Of 3413 bone marrow specimens examined by immunocytochemistry, 104 (3.0%) were positive for tumours. At a median follow-up of 6.3 yrs, 435 pts had died and 376 had disease recurrence. Immunohistochemical evidence of SLN metastases was not significantly associated with OS (5-yr rates: 95.7%; [95% CI, 95.0% to 96.5%] for immunohistochemical negative, and 95.1% [95% CI, 92.7% to 97.5%] for immunohistochemical positive disease; p=0.64; unadjusted HR, 0.90; [95% CI, 0.59 to 1.39; p=0.64]). Bone marrow metastases were associated with decreased OS (unadjusted HR for mortality, 1.94 [95% CI, 1.02 to 3.67] p=0.04), but neither immunohistochemical evidence of tumour in SLNs (adjusted HR, 0.88 [95% CI, 0.45-1.71] p=0.70) nor immunocytochemical evidence of tumour in bone marrow (adjusted HR, 1.83 [95% CI, 0.79 to 4.26] p=0.15) was statistically significant on multivariable analysis.
	Lucci, 2007 [27] **Objectives:** To compare complications associated with SLNB plus ALND, versus SLND alone	Adverse surgical effects were reported in 70% (278 of 399) of pts after SLNB + ALND and 25% (103 of 411) after SLNB alone (p<0.001). Pts in the SLNB+ ALND group had more wound infections (p≤0.0016), seromas (p≤0.0001), and paresthesias (p≤0.0001) than those in the SLNB-alone group. At 1 yr, lymphedema was reported subjectively by 13% (37/288) of pts after SLNB + ALND and 2% (6/ 268) after SLNB alone (p≤0.0001). The difference between the two groups' lymphedema, assessed by arm measurements at 30 days (p=0.36), 6 mos (p=0.22), and 1 yr (p=0.078), although close to the cutoff for significance at 1 yr, was not significant. BPIs occurred in less than 1% of pts.

Main study; Comparison; Objectives	Companion publications; Objecives	Summary results of the companion publication
Galimberti, 2013 [30] Galimberti, 2013, IBCSG 23-01 **Objectives:** To determine whether ALND is necessary in pts with minimal SN involvement	Galimberti, 2018 [150] **Objectives:** To report the 10 yr follow-up of the original study	934 pts were randomly assigned to no ALND (n=469) or ALND (n=465). Ten-yrs DFS rate: 76.8% (95% CI, 72.5 to 81.0) in the no ALND group, compared with 74.9% (95% CI, 70.5 to 79.3) in the ALND group (HR 0.85, [95% CI 0.65 to 1.11]; log-rank p=0.24; p=0.0024 for non-inferiority). Long-term surgical complications included lymphedema of any grade in 4% (16/453) of pts in the no ALND group and 13% (60/447) in the ALND group, sensory neuropathy of any grade in 13% in the no ALND group versus 19%in the ALND group, and motor neuropathy of any grade (3% in the no ALND group vs. 9% in the ALND group). One serious AE (postoperative infection and inflamed axilla requiring hospital admission) was attributed to ALND; the event resolved without sequelae.
	Galimberti, 2017 ABS [129] **Objectives:** Report the 9.8-yr (median) follow-up results	10-year DFS 75% (95% CI, 72%-81%) in the no-AD group and 75% (95% CI, 71% to 79%) in the AD group (HR [no-AD vs. AD]=0.85; 95% CI, 0.65 to 1.11; log-rank p=0.23; non-inferiority p=0.002) 10-year OS: 91% (95% CI, 88% to 94%) in the no-AD group and 88% (95% CI, 85% to 92%) in the AD group (HR [no-AD vs. AD] 0.77; [95% CI, 0.56 to 1.07] log-rank p=0.19). Findings after a median follow-up of 9.8 yrs fully support the findings at 5 yrs in that no-AD is not inferior to AD with respect to DFS, and there is no significant difference between the arms for DFS and OS.
SERC Ongoing trial [152] (NCT01717131) **Objectives:** to demonstrate non inferiority of cALND omission	Houvenaeghel, 2018 [159] **Objectives:** Interim analysis of the first 1000 pts included	Of 963 pts included in this analysis, 478 were randomized to receive ALND and 485 SLNB alone. Isolated tumour cells were present in 6.3% of pts (57/903), micro metastases in 33.0% (298), macro metastases in 60.7% (548) and 289 pts (34.2%) were non eligible to Z0011 trial criteria. Whole breast or chest wall irradiation was delivered in 95.9% (896/934) of pts, adjuvant chemotherapy in 69.5% (644/926), endocrine therapy in 89.6% (673/751). The overall rate of positive nonsentnel nodes was 19% (84/442) for pts with ALND. Crude rates of positive nonsentinel node according to SN status were 4.5% for ITC (1/22), 9.5% for micro metastases (13/137), 23.9% for macro metastases (61/255) and were respectively 29.36% (64/218), 9.33% (7/75) and 7.94% (10/126) when chemotherapy was administered after ALND, before ALND and for pts without chemotherapy.
Comparison B: RT axilla (regional) vs. whole breast irradiation		
No corollary trials identified		
Comparison C: RT vs. Surgery		
Donker, 2014 [36] AMAROS (EORTC 10981/22023) Trial **Objectives:** To assess whether axillary RT provides comparable regional control with fewer side-effects than ALND	Donker, 2013 [38] **Objectives:** To evaluate the SLN identification rate and nodal involvement in pts with a multifocal tumour in the EORTC 10981-22023 AMAROS trial. Analysis of 342 pts	The SLN was identified in 96% of the pts with a multifocal tumour and in 98% of those with unifocal disease. In the multifocal group, 51% had a metastasis in the SLN compared to 28% in the unifocal group; and further nodal involvement after a positive SLN was found in 40% (38/95) and 39% (39/101) respectively. Surgeon experience: *nr*
	Rutgers, 2019 ABS [37] **Objectives:** To present the 10-yr follow-up data of the original study (ITT population)	Of the 4806 pts entered, 1425 pts were positive at SLNB: 744 in the ALND arm and 681 in the RNI arm. Sixty percent had macrometastasis. In the ALND group, the 5-yr axillary recurrence was 0.41% (95% CI, 0.00 to 0.88) and the 10-yr axillary recurrence was 0.93% (95% CI, 0.18 to 1.68). In the group who had RNI, axillary recurrence was 1.04% (95% CI, 0.27 to 1.81) at 5-yr, and 1.82% (95% CI, 0.74 to 2.94) at 10-yr (HR 1.71, 95% CI, 0.67 to 4.39, p=0.37). OS was not significantly different between arms: ALND: 84.6% (95% CI, 81.5 to 87.1), vs. RNI 81.4% (95% CI, 77.9 to 84.4), (HR 1.17, 95% CI, 0.89 to 1.52, p=0.26). As well, DMFS as not significantly different between arms: ALND: 81.7% (95% CI, 78.5 to 84.4, RNI: 78.2% (95% CI, 74.6 to 81.3), HR 1.18 (95% CI, 0.92 to 1.50, p=0.19). Cumulative incidence estimates of 10-yr LRR are 3.59% (95% CI, 2.12 to 5.06) for ALND vs. 4.07% (95% CI, 2.49 to 5.65) for RNI, p=0.69.

Main study; Comparison; Objectives	Companion publications; Objecives	Summary results of the companion publication
OTOASOR Savolt, 2013 [33] **Objectives:** To compare ALND with RNI in pts with SLN+ primary invasive breast cancer.	Savolt, 2016 [160] **Objectives:** Preliminary ABS publication. NOTE: The Schmidt-Hansen review [31] is based on this publication	Between August 2002 and June 2009, 2106 pts were randomized for ALND (arm A-standard treatment, 1054 pts) or ANI (arm B-investigational treatment, 1052 pts). SLN was identified in 2073 pts (98.4%) and was positive in 526 pts (25.4%). 52 SLN-positive pts were excluded from the study (protocol violation, pt's preference). Clinical and tumour characteristics were similar between 244 of 474 pts randomized to cALND and 230 randomized to SLNB + ANI. Primary endpoint of the study was axillary recurrence and secondary endpoints were OS, BC specific survival, DFS, distant DFS. Mean length of follow-up was 97 ms (range 54-134). Axillary recurrence (primary end point) was 2.0% vs. 1.7% (p=NS). OS at 8 yrs was 77.9% vs 84.8%; DFS was 72.1% with ALND and 77.4% with SLNB + ANI. Surgeon experience: *nr*
	Savolt, 2017 [161] **Objectives:** Eight-yr follow-up of the main study	Mean follow-up was 97 mos (range: 80-120 mos). Axillary recurrence was 2.0% in ALND arm vs. 1.7% in RNI arm (p=1.00). OS at 8 yrs was 77.9% vs. 84.8% (p=0.060), and DFS was 72.1% for ALND and 77.4% for RNI (p=0.51). The results show that RNI is statistically not inferior to ALND treatment. Surgeon experience: *nr*
	Savolt, 2011 ABS [162] **Objectives:** To evaluate the therapeutic effect of the axillary nodal irradiation and to detect early axillary recurrences or residual diseases on 45 T1-2 SLNB positive pts retrospectively selected from the investigational arm of the OTOASOR trial	Five out of 45 pts had suspicious findings in the axillary tail on mammography combined with breast and axillary US. In those 5 pts PET/CT suggested loco-regional residual disease in only one pt that was confirmed by core biopsy. In the remaining four cases both the PET/CT and the biopsy showed no evidence of malignancy. Surgeon experience: *nr*
	Savolt, 2017 [39] **Objectives:** 8 yrs follow-up of original study	Mean follow-up was 97 mos. Axillary recurrence was 2.0% for ALND arm vs. 1.7% for RNI (p=1.00). OS at 8 yrs was 77.9% vs. 84.8% (p=0.060), and DFS was 72.1% forALND and 77.4% for RNI (p=0.51). The long term follow-up results of this prospective-randomized trial suggest that RNI without ALND does not increase the risk of axillary failure in selected pts with early-stage invasive BC (cT 3 cm, cN0) and pN1(SLN). Axillary RT should be an alternative treatment for selected pts with SLN metastases Surgeon experience: *nr*
Comparison D: Radiotherapy vs. No treatment		
Killander, 2009 [41] Killander, 2007 [40] **Objectives:** To evaluate long-term effects of RT and Tam or RT and C after mastectomy on	Killander, 2014 [42] **Objectives:** To report on long term AE and mortality of the two studies combined	**Overall mortality at 25 yrs:** Premenopausal women: C vs. RT+C, p=0.72 Postmenopausal women: Tam vs. RT+Tam, p=0.49 <u>BC mortality:</u> p=NS in pre- and post-menopausal women <u>Cumulative mortalty from heart disease at 25 yrs</u>: RT+C vs. RT: NS RT+Tam vs. Tam: 8.7% vs. 3.4%, p=0.015

Main study; Comparison; Objectives	Companion publications; Objecives	Summary results of the companion publication
recurrence and survival in stage II BC		Cumulative mortalty from heart disease: RT+C vs. RT: 0.8 (95% CI, 0.1 to 4.1) vs. 0 (95% CI, 2.0 to 9.7), p=0.04 RT+Tam vs. Tam: 18.4 (95% CI, 13.5 to 23.8) vs.10.5 (95% CI, 7 to 14.8), p=0.005 Cumulative cerebrovascular disese mortalty: RT+C vs. RT vs. C: 1.7% (95% CI, 0.3 to 5.4) vs. 1.6% (95% CI, 0.3 to 5.2) vs. 0.8% (95% CI, 0.1 to 4.1), p=0.52 RT+Tam vs. Tam vs. RT: 8.7% (95% CI, 5.4 to 12.9) vs. 3.4% (95% CI, 1.6 to 6.2) vs. 5% (95% CI 2.7 to 8.5), p=0.015 Mortality and morbidity from lung disease: OS: p=NS in both pre- and postmenopausal women Morbidity: p=NS in both groups Surgeon experience: *nr*

α = alpha; ABS = abstract; AD = axillary dissection; AE = adverse event; ALND = axillary lymph node dissection; ANI = axillary nodal irradiation; aRT = axillary radiotherapy; BC = breast cancer; BCT: breast conserving therapy; BPI = brachial plexus injury C = cyclophosphamide; CG: control group; CI = confidence interval; CT = computed topography; DFS = disease-free survival; DDFS = distant disease-free survival; DMFS = distant metastases –free survival; Gy = gray (unit); HR = hazard ratio; IQR = interquartile range; LN(S) = lymph node(s); LRR = loco-regional recurrence; mos = months; nr = not reported; NS = not significant; OS = overall survival; PET = positron emission tomography; pts = patients; QOL = quality of life; RCT = randomized controlled trial; RFS = relapse-free survival; RNI = regional nodal irradiation; RT = radiotherapy; SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy; SN = sentinel node; Tam = tamoxifen; US = ultrasound; WBI = whole breast irradiation; yr(s) = year(s)

Table 4-15. Question 3: Patients with positive lymph nodes who did not receive NAC. Summary results of included studies with patient-level data. Primary outcome results in bold font.

Study, date, study name	Comparison	OS / Mortality	DFS / Recurrence	AE / Surgical complications
Comparison A: SLNB vs. ALND				
See description of Schmidt-Hansen et al. systematic review and meta-analysis [31] in Table 4-2 and more description in text				
Galimberti, 2013, [30,150] IBCSG 23-01	No ALND vs. ALND	OS at 5 yrs: 97.5% (95% CI, 95.8 to 99.1) vs. 97.6% (95% CI, 96.0 to 99.2); HR 0.89; 95% CI, 0.52 to 1.54, p=0.73	**DFS rate at 5 yrs:** 87.8%, (95% CI, 84.4 to 91.2) vs. 84.4% (95% CI, 80.7 to 88.1),), HR 0.78; 95% CI, 0.55-1.11, p=0.16. No ALND was noninferior to ALND (per protocol population): HR 0.80; 95% CI, 0.56 to 1.14, noninferiority p=0.0073. **Recurrence:** Distant metastases: 6% vs. 8% Local recurrence: 3% vs. 2% Regional recurrence: 0.2% vs. 1% Cumulative incidence of cancer events at 5 yrs[g]: 10.6% (95% CI, 7.5 to 13.8) vs. 10.8% (95% CI, 7.6 to 14.0), HR 0.97, (95% CI, 0.65 to 1.46), p=0.90	Sensory neuropathy[b]: 12% vs. 18%, p=0.012 Lymphedema[f]; 3% vs. 13%, p<0.0001 Motor neuropathy[b]: 3% vs. 8%, p=0.0004 Serious AE: infection: 0% vs. 0.2% p=*nr*
Sola, 2013 [32] ATTRM-048-13-2000	SLNB + observation vs. SLNB + ALND	*nr*	**Recurrence**: 2.5% vs. 1% p=0.348 **DFS:** p=NS	*nr*
Giuliano, 2011 [13,27] ACOSOG Z0011	SLNB vs. SLNB + ALND	**OS at 5 yrs:** 92.5% (95% CI, 90.0% to 95.1%) vs. 91.8% (95% CI, 89.1% to 94.5%) HR 0.87 (90% CI, 0.62 to 1.23), p=0.03 for noninferiority	**DFS rate at 5 yrs:** 83.9% (95% CI, 80.2% to 87.9%) vs. 82.2% (95% CI, 78.3% to 86.3%) p=0.14 **DFS:** HR 0.88 (95% CI, 0.62 to 1.25), p=0.47	Wound infections: 3% vs. 8%, p=0.0016 Axillary seromas: 6% vs. 14%, p=0.0001 Axillary paresthesias: at 1 mo: 12% vs. 47%, p<0.0001 at 6 mos: 12% vs. 44%, p<0.0001 at 12 mos: 9% vs. 39%, p<0.0001 Lymphedema (subjective): at 6 mos 6% vs. 8%, p=0.1772 at 12 mos 2% vs. 13%, p<0.0001 after 12 mos 6% vs. 19%, p<0.0001 Lymphedema (objective) at 1 mo: 6% vs. 8%, p=0.3609 at 6 mos: 8% vs. 11%, p=0.2296 at 12 mos: 6% vs. 11%, p=0.0786
Comparison B: RT axilla (regional) vs. whole breast irradiation				
Whelan, 2015 [24] **MA-20 Trial**	WBI + RNI vs. WBI alone	**OS rates at 9.5 yrs:** 82.8% vs. 81.8%, p=NS HR for death 0.91 (95% CI, 0.72 to 1.13) p=0.38 Mortality rate at 9.5-yr: 10.3% vs. 12.3%, HR 0.80 (95% CI, 0.61 to 1.5) p=0.11	At 10-yr follow-up DFS rates: 82% vs. 77%, HR 0.76 (95% CI, 0.61 to 0.94) p=0.01 Isolated loco-regional DFS rates: 95.2% vs. 92.2%, HR 0.59 (95% CI, 0.39 to 0.88) p=0.009	AE rates Grade≥2 rates: <u>Acute:</u> Fatigue: 19% vs. 18.2%, p=0.67 Pain: 5.9% vs. 4.3%, p=0.14 Pneumonitis: 1.2% vs. 0.2%, p=0.01 Radiation dermatitis: 49.5% vs. 40.1%, p<0.001 <u>Delayed:</u>

Study, date, study name	Comparison	OS / Mortality	DFS / Recurrence	AE / Surgical complications
		Subgroup (pre-specified) ER-negative pts: 81.3% vs. 73.9%, HR 0.69 (95% CI, 0.47 to 1.00, p=0.05)	Distant DFS rates: 86.3% 82.4%, HR 0.76 (95% CI, 0.60 to 0.97, p=0.03) Isolated loco-regional recurrence rates: 6.8% vs. 4.3% Regional recurrence rate only: 2.5% vs. 0.5% Distant recurrence: 16.5% vs. 12.9% (p=NS) *Subgroup (pre-specified)*[a] ER-negative: 81.3% vs. 73.9%, HR 0.69 (95% CI, 0.45-1.00), p=0.05, I^2=0.08 PR-negative: 83.5% vs. 78.9%, HR 0.76 (95% CI, 0.55-1.06), I^2= 0.2 76.2% vs. 61.6%, HR 0 56, 95% CI, 0.39 to 0.81, p=0.04 PR-negative 81.9% vs. 70.5%, HR 0.57, 95% CI, 0.41 to 0.80, p=0.03	Cardiac: 0.9% vs. 0.4%, p=0.26 Lymphedema: 8.4% vs. 4.5%, p=0.001 Neuropathy: 2.5% vs.1.8, p=0.42 Pneumonitis or fibrosis: 0.4% vs. 0.3%, p=0.72 Joint: 2.4% vs. 1.5%, p=0.23 Skin: 6.9% vs. 4.3%, p=0.02 Subcutaneous tissue: 4.1% vs. 2.0%, p=0.01 Second cancer: 11% vs. 10%, p=0.54
Comparison C: RT vs. Surgery				
See description of Schmidt-Hansen et al. systematic review and meta-analysis [31] in Table 4-2 and more description in text				
Savolt, 2013 [33,39] **OTOASOR**	ALND vs. aRT	Overall rates *nr*	DFS: 94.3% vs. 97%; p=NS Recurrence rate in the axilla: 0.82% vs. 1.3%, p=NS	*nr*
Straver, 2010 [34-36]* **AMAROS**	ALND vs. aRT	OS rates at 5-yr: 93.3% (95% CI, 91.0 to 95.0) vs. 92.5% (95% CI, 90 to 94.4), HR 1.17; 95% CI, 0.85 to 1.62; p=0.34 At 8 yrs follow-up: OS rates 77.9% vs. 84.8%, p=0.06	**DFS:** Rates at 5-yr: 86.9% (95% CI, 84.1 to 89.3) vs. 82.7% (95 % CI, 79.3 to 85.5); HR=1.18 (95 % CI, 0.93 to 1.51), p=0.18 Recurrence rates in the axilla: At 5-yr: 0.43 % (95% CI, 0.00 to 0.92) vs. 1.19% (95% CI, 0.31 to 2.08), p=NS At 8 years follow-up: DFS rate: 7201% vs. 77.4%, p=0.51 Recurrence rate: 2.0% vs. 1.7%, p=1.00	Short term: *nr* Long-term: Shoulder mobility: at 1 yr: p=0.29; at 5-yr: p=0.47 Sign of lymphedema rates: Baseline: 0.46% (3/655) vs. 0 (0/586), p=0.25; 12 mos: 28% (114/410) vs. 15% (62/410), p< 0.0001; 3 yrs: 23% (84/373) vs. 14% (47/341), p=0.003; 5 yrs: 23% (76/328) vs. 11% (31/286), p<0.0001; Arm circumference increase rates ≥10%: Baseline: 5% (33/655) vs 4% (24/586), p=0.5; 12 months: 8% (32/410) vs. 6% (24/410), p=0.332; 3 years: 10% (38/373) vs. 6% (22/341), p=0.08; 5 years: 13% (43/328) vs.6% (16/286), p=0.0009
Early Breast Cancer Trialists' Collaborative Group, 2014 [86] IPD meta-analysis	ALND or axillary sampling + RT of the chest wall, internal mammary chain, and supraclavicular	At 20-yr: 1314 women who had pN1-3 treated with mastectomy and ALND: BC mortality rates: 42.3% vs. 50.2%, 20-yr gain 7.9% (SE 3.1), RR 0.80 (95% CI, 0.67 to 0.95), log-rank 2-sided p=0.01	1314 women who had pN1-3 treated with mastectomy and ALND: **Loco-regional recurrence rate at 10 yrs:** 3.8% vs. 20.3%, log-rank 2-sided p<0.0001 **Overall recurrence rate at 10 yrs:** 34.2% vs. 45.7%; 10-yr gain 11.5% (SE 2.9), RR 0.68 (95% CI, 0. 57 to 0.82, p=0.00006)	*nr*

Study, date, study name	Comparison	OS / Mortality	DFS / Recurrence	AE / Surgical complications
	and/or axillary lymph nodes vs. ALND or axillary sampling[c]	Subgroups: In 1133 women who had pN1-3 in trials treated with mastectomy plus ALND, and chemotherapy, RT reduced breast cancer mortality by slightly more than a fifth: RR 0.78 (95% CI, 0.64 to 0.94), 2-sided p=0.01 2541 pN+ women[d] treated with mastectomy and axillary sampling: BC mortality rates: 55.6% vs. 68.2%, RR 0.75, (95% CI, 0.67 to 0.83), log-rank 2-sided p<0.00001 Death rates from any causes: 63.1% vs. 71.8%, RR 0.79, (95% CI, 0.71 to 0.87), log-rank 2-sided p<0.00001	2541 pN+ women[d] treated with mastectomy and axillary sampling: **Loco-regional first recurrence rates:** 6.3% vs. 37.2% RR 0.21 (95% CI, 0.17 to 0.26), log-rank 2-sided p<0.00001 **Overall recurrence rate:** 48.3% vs. 67%, RR 0.59 (95% CI, 0.53 to 0.66), log-rank 2-sided p<0.00001 Overall recurrence rate was larger in pts treated with axillary sampling than with ALND. Difference between RR, 0.003. Subgroups: In 1133 women who had pN1-3 in trials treated with mastectomy and ALND, plus chemotherapy, RT reduced overall recurrence rates by a third: RR 0.67 (95% CI, 0.55 to 0.82, 2-sided p=0.00009 Of 318 women with only one positive node: Loco-regional recurrence rate: 2.3% vs. 17.8%, 2-sided p<0.00001 At 9 yrs overall recurrence rate: 36.4% vs. 24.1%, RR 0.60 (95% CI, 0.39 to 0.92, 2-sided p=0.02	
Comparison D: RT vs. No treatment				
Killander, 2009 [41]	1) RT 2) RT+ C 3) C alone	Overall mortality at 20 yrs: p=NS	Loco-regional recurrence at 20 yrs: Cumulative incidence: RT vs. C: 3.5% vs. 13.9%, p=0.0071	*nr*
Killander, 2007 [40]	1) RT 2) RT + Tam 3) Tam alone	**Overall mortality rate at 20 yrs:** RT: 71% RT + Tam: 68% Tam: 62% RT + Tam vs. Tam NS **Subgroup** of Receptor + pts**:** RT vs. RT+Tam: p=0.047	Loco-regional recurrence reduction: RT + tam vs. Tam: 5.3% (95% CI, 2.8 to 8.9%) vs. 18.5% (95% CI, 13.8 to 23.8%), p<0.001 RT: 6.7% (95% CI, 3.8 to 10.4%) Recurrence of systemic disease at 20 yrs: RT+tam vs. tam: 40% vs. 50%, p=0.047	*nr*

[a]Cumulative incidence of cancer events is defined by Galimberti et al. [30] as invasive relapse at any site or contralateral breast cancer
[b]Grade 1 to 4 adverse events
[c]Includes also women with N2 disease. A note is made to the results that report indirect evidence because the N1 and N2 pts are not separated out
[d]This may include also women with N2 disease

AE = adverse events; ALND = axillary lymph node dissection; aRT = axillary radiotherapy; BC = breast cancer; C = cyclophosphamide; CI = confidence interval; DFS = disease-free survival; ER = estrogen receptor; HR = hazard ratio; IPD = individual patient data; mo(s) = month(s); NAC = neo-adjuvant chemotherapy; nr = not reported; NS = not significant; OS = overall survival; pts = patients; QOL = quality of life; PR = progesterone receptor; RNI = regional nodal irradiation; RR = relative risk; RT = radiotherapy; SE = standard error; SLNB = sentinel lymph node biopsy; Tam = tamoxifen; WBI = whole breast irradiation; yr(s) = year(s)

Outcomes

Table 4-15 reports the results of the completed trials. Table 4-14 reports the summary results of the companion publications of the included studies.

Comparison A: No further surgery beyond SLNB compared with ALND

For Question 3 we endorsed Recommendation 2.1 of the ASCO 2017 guideline [3,4] for this comparison.

OS, DFS, and recurrence

When summarized in meta-analysis by Schmidt-Hansen [31], data from the ACOSOG Z0011, the ATTRM-048-13-2000, and the IBCSG 23–01 trials [13,30,32] showed no statistically significant difference for OS (HR, 0.82; 95% CI, 0.58 to 1.15, p=0.25, I^2=0%), or for DFS (HR, 0.81; 95% CI, 0.63 to 1.04, p=0.1, I^2=0%) between SLNB and ALND. As well, no statistically significant between-group differences were found in axillary (RR, 0.46; 95% CI, 0.14 to 1.49, p=0.2, I^2=0%), local (RR, 1.6; 95% CI, 0.86 to 2.97, p=0.14, I^2=0%), regional (RR, 0.34; 95% CI, 0.1 to 1.15, p=0.08, I^2=0%) and distant breast cancer recurrences (RR, 1.31; 95% CI, 0.8 to 2.15, p=0.28, I^2=0%).

Adverse events

The ACOSOG Z0011 [27] showed that patients who received SLNB alone experienced significantly less surgical adverse effects than those who had SLNB and ALND (25% vs. 70%, p≤0.001). Patients in the SLNB-alone group experienced significantly less wound infections (3% vs. 8%, p=0.0016), axillary seromas (6% vs. 14%, p=0.0001); axillary paresthesias at one, six, and 12 months (respectively: 12% vs. 47%, 12% vs 44%, 9% vs. 39%; p<0.0001 for all); subjective lymphedema at 12, and over 12 months (respectively: 2% vs. 13% and 6% vs. 19%, p<0.0001 for all); however objective lymphedema by arm measurements at one, six, and 12 months did not statistically significantly differ between arms.

The IBCSG-23-01 [29,30,150], after a follow-up of 9.7 years (range, 7.8 to 12.7 years) reported in the ALND group statistically significantly greater sensory neuropathy (19% vs. 13%, p=0.01), lymphedema (13% vs. 4%, p,0.0001), and motor neuropathy (9% vs. 3%, p=0.0002).

Comparison B: Radiotherapy of the axilla (loco-regional node irradiation) versus no irradiation to the loco-regional lymph nodes.

OS/mortality

The MA.20 trial at 9.5 years follow-up did not detect any statistically significant difference in OS between patients treated with WBI plus RNI and patients treated with WBI alone.

Disease-free survival and Recurrence

In the MA.20 trial [24], at 9.5 years follow up DFS rates for recurrence were higher for patients who received WBI plus RNI than for patients who received WBI alone, HR, 0.76; 95% CI, 0.61 to 0.94, p=0.01. Loco-regional and distant DFS rates were also statistically significantly higher for patients treated with the additional RNI than for controls (respectively: HR, 0.59; 95% CI, 0.39 to 0.88, p=0.009, and HR, 0.76; 95% CI, 0.60 to 0.97, p=0.03). More patients in the WBI alone than patients in the WBI and RNI group experienced isolated local recurrence (6.8% vs. 4.3%, p value not reported), and distant recurrence (16.5% vs.12.9%, p value not reported).

Quality of Life

No data on this outcome were reported.

Adverse events

Among grade ≥2 acute adverse events, pneumonitis and radiation dermatitis were statistically significantly more prevalent among patients treated with WBI plus RNI than those treated with WBI alone (1.2% vs. 0.2%, p=0.01, and 49.5% vs. 40.1%. p<0.001 respectively).

Among the grade ≥2 delayed adverse events lymphedema, and damage to skin and subcutaneous tissue were statistically significantly worse for patients who had received WBI plus RNI (respectively: 8.4% vs. 4.5%, p=0.001; 6.9% vs. 4.3%, p=0.02; and 4.1% vs. 2%, p=0.01) [24]. The follow-up of this study was not long enough to detect any second cancers.

Subgroups

The MA20 study [24] examined subgroups of ER+ and ER– and PR– patients. No between-group statistically significant difference was noted within subgroups for OS. Patients with ER– and PR– receptor status may have a better DFS at 10-year follow-up when treated with additional RNI than with WBI alone (respectively: 76.2% vs. 61.6%, HR, 0 56; 95% CI, 0.39 to 0.81, p=0.04; and 81.9% vs. 70.5%, HR, 0.57; 95% CI, 0.41 to 0.80, p=0.03).

Comparison C: Radiotherapy to the axilla versus further surgery (ALND)

OS/mortality

The OTOASOR trial [33] did not find any statistically significant differences in OS between patients treated with ALND and those treated with radiotherapy, but did not report overall rates.

The AMAROS trial [34-36], at five-year follow-up, did not detect any between-group differences in OS at five years (ALND: 93.3% vs. radiotherapy: 92.5%, HR, 1.17; 95% CI, 0.85 to 1.62, p=0.34). After 10 years of follow-up OS was still not different between arms: ALND: 84.6% (95% CI, 81.5 to 87.1), versus RNI 81.4% (95% CI, 77.9 to84.4), HR 1.17; 95% CI, 0.89-1.52, p=0.26 [37].

The individual patient data meta-analysis [86] showed an improvement in breast cancer mortality for patients treated with irradiation compared with patients treated with ALND (42.3% vs. 50.2%, RR, 0.80; 95% CI, 0.67 to 0.95), log-rank 2-sided p=0.01). This study [86] did not present data on long-term adverse events, but at 20 years, death rate from any cause was still statistically significantly more favourable for patients treated with irradiation than for patients treated with surgery (63.1% vs. 71.8%, RR, 0.79; 95% CI,0.71 to 0.87, p<0.00001).

DFS and Recurrence

The OTOASOR trial [33] did not find any statistically significant between-group differences in DFS, and axillary recurrence between women treated with ALND compared with those treated with axillary radiotherapy (respectively 94.3% vs. 97%; p value not significant; and 0.82% vs. 1.3%; p value not significant).

The AMAROS trial [34-36], at five-year follow-up showed no statistically significant difference in DFS (ALND: 86.9% vs. radiotherapy: 82.7%, HR, 1.18; 95% CI, 0.93 to 1.51, p=0.18), and in axillary recurrence (ALND: 0.43% vs. RT: 1.19%, p value not significant)

Quality of Life

The OTOASOR trial [33] did not report on this outcome.

The AMAROS trial [34-36] did not detect any statistically significant difference in shoulder mobility at one year (p=0.29), and at five years (p=0.47).

Adverse events

The OTOASOR trial [33] did not report on this outcome. The AMAROS trial [34-36] did not report short-term adverse events. At long-term follow-up lymphedema was statistically significantly worse for patients who received ALND than for those in the radiotherapy arm at one-year (ALND: 28% vs. radiotherapy: 15%, p<0.0001; at three-year (ALND: 23% vs. radiotherapy: 14%, p=0.003), and at five-year follow-up (ALND: 23% vs. RT: 11%, p<0.0001). Arm circumference increase was statistically significantly worse for patients who received ALND than for those in the radiotherapy arm at five-year follow-up (ALND: 13% vs. RT: 6%, p=0.0009), but no difference was detected at one-year (ALND: 8% vs. RT: 6%, p=0.332), and three-year follow-up (ALND: 10% vs. RT: 6%, p=0.08).

Subgroups

The AMAROS trial [34-36] did not detect any statistically significant difference in any subgroups**.**

Comparison D: Radiotherapy compared with no treatment

Overall Survival/mortality

At 25-year follow-up Killander et al. [42] did not detect any between-group statistically significant differences for OS in both pre- and postmenopausal women. Adding radiotherapy to either cyclophosphamide or tamoxifen increased mortality from heart disease from zero to 0.8% (p=0.04) in premenopausal women, and from 10.5% to 18.4% (p=0.005) in postmenopausal women. Adding radiotherapy to hormonal therapy in postmenopausal women, increased mortality due to cerebrovascular disease from 3.4% to 8.7% (p=0.015), while adding irradiation to chemotherapy in premenopausal women did not result in any statistically significant differences (cumulative cerebrovascular mortality: cyclophosphamide: 0.8% vs. radiotherapy + cyclophosphamide: 1.7%, p=0.52).

DFS and Recurrence

Recurrence at 20 year follow-up:

In postmenopausal women [40] loco-regional recurrence was 18.5% (95% CI, 13.8 to 23.8%) in the tamoxifen-only arm, 5.3% (95% CI, 2.8 to 8.9%) in the tamoxifen plus radiotherapy arm (combination treatment), and 6.7% (95% CI, 3.8 to 10.4%) in the radiotherapy-only arm. The combination treatment was statistically significantly better than hormonal therapy alone, p<0.001.

No statistically significant difference in between-group cumulative incidence of systemic disease was shown.

In premenopausal women, adding irradiation to cyclophosphamide statistically significantly improved loco-regional recurrence from 13.9% in the chemotherapy-only arm to 3.5% in the combination arm, p=0.0071.

Quality of Life

No data on this outcome were reported.

Adverse events

No data on this outcome were reported.

Subgroups

In node-positive postmenopausal women adding irradiation to tamoxifen significantly decreased the cumulative incidence of systemic disease (p=0.047).

Literature Search Results for Primary Studies
Question 4: Women who were treated with NAC

The flow diagram for primary studies is reported in Appendix 4B. Table 4-16 shows the evidence that forms the basis for recommendation 4. The evidence provided by the Lyman et al. guideline [3,4], and by three systematic reviews that initially met our inclusion criteria [49,96,109] was largely outdated, or did not provide the data of interest for this question, and we did not identify any RCTs for this question. Therefore, we undertook a systematic review of non-randomized comparative studies. The search strategy for observational studies is reported in Appendix 2C.

Eighteen studies (in 11 publications) met our inclusion criteria [43-46,48,53,54,168-179]. Six studies [174-179] did not control for confounding, and we considered them at critical risk of bias; therefore, we did not extract data from them.

Table 4-16. Literature search results for question 4

Comparisons in Question 4		Endorsed guidelines	Included high quality SRs	Included RCTs	Included Observational comparative trials	Ongoing trials
Interventions	**Controls**					
Patients who were node negative at diagnosis						
Further axillary treatment	No further axillary treatment	NA	NA	NA	NA	INSEMA (NCT02466737)
Patients who were node positive at diagnosis						
Surgical Interventions		NA	NA	NA	Kim, 2015 [44]	NA
SLNB Surgery	ALND No treatment					
Radiotherapy Interventions		NA	NA	NA	Rusthoven, 2016 [45] Krug, 2019 [43]	MAC.19 trial (NCT01901094) RTOG 1304 / NSABP B51 (NCT01872975)
RT+ surgery	No treatment Surgery (ALND)					
Timing of SLNB						
SLNB before NAC	SLNB after NAC	NA	NA	NA	**Studies of direct patient outcomes:** Fernandez-Gonzalez, 2018 [168], Hunt, 2009 [53], Papa, 2008 [173] **Studies of diagnostic outcomes:** Classe, 2019 [169], Zetterlund, 2017 [170,171], van der Heiden-van der Loo, 2015 [172], Kuehn, 2013 [46], Tausch, 2011 [48], Papa, 2008 [173], Gimbergues, 2008 [54]	NA

ALND = axillary lymph node dissection; NA = not applicable; NAC = neoadjuvant chemotherapy; RCTs = randomized controlled trials; RT = radiotherapy; SLNB = sentinel lymph node biopsy; SRs = systematic reviews

Study design, risk of bias and certainty of the evidence

A) Patients who were pathologically node negative at diagnosis

We did not identify any completed and fully published randomized or non-randomized studies for this group of patients.

B) Patients who are pathologically node positive at diagnosis

We identified five studies that reported direct patient outcomes [43-45,180,181]. All the trials that met our inclusion criteria for Question 4 were nonrandomized and controlled for confounding. Kim et al. [44] examined surgical interventions (i.e., SLNB vs. ALND). Kantor et al. [180], Rusthoven et al. [45], and Liu et al. [181] examined radiotherapy interventions plus surgery compared with no treatment. Krug et al. [43] pooled data from three RCTs and compared PMRT before surgery with no radiotherapy. We did not conduct a meta-analysis of these trials because the studies were either heterogeneous or they used the same source of data, and possibly, some of the same patients. We did not locate any completed trial comparing radiotherapy with ALND.

SLNB compared with ALND, and ALND compared with no treatment (surgery trials)

Kim et al. [44] was a retrospective cohort study collecting data of 386 patients from two institutions. The vast majority of the patients had stage T0, T1-T2 after NAC. The authors compared outcomes among five groups of initially cytologically proven positive patients treated with NAC:

1. those who received SLNB, and for whom SLNB revealed no residual axillary metastasis, and no further dissection was performed (n=31);
2. those who received SLNB, had negative sentinel node status, and underwent further ALND (n=20);
3. those who received SLNB, had positive or undetected sentinel nodes, and undergoing further ALND (n=69);
4. those who received complete ALND, had no residual axillary metastasis on pathology (n=79); and
5. those who received ALND, and had pathologically positive disease (n=187).

No description is provided about how SLNB was performed, about surgeons' expertise, and about the characteristics of the settings where data were collected. Kim et al. [44] reported on patient-relevant outcomes such as OS, recurrence rate, and DFS.

Although the authors conducted a multivariate analysis to control for confounding factors, we considered the Kim et al. [44] study at serious to very serious risk of bias for all outcomes (see Table 1 in Appendix 6) because its data were retrospectively collected, and because the outcome measure might have been influenced by knowledge of the intervention received.

For this comparison we identified the abstract publication [182] of a cohort single centre study. This study evaluated OS, DFS, recurrence, and adverse events. We did not evaluate the risk of bias because not enough information was provided.

The certainty of this evidence for SLNB compared to ALND is low to very low. A small proportion of the patients (9.5%) of the Kim et al. [44] study had stage T3 disease; therefore, this evidence is partially indirect. A single study [44], with a relatively small sample, was identified for this comparison; the number of patients in each group was very small making the results quite imprecise for all outcomes.

Radiotherapy compared with ALND, and radiotherapy and ALND compared with no treatment (radiotherapy trials).

Among the three studies that analyzed the National Cancer Database [45,180,181], we chose to use the results of the Rusthoven et al. trial [45], and set the other two studies [180,181] aside because: a) Rusthoven et al. [45] included patients who had received mastectomy, as well as patients who had received breast-conserving surgery; b) the majority of the included patients had stage T1 and T2, and a small proportion had stage T3, while the Kantor et al. [180] and the Liu et al. [181] trials included a substantial proportion of patients with stage T3 and T4; and c) the risk of bias of Rusthoven et al. [45] was considered moderate. Table 4-17 presents the detailed results of the Rusthoven et al. trial [45]. Krug et al. [43] was a pooled retrospective analysis of three RCTs. Table 4B in Appendix 7 shows a comparison of the general characteristics and summary results of the four included studies, and Table 1 in Appendix 6 shows the evaluation of the risk of bias of the three retrospective studies [45,180,181] as appraised with the ROBINS-I tool [78].

For this comparison we identified the abstract publication [183] of a registry analysis. This study compared PMRT versus no radiotherapy, and evaluated loco-regional recurrence, DDFS, and OS. We did not evaluate the risk of bias because not enough information was provided.

The certainty of the evidence for radiotherapy interventions compared to no intervention is moderate. For OS, the Rusthoven et al. study [45] is at moderate risk of bias: this trial was a retrospective analysis of prospectively collected data; imprecision was unlikely since the sample was extremely large (n=15315). The cancer registry source of the data did not report a pathological classification at diagnosis, but only a clinical classification, which could have introduced selection bias. This study included a variable percentage (15% to 46%) of patients with clinical stage T3, making the evidence indirect; however, multivariate analysis showed that similar results were found when patients with stage T1-T2 and T3 were considered (Table 4-17). The Krug et al. trial [43] was considered at moderate risk of bias for loco-regional recurrence (Table 1, Appendix 6). This study included 31%, and 14.6% of patients with stage T3 and T4, respectively; therefore, this evidence is partially indirect.

C) Timing of SLNB: SLNB performed before compared with after NAC

We identified three studies that reported on direct patient outcomes along with diagnostic outcomes [53,168,173], and seven studies in eight publications that reported exclusively on diagnostic outcomes such as false negative rate or identification rate [46,48,54,169-173]. We did not conduct a meta-analysis because the included studies were heterogeneous.

Studies of Direct Patient Outcomes

Study Design, Risk of Bias, and Certainty of the Evidence

All the included studies had a non-randomized design. Fernandez-Gonzalez et al. [168] and Hunt et al. [53] were at moderate risk of bias (Appendix 5, Table 1), and Papa [173] at serious risk of bias (Appendix 5, Table 2). Fernandez-Gonzalez et al. [168] included a population of 172 patients of clinical stage T1c to T3 at diagnosis with clinically negative axilla. SLNB was performed using radiocolloid before (n=122) or after (n=50) NAC; the primary outcomes were ALND rate, and recurrence rate; the authors reported also on progression-free survival, and identification rate.

Hunt et al. [53] included a large sample (n=3746) of clinically node-negative patients with stage T1-T3. SLNB was performed using blue dye with or without radiocolloid. The primary outcome was technical success rate, and a secondary outcome was false negative rate.

Papa et al. [173] included a relatively smaller sample of clinically negative patients (n=117). SLNB was performed with radiocolloid and blue dye. The authors reported response rate, identification rate, false negative rate, and false negative rate according to mapping technique, which we will discuss in the relative section in Question 5. We did not conduct a meta-analysis because the studies were heterogeneous.

Certainty of the evidence

The certainty of the body of evidence comparing SLNB before with SLNB after NAC is moderate to low. There was no inconsistency in results: Fernandez-Gonzalez et al. [168] and Hunt et al. [53] reported similar results for recurrence rate. All three studies included some patients with stage T3 making the evidence partially indirect. Hunt et al. [53] had a fairly large sample, while the other two studies [168,173] were institutional cohorts of a smaller size, making this body of evidence moderately imprecise.

Studies of diagnostic outcomes (i.e., indirect outcomes)

Study Design, Risk of Bias, and Certainty of the Evidence

Classe et al. (2019) [169] conducted a prospective multicentre cohort trial that included a population of cytologically proven node positive or negative at diagnosis with tumour stage T1 to T3 who received SLNB and/or ALND after NAC. The authors used ALND as a reference standard. The outcomes were false negative and identification rates.

Zetterlung et al. [170] conducted a prospective study that included a population of clinically node-negative patients (n=224) with tumour stage T1 to T3, who received SLNB, with the purpose of staging, before NAC and clinically node-positive patients [171] (n=195) who received SLNB after NAC. The authors used ALND after NAC as a reference standard. The outcomes were identification rate, and false negative rate.

van der Heiden-van der Loo et al. [172] conducted a retrospective study that included a population of clinically node-negative patients (n=1183) with tumour stage T1 and T2. The authors compared SLNB for staging performed before NAC with SLNB performed after NAC, and used ALND as a reference standard. The outcomes were identification rate, false negative rate, and the proportion of patients receiving ALND.

The SENTinel NeoAdjuvant (SENTINA) trial [46] was a prospective cohort study that included a population of initially clinically negative or clinically positive patients treated with NAC (n=1737). Tumour stage was cN0, cN1, and cN2. The authors compared SLNB before or after NAC with the reference standard (ALND). The study had four arms: arm A and B included patients who were initially clinically node negative (cN0), and who were given SLNB before NAC. Patients in arm A were pathologically node negative after SLNB, and did not receive any ALND after NAC; patients in arm B were pathologically node positive after SLNB and were treated with ALND after NAC. Arms C and D included patients who were initially clinically node positive (cN1 or cN2), and were given SLNB after NAC. Patients in arm C had converted to clinically node negative (ycN0) after NAC; patients in arm D had remained clinically positive after NAC and did not receive SLNB. Outcomes were FNR in arm C; detection rate of SLNB before and after NAC in arms B and C; and detection rate and false negative rate of a second SLNB procedure after identification and removal of a positive SLN before NAC in patients in arm B. This study also reports false negative rate by type of tracer: these results are relevant to our question 5, and they will be discussed later in the section relative to question 5.

Tausch et al. [48] was a prospective cohort study, and included pathologically node positive patients with all breast cancer stages, excluded inflammatory breast cancer (n=111). The authors compared SLNB with the purpose of staging with ALND as a reference standard. The outcomes sought were identification rate, false negative rate, sensitivity, and number of lymph nodes removed.

Gimbergues et al. [54] tested in a prospective trial the accuracy of SLNB with the purpose of staging, and used ALND of level I and level II nodes as a reference standard on pathologically node-positive patients (n=129) with stage T1 to T3, N1, N2 disease.

Papa et al. [173], Fernandez-Gonzalez et al. [168], and Hunt et al. [53], besides the direct patient outcomes, described above, reported also on diagnostic outcomes. Since Hunt et al. [53] and Fernandez-Gonzalez et al. [168] considered diagnostic outcomes as secondary endpoints, we reported their results in Table 4-17, but we did not conduct a quality assessment of these studies for diagnostic outcomes.

The studies that included populations that were pathologically positive [46,48,54,169,171] were at a variable risk of bias (Table 2 in Appendix 6).

Among all the studies included for this question, Tausch et al. [48] reported on the expertise of the operator and included institutions that had performed at least 50 procedures with a sensitivity of at least 95% to avoid including learning curves.

We did not conduct a meta-analysis because the studies were heterogeneous (Table 4-D in Appendix 7).

Certainty of the evidence

The certainty of the body of evidence comparing SLNB to ALND (reference standard) is low. Two studies [46,170,171] were at low risk of bias, while the others were all at high or unclear risk of bias as measured with the QUADAS-2 [79] (Table 2 in Appendix 6). All of the studies included some patients who had stage T3 or higher disease, making the results indirect. Often the results were inconsistent across studies, possibly because of the small sample size of some trials, making the results imprecise.

Companion studies

We identified seven corollary studies of two of the included trials for question 4. Six were subgroup analyses [184-186]189] of the SENTINA trial [46], and the other [187] was a feasibility study of the Tausch et al. trial [48]. The studies are summarized in Table 4-18.

Ongoing, Unpublished, or Incomplete Studies

We identified the abstract of the INSEMA ongoing trial. 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) trial (https://sunnybrook.ca/trials/item/?i=240&page=49335). Table 4-19 provides a summary for these trials. Table 1, Appendix 8 reports all the ongoing trials that were identified.

Table 4-17. General characteristics and summary results of primary studies included for Question 4: Interventions for women treated with NAC

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Intervention / Comparison / Reference standard	Outcomes	Intervention Methods/ Adjuvant treatment	Summary results
A) Patients who are pathologically node negative at diagnosis						
No studies were identified for this population that were fully published						
B) Patients who are pathologically node positive at diagnosis						
STUDIES OF DIRECT PATIENT OUTCOMES (i.e., studies of treatment interventions)						
a) Surgical studies: SLNB vs. ALND						
Kim, 2015 [44] **Country:** Korea **Funding:** *nr*	Retrospective study, multicentre (2 centres). **Accrual period** Jan 2007 to Aug 2013 **Aim** To test the feasibility and accuracy of SLNB after NAC in pts with ALN metastasis at diagnosis **Follow-up (median):** 19.5 mos (range, 2–65 mos)	**N**=386 pts with invasive BC and pathologically node positive axilla at diagnosis **Age (mean ± SD)** 45.6±9.3 yrs **Stage (Groups 1-4)**: ypT0-is 42.2% ypT1-2: 48.2% ypT3 9.5%	**SLNB n**=120 vs. **ALND n**=266 Group 1: ypSLNB- n= 31 (no ALND) Group 2: ypN- n=20 (ALND) Group 3: ypN+ n=69 (ALND) Group 4: ypN- n=79 (ALND) Group 5: ypN+ n=187 (ALND)	OS DFS Recurrence FNR IR FNR definition: *nr*	Methods of SLNB: Radioactive colloid and blue dye were used for SLN detection. Nonblue or non-hot nodes with suspicious features for metastases, and enlarged or hard nodes on palpation, were also harvested. Blue or hot nodes as well as suspicious lymph nodes, were defined as sentinel nodes. Adjuvant treatment: *nr*	OS (Groups 1 vs. 2 vs.3 vs.4): p=NS DFS (Groups 1 vs. 2): p=NS DFS (Groups 1 vs. 4): 77.1% vs. 85.4% (pts with pCR treated with ALND): p=0.031 Axillary recurrence rate: (3.3%, 5.0%, and 1.3% for groups 1, 2, and 4, respectively, p>0.05). FNR was calculated for group 2: 2/20 (11%)
b) Studies of radiotherapy: Radiaton therapy and surgery vs. no treatment						
Rusthoven, 2016 [45] **Country:** USA **Funding:** *nr*	Retrospective population study. Analysis of a cohort from the NCDB. **Accrual period** 2003 to 2011 **Aim** To evaluate the impact of PMRT and RNI after BCS approaches for women with clinically node-positive breast	**N**= 15315 Adult women with cT1–3 cN1 M0 BC treated with NAC Separate results are provided for T1-T2 pts. Mast-ypN0: n= 3040 (19.8%), Mast ypN+: n=7243 (47.3%), BCS-ypN0: n=2070 (13.5%) BCS-ypN+: n=2962 (19.3%). **Age:** No PMRT vs. PMRT Mast / ypN0 : <50 yrs: 53% vs. 57% ≥50 yrs: 47% vs. 43% Mastectomy / ypN+ :	**Mastectomy cohorts: no PMRT vs. PMRT** Mast-ypN0: **n**=1078 vs. **n**=1962 Mast-ypN+: **n**=1819 vs. **n**=5424 **BCS cohorts: Breast RT vs. Breast RT + RNI.** BCS-ypN0 **n**=1154 vs. **n**=916 BCS-ypN+: **n**=1337 vs. **n**=1625	Mast pts:No PMRT vs. PMRT *OS BCS pts: Breast RT vs. Breast RT+RNI *OS	Methods of SLNB: NA Adjuvant treatment: Mastectomy (n=10283) or BCS (n=5032)	**OS** *On multivariate analysis:* **Mastectomy cohorts:** Mast-ypN0: HR 0.729 (95% CI, 0.566–0.939), p=0.015; Mast-ypN+: HR 0.772, (95% CI, 0.689–0.866), p<0.001. **BCS cohorts:** BCS-ypN0: HR 0.969 (95% CI, 0.699–1.344), p=0.851; BCS-ypN+: HR 1.037 (95% CI 0.862–1.248), p=0.700). *On propensity score-matched analysis:* **Mastectomy cohorts:**

<table>
<tr><th>Study, date, country, study name, Funding</th><th>Design, Accrual period Aim Follow-up</th><th>Population</th><th>Intervention / Comparison / Reference standard</th><th>Outcomes</th><th>Intervention Methods/ Adjuvant treatment</th><th>Summary results</th></tr>
<tr><td></td><td>cancer treated with NAC in the NCDB

Follow-up (median):
Overall: 39 mos (range 1–132 mos); Survivors: 41 mos</td><td><50 yrs: 48% vs. 52%
≥50 yrs: 52% vs. 48%
BCS / ypN0
<50 yrs: 48% vs. 47%
≥50 yrs: 52% vs. 54%
BCS / ypN+
<50 yrs: 44% vs. 43%
≥50 yrs: 56% vs. 57%

Stage: No PMRT vs. PMRT
Mast / ypN0 :
cT1: 16% vs. 9.6%
cT2: 55% vs. 45%
cT3: 29% vs. 46%
Mastectomy / ypN+ :
cT1: 19% vs. 11%
cT2: 49% vs. 46%
cT3: 32% vs. 43%
BCS / ypN0
cT1: 15% vs. 14%
cT2: 64% vs. 64%
cT3: 22% vs. 22%
BCS / ypN+
cT1: 19% vs. 19%
cT2: 66% vs. 62%
cT3: 15% vs. 19%</td><td></td><td></td><td>Mast-ypN0: (n=1039 PMRT vs. n=1039 no-RT): HR 0.695 (95% CI, 0.518–0.929), p=0.014
Mast-ypN+: (1787 PMRT vs. 1787 no-RT: HR 0.845 (95% CI, 0.738–0.968), p=0.015
BCS cohorts:
BCS-ypN0: (n=860 RNI vs. n=860 no-RNI): HR 1.028 (95% CI, 0.716–1.477), p=0.880
BCS-ypN+ (n=1244 RNI vs.n=1244 no-RN): HR 0.962 (95% CI, 0.785–1.175), p=0.704

Subgroups
Mastectomy pts who received PMRT and RNI, vs. PMRT p=NS
All cohorts: No significant interactions between the survival impact of PMRT or RNI based on age, axillary surgery, ypN stage, or in-breast pathologic response.
Mast/ypN+: PMRT vs. no RT
cT1-2: 559 vs. 238 events, p=0.03 (multivariate analysis)
cT3: 545 vs. 202 events, p<0.001</td></tr>
<tr><td>Krug, 2019 [43]

Country:
Germany

Funding:
(of the original trials) Amgen, Chugai, GlaxoSmithKline, Roche, and Sanofi-Aventis.</td><td>Pooled retrospective analysis of 3 RCTs[f]

Accrual Period:
Sept 2002 to Jul 2010

Aim:
1) To ascertain to what extent PMRT improves loco-regional recurrence and OS in pts who</td><td>817 pts who received NAC

Age: % in each group
<table><tr><td></td><td>RT</td><td>No RT</td></tr><tr><td><40</td><td>13.2</td><td>24.1</td></tr><tr><td>40-49</td><td>38.2</td><td>31.9</td></tr><tr><td>≥50</td><td>48.7</td><td>44.0</td></tr></table>
Stage: % in each group
<table><tr><td></td><td>RT</td><td>No RT</td></tr><tr><td>cT1</td><td>4.1</td><td>7.1</td></tr><tr><td>cT2</td><td>46.6</td><td>62.4</td></tr><tr><td>cT3</td><td>32.8</td><td>22.0</td></tr></table></td><td>RT (n= 676) vs. No RT (n=141)</td><td>5-yr cumulative
LRR
DFS</td><td>NAC in the included studies consisted of: Docetaxel, anthracycline and cyclophosphamide; or vinorelbine and capecitabine (Gepar Trio); epirubicin/ cyclophosphamide (EC) followed by a randomization to 4 cycles of docetaxel with or without capecitabine;</td><td>Primary outcome:
Multivariate analysis
LRR: HR 0.51 (95% CI, 0.27-1.0, p=0.05
For pts with cN+:
LRR:
HR 2.14 (95% CI, 1.19–3.87, p=0.01)

Secondary outcomes:
DFS: HR 1.87 (95% CI, 1.35-2.60, p<0.01)</td></tr>
</table>

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Intervention / Comparison / Reference standard	Outcomes	Intervention Methods/ Adjuvant treatment	Summary results
	received NAC that included contemporary systemic treatment agents. 2) A secondary aim is to see if PMRT improves results in pts with response to NAC, especially with a pCR or conversion from clinically involved lymph nodes (cN?) to pathologically negative lymph nodes (ypN0). **Follow-up (median):** 51.5 mos	cT4 16 7.8 Missing 0.4 0.7 ypT0 8.6 14.2 ypT1 23.4 34.8 ypT2 22.3 15.6 ypT3 16.1 4.3 ypT4ac 3.6 0.7 ypT4 0.7 0 ypTis 4.2 6.4 Nodals stage: RT / No RT cN ▫35.2 / 50.4 cN+ 63.9 / 48.9			(GeparQuattro). Four cycles of EC followed by docetaxel (GeparQuinto). Pts with HER2-overexpressing tumours were given trastuzumab. PMRT was given at 45-50 Gy, 10 Gy boost for close margins. RT of the supra/infraclavicular lymphatic drainage was given if lymph node involvement after chemotherapy or >3 lymph nodes involved at first diagnosis	
C) Timing						
STUDIES REPORTING ON DIRECT PATIENT OUTCOMES						
Fernandez-Gonzalez, 2018 [168] **Country:** Spain **Funding:** None declared	Retrospective cohort study of prospectively collected data at one institution (historical control) **Accrual period** Pre-NAC: Dec 2006 to Apr 2014 Post-NAC: May 2014 to Jul 2016 **Aim:** To compare advantages and disadvantages of SLNB before or after NAC. The hypothesis was that SLNB after	**N**=172 adult pts (age 18-80 yrs), with palpable primary tumours >10 mm, negative axillary lymph nodes, infiltrating BC receiving NAC **Age** (mean±SD): Pre-NAC: 52.1±13.4 yrs Post-NAC: 54.9±14.1 yrs **Stage**: T1c to T3 and N0 (clinically and according to US)	Pre-NAC **n**=122 vs. Post-NAC **n**=50 Reference standard is ALND or histopathology for the diagnostic outcome	*ALND rate *Recurrence rate PFS IR	Methods of SLNB: radiocolloid Adjuvant treatment: NAC = Endocrine NAC: letrozole (2.5 mg/d for 6 to 12 mos), or Chemotherapy NAC: a regimen that included anthracyclines + taxanes for 6 mos; trastuzumab in HER2-positive Surgery: conservative or radical depended on response to NAC. Pts with negative SLNs or micrometastases did	Pre-NAC vs. post-NAC: ALND rate: 28.3% vs. 8%, OR 3.48 (95% CI, 1.3 to 9.3), p=0.004. Recurrence rate: 11.5% vs. 0 at 16 mos follow-up, p=0.85 Probability of PFS at 60 mos: Pre-NAC vs. Post NAC: 8.4% vs. 1% p=0.85 IR >98% in both groups, p=0.118

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Intervention / Comparison / Reference standard	Outcomes	Intervention Methods/ Adjuvant treatment	Summary results
	NAC reduces the ALND rate without an increase in the number of axillary recurrences. Additionally, a comparison was made between the delay in starting NAC and SLNB IR. **Follow-up median, (range):** Pre-NAC group: 5.2 yrs, (0.75-10.1 yrs) Post-NAC: 1.3 yrs, (0.42-4.75 yrs)				not undergo further axillary treatment	
Hunt, 2009 [53] **Country:** US **Funding:** *nr*	Retrospective cohort study **Accrual period** March 1994 to 2007 **Aim:** 1) To evaluate the accuracy of SLNB for pts undergoing NAC first versus pts undergoing surgery first. 2) To evaluate the impact of NAC on the incidence of positive SLNs after chemotherapy and the need for completion ALND in pts with large primary tumours Follow-up (median (range): SLNB after NAC: 47 mos (0-169 mos) SLNB before NAC: 55 mos (2-168 mos)	**N**=3746 clinically negative pts A clinically node negative axilla was defined as the absence of palpable disease in the nodal basin & the absence of suspicious or abnormal appearing lymph nodes based on imaging studies (US & CT scanning) when performed. **Age (median)** SLNB before NAC: 57 yrs (range: 22-92) SLNB after NAC: 51 yrs (range: 25-84), p<0.0001 **Stage**: SLNB before NAC: T1: 81.2% T2: 17.7% T3: 1.1% SLNB after NAC: T1: 12.7% T2: 75% T3: 12.3%	SLNB after NAC n=575 (15.3%) vs. SLNB before NAC **n**=3171 (84.7%) Reference standard: ALND (conducted on 542 pts [27.1% vs. 28.9%, p=0.38])	*Technical success rate in identifying and removing a SLN in pts in whom surgery was attempted. FNR[a] of SLN surgery in pts who were found to have >1 positive SLN or non-SLN Number of ALND performed Loco-regional and distant recurrence FNR	Methods of SLNB: Blue dye with or without radiocolloid Adjuvant treatment: *nr*	*Overall **technical success** (ability to map) rate: 98.5% **Mapping success**: With 1 agent: 1209 of 1240 pts: 97.5% vs. Combination of two agents: 2481 of 2506 pts: 99%, p<0.0001 In multivariate analysis: **FNR**: SLNB before NAC group: 4.1% (22 events over 542), SLNB after NAC group: 5.9% (5 events over 84 pts), p=0.39 **FNR[b] by mapping techniques**: Mapping with blue dye vs. mapping with blue dye plus radiocolloid: OR 2.61 (95% CI, 0.78 to 8.76), p<0.0001 Number of ALND performed: p=NS **Recurrence at 47 months follow-up** SLNB before NAC group vs. SLNB after NAC group:

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Intervention / Comparison / Reference standard	Outcomes	Intervention Methods/ Adjuvant treatment	Summary results
						Local recurrence rate: 1.2% vs. 2.1% Regional recurrence rate: 0.9% vs.1.2% Distant recurrence rate: 2.7% vs. 7.5% After adjusting for clinical stage p=NS
Papa, 2008 [173] **Country:** Israel **Funding:** *nr*	Prospective cohort study **Accrual period** Jan 2002 to Mar 2005 **Aim** To address optimal timing of SLNB in BC pts undergoing NAC Follow-up: *nr*	**N**=117 clinically node negative pts treated with NAC **Age (mean):** 45.4 yrs **Stage**: IIA T2N0M0 and IIB T3N0M0	**Group 1:** NAC followed by SLNB +ALND+ lumpectomy/mastectomy a **n**= 31 vs. **Group 2:** SLNB followed by NAC then surgery and ALND **n**=58 vs. **Group 3:** SLNB followed by NAC then surgery and, only for pts with positive SLN, ALND **n**=28 (21 ALND, and 7 only surgery) Reference standard: *nr*	Response rate IR FNR[a]	Methods of SLNB: Pts underwent prior lymphatic mapping with radiocolloid in the nuclear medicine suite. Subsequently, in the operating room, they underwent periareolar injection of blue dye. The axilla was then approached using a small incision, and an intraoperative gamma probe was used, in conjunction with blue dye identification to identify the sentinel node. Adjuvant treatment: NAC was an anthracycline based chemotherapy	Response rate: Group 1: 12.9% Group 2: 13.8% Group 3: 14% p=NS
STUDIES OF DIAGNOSTIC OUTCOMES						
Classe, 2019 [169] **Country:** France GANEA 2 (Ganglion sentinel après chimiotherapie NEoAdjuvante) **Funding:** French	Prospective multicentre (17 institutions) cohort **Accrual period** **Jul 2010 to Jul 2014** **Aim** To assess the accuracy and safety	957 adult women with primary infiltrative BC, clinical stages T1-T3, N0 to N2, M0 treated with NAC: 351 pN1, 606 cN0. 816 pts in analysis **Age (median):** 52 yrs **Stage (only pN1 group**	SLNB vs. ALND (reference standard)	FNR[i] of SLNB for pts with pN1 after NAC (n=307) because they all had the reference standard IR	SLNB was performed with blue dye and radiocolloid Pts were treated with lumpectomy or mastectomy and RT (not RNI) NAC treatment at the discretion of clinician	Only pN1 group: IR: 79.5% (95% CI, 74.5-83.9) FNR (of 160 pts with involved nodes): 11.9% (19/160, 95% CI 17.3-17.9%)

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Intervention / Comparison / Reference standard	Outcomes	Intervention Methods/ Adjuvant treatment	Summary results
National Institute of Oncology	of SLNB after NAC for pts treated for an operable BC. To dermine predictive factors of positive ALND when SLNB was negative in pts in the pN1 group **Follow-up (median):** 36 mos	Clinmical stage at presentation: T1: 4.6% T2: 68.7% T3: 25.4% T4: 1.0% Unknown: 0.3% N0: 18.3% N1: 75.2% N2: 6.5% Unknown: 0.0				
Zetterlund, 2017 [170] **Country:** Sweden **Funding:** Swedish Breast Cancer Association, the Stockholm County Council, and Olle Engkvist Byggmastare Foundation	Prospective multicentre chort (13 hospitals) **Accrual period** Oct 2010 to Dec 2015 **Aim** 1) To study the agreement of SLNB before NAC with the ALND after NAC in cN0 BC pts. 2) To evaluate the feasibility and false negative rate of repeat SLNB **Follow-up:** *nr*	**N**=224 pts clinically node negative (cN0) (undefined) **Age (median):** 47 yrs (range 22-78) **Stage**: **T1** 8.0% **T2** 66.5% **T3** 25.4% Radiological tumour size median 39 mm, (range 9-127)	**n**=224 SLNB before NAC vs. **n**=224 ALND (level I and II) IR after NAC Reference standard: ALND or histopathology	FNR[c] IR	Methods of SLNB: Blue dye, radiocolloid, or both Adjuvant treatment: BCS or mastectomy	IR rate = 100% FNR after NAC = 7.4% (95% CI, 4 to 13.5) True positive: 23.2%
Zetterlund, 2017 [171] **Country:** Sweden **Funding:** Swedish Breast Cancer Association, the Stockholm County Council, and Olle Engkvist	Prospective multicentre (10 hospitals) **Accrual period** Oct 2010 to Dec 2015 **Aim** To define the accuracy of SLNB after NAC in a	**N**=195 clinically node negative (undefined) pts with biopsy proven invasive T1-4d BC or inflammatory BC **Age (median)** 50 yrs, range 27–84 **Stage (at presentation)**: T1:12.8% T2:48.2% T3:31.3%	**n**=195 SLNB vs. **n**=195 ALND Reference standard: ALND or histopathology	IR[d] FNR[e]	Methods of SLNB: Blue dye (3.6%), isotope alone (5.2%) or both (87.5%) or magnetic tracer alone or incombination with blue dye (3.6%) Adjuvant treatment: NAC (anthracyclines and taxanes) or	**IR** All mapping methods IR=77.9% (152 of 195 pts) Dual mapping: IR=80.7% (138 of 171) **FNR** Overall: 14.1% (13 over 92 pts)

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Intervention / Comparison / Reference standard	Outcomes	Intervention Methods/ Adjuvant treatment	Summary results
Byggmastare Foundation	multicenter setting in upfront clinically node-positive patients with T1–4d BC **Follow-up:***nr*				endocrine (aromatase inhibitors) therapy Breast-conserving surgery or mastectomy	
van der Heiden-van der Loo [172] **Country:** the Netherlands **Funding:** *nr*	Retrospective population-based study (Netherland Cancer Registry) focussing on clinically node negative pts **Accrual period** Jan 2010 to Jun 2013 **Aim** To give precise estimates of IR in SLNB before and after NAC, outcome of SLNB and axillary treatment given in pts with clinically node negative BC **Follow-up:** *nr*	**N**=1183 clinically negative pts **Age (median, range)** 49 yrs, 23 to 77 yrs **Stage: SLNB before vs. after NAC**: cT1-(≤20mm) 11% vs. 17% cT2 (21-50mm) 70% vs. 51%	**SLNB** (cN0, SLNB before NAC) **n**=980 (83%) vs. **SLNB** (cN0, SLNB after NAC) **n**=203 (17%) Reference standard: ALND or histopathology	IR Proportion of pts with negative SLNB FNR[h] Proportion of pts receiving ALND	Methods of SLNB: *nr* Adjuvant treatment:	SLNB before vs. SLNB after NAC: IR: 98% vs. 95%, p=0.032 Proportion of pts with with negative SLNB (including isolated tumour cells only): 54% vs. 67%, p=0.001 Proportion of pts receiving ALND 45% versus 33%; p=0.006
Kuehn, 2013 [46] SENTinel NeoAdjuvant (SENTINA) trial **Country:** Germany, Austria **Funding:** Arbeitsgemeinschaft für Gynäkologische Onkologie–Breast, the German Breast Group, and	Four-arm prospective multicentre (103 institutions) cohort study **Accrual Period:** Sept 2009 to May 2012 **Aim** To evaluate a specific algorithm for timing of a standardised SLNB	**N**=2234, Initially clinically positive pts who are downstaged after NAC; 1737 in the per protocol analysis **Age: median (range) yrs** **Arm A:** 48 (20–75) **Arm B:** 48 (26–78) **Arm C:** 49 (22–98) **Arm D:** 50 (29–87) **Stage**: cN0, cN1, and cN2	**Index test:** SLNB; **Reference standard :** ALND (only arms B and C) **Arm A: n**=662 **Arm B: n**=360 **Arm C: n**=592 **Arm D: n**=123 **Arm A:** Clinically node-negative pts (cN0) who had SLNB before NAC and received no further axillary	*FNR in Arm C Detection rate of SLNB before and after NAC in pts in arms B and C Detection rate and FNR of a second SLNB procedure after identifycation	Methods of SLNB: radiocolloid alone: **A&B before NAC:** 57% **B, after NAC:** 66% **C, after NAC:** 66% Blue dye alone: **A&B before NAC:** 1% **B, after NAC:** 1% **C, after NAC:** 1% Combined: **A&B before NAC:** 39% **B, after NAC:** 29%	Factors having an impact on FNR: In arm C: FNR was consistently <10% for pts who had ≥3 SLN removed Number of sentinel nodes (per 1 sentinel node): OR 0.487 (95% CI, 0.287 to 0·825), p=0.008 **FNR Arms B and C:** B: 51.6% [33 of 64 pts]; (95% CI, 38.7 to 64.2)

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Intervention / Comparison / Reference standard	Outcomes	Intervention Methods/ Adjuvant treatment	Summary results
Brustkrebs Deutschland	procedure in pts who undergo NAC **Follow-up:** *nr*	Tumour size >20mm to ≤50mm: **Arm A:** 75% **Arm B:** 71% **Arm C:** 80% **Arm D**: 76%	surgery if they were pN0sn. **Arm B**: cN0 pts with a pathologically positive SN ($pN1_{sn}$) before NAC who underwent a second SLNB followed by ALND **Arm C:** Initially cN1 or cN2 pts who had NAC then had SLNB and ALND (if they converted to a clinically negative axillary status)(ycN0). **Arm D:** Pts with suspicious nodes before and after NAC (ycN1) and who received ALND Reference standard: ALND or histopathology	and removal of a positive SLN before NAC in pts in arm B FNR defined as: the ratio of the number of pts with a negative SLN and one or more positive non-SLN to the number of pts with at least one involved LN among people in whom ≥1 SN was detected	**C, after NAC:** 28% Adjuvant treatment: NAC consisted of ≥6 cycles of anthracycline	C, 14·2% [32 of 226 pts]; (95% CI, 9.9 to 19.4) **FNR according to number of SNs removed (arms B and C)** 1 node removed: B: 66.7% (16/24), C: 24.3% (17/70) 2 nodes removed: B: 53.8% (7/13), C: 18.5% (10/54) 3 nodes removed: B: 50% (5/10), C: 7.3% (3/41) 4 nodes removed: B: 50% (3/6), C 0% (0/28) 5 nodes removed: B:18.2% (2/11), C: 6.1% (2/33)
Tausch, 2011 [48] Sub-protocol of the ABCSG-Trial 14 **Country:** Austria, Switzerland **Funding:** *nr*	Prospective subprotocol of the Austrian Breast and Colorectal Cancer Study Group, ABCSG-14 RCT in which pts were randomized to two groups receiving either 3 cycles (control group) or 6 cycles (experimental group) of a preoperative epirubicin 75 mg/m^2 and docetaxel 75 mg/m^2 combination combined with GCSF. Pts recruited from 11 centres.	**N**=111, 98 eligible (all 111 pts in analysis) pathologically positive pts **Age (mean):** 48.4 yrs (range 28 to 70) **Stage**: All M0 tumour sizes and stages, except for T4d (inflammatory BC)	**Index test:** SLNB**;** Reference standard**:** ALND	IR FNR[i] Sensitivity Number of LN removed	Methods of SLNB: Only blue dye was used in 28 (25%) cases, radionuclide was used as a single method in 13 (12%), and the combination of both methods was applied in 70 (63%) cases Injection site and methods were at the discretion of the surgeon.	IR: 90% (≥1 LN removed in 100 pts) Number of LN removed (median): 1.79 FNR: 12.8% (6 of 47 pts) **Subgroups:** IR was significantly lower when lymphatic mapping was performed in women >50 yrs of age (p=0.029) and in patients clinically progressing on chemotherapy (p=0.017). No difference was found for FNR and IR according to tumour grading receptor status, menopausal status, tumour stage, location clinical nodal status before chemo, pathological

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Intervention / Comparison / Reference standard	Outcomes	Intervention Methods/ Adjuvant treatment	Summary results
	Accrual period *nr* **Aim** To investigate feasibility and sensitivity of SLNB after NAC with the goal to achieve a FNR comparable to SLNB without NAC **Follow-up:** *nr*					response to chemo, injection method or site.
Papa, 2008 [173] **Country:** Israel **Funding:** *nr*	Prospective cohort study **Accrual period** Jan 2002 to Mar 2005 **Aim** To address optimal timing of SLNB in BC pts undergoing NAC **Follow-up:** *nr*	**N**=117 clinically node negative pts treated with NAC **Age (mean):** 45.4 **Stage**: IIA T2N0M0 and IIB T3N0M0	**Group 1:** NAC followed by SLNB +ALND+ lumpectomy/mastectomy a **n**= 31 vs. **Group 2:** SLNB followed by NAC then surgery and ALND **n**=58 vs. **Group 3:** SLNB followed by NAC then surgery and, only for pts with positive SNL, ALND **n**=28 (21 ALND, and 7 only surgery) Reference standard: ALND or histopathology	Response rate IR FNR[j]	Methods of SLNB: Pts underwent prior lymphatic mapping with radiocolloid. Subsequently, they underwent periareolar injection of blue dye. Intraoperative gamma probe, combined with blue dye was used for the identification of the SLN. Adjuvant treatment: NAC was an anthracycline based chemotherapy	IR: group 1 (SLNB after NAC): 87% group 2 (SLNB before NAC): 97%% and group 3 (SLNB, NAC, +ALND [only node positive pts]: 100% Group 1 vs. groups 2 &3, p<0.05 FNR: group 1: 15.8% (3 of 19) group: 2: 0% Group 1 vs. group 2 p=0.04, group 3 NA because pts did not receive the reference standard
Gimbergues, 2008 [54] **Country:** France **Funding:** *nr*	Prospective cohort study **Accrual period** Mar 2001 to Dec 2006 **Aim** To determine clinicopathological factors that may influence the accuracy of SLN biopsy after NAC	**N**=129 pts with infiltrating BC who were treated with NAC **Age (median range):** 53 yrs, 25 to 84 yrs **Stage**: T1: 1.6% T2: 71.3% T3: 27.1%	**Index test:** SLNB Reference standard**:** ALND of level I and II	IR FNR[a]	Methods of SLNB: radioisotope Adjuvant treatment: NAC: 5-fluorouracil, epirubicin, and cyclophosphamide, or docetaxel and epirubicin, or docetaxel alone.	IR: 93.8% Factors impacting IR: Age ≥60 yrs vs. <60 yrs: 82.1% vs. 97.9%, p=0.0063 FNR: 14.3% (all pts) Factors impacting FNR: Larger tumour size before NAC: 5.7% for T1-T2 vs. 28.5% for T3 cases, p=0.045 Positive clinical LN status before NAC: 0% for N0 vs. 29.6% for N1-N2 cases; p=0.003.

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Intervention / Comparison / Reference standard	Outcomes	Intervention Methods/ Adjuvant treatment	Summary results
	Follow-up: 35.64 mos					
ABSTRACT PUBLICATIONS OF COMPLETED STUDIES						
Kwak, 2019 [182] ABS **Comparison: SLNB vs. ALND** **Country:** *nr* **Funding:** *nr*	Cohort, single centre study **Accrual period** Jan 2006 to Dec 2015 **Aim:** To evaluate OS and recurrence in pts that converted to pN0 after NAC **Follow-up**: SLNB: 58 mos (range 12-147); ALND: 103 mos (range 9-174)	225 pts who converted to pN0 after NAC **Age:** *nr* **Stage:** *nr*	SLNB (n=100) vs. ALND (n=125)	OS DFS Recurrence AE	*nr*	SLNB VS. ALND OS rate at 5 yrs: 94% vs. 95.7% (p=0.786) DFS rate at 5 yrs: 91.9% vs. 91.6%, (p=0.753) AE: shoulder stiffness: 7% vs. 10.4%, p=0.384 Lymphedema: 4% vs. 23.2%, p=0.271
Miyashita, 2017 [183] ABS **Comparison: RT vs. no RT** **Country:** Japan **Funding**: *nr*	Retrospective cohort (registry analysis) **Accrual period**: 2004-2009 **Aim**: To evaluate the efficacy of RT for BC pts treated with NAC and mastectomy **Follow-up:** 60 mos	N=3226 pts **Age**: *nr* **Stage**: T1-T4 ypN0: 1,299, ypN1: 1,036, ypN2-3: 879	PMRT (n=185, 14.2% with ypN0, n=265, 25.6% with ypN1, and n=543, 61.8% with ypN2-3) vs. no PMRT (n=2233)	LRR, DDFS, OS	PMRT vs. no PMRT	Multivariate analysis: LRR, DDFS, OS: ypN1 and ypN0: NS ypN2-3: better for PMRT gropup: LRR: HR 0.608, 95% CI 0.452-0.818, p=0.001 OS: HR 0.685, 95% CI 0.531-0.885, p=0.004 DDFS: NS
Matsumoto, 2019 [188] ABS **Comparison B:SLNB vs. ALND**	Retrospective cohort (institutional review) **Accrual period:** Mar 2006 to Mar 2017 **Aim:** To evaluate if ALND could be	N= 128 pts initially clinically node + BC treated with NAC **Age (median)**: 56.5 (range: 29-79) **Stage**: *nr*	ALND vs. no ALND	Axillary recurrence DFS	SLNB was performed with a combined method, radioisotope and blue dye	Axillary recurrence: 0 in both groups DFS: 85.5% vs. 87.5%, p=0.965

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Intervention / Comparison / Reference standard	Outcomes	Intervention Methods/ Adjuvant treatment	Summary results
	omitted when treated with NAC **Follow-up:** 53.2 mos					

*= primary outcome
[a]FNR undefined
[b]A false-negative event was defined as a case where the SLN(s) was negative but an axillary (non-SLN) node was positive on pathologic examination.
[c]FNR was defined as the proportion of pts with a negative SLNB pre-NAC but ≥1 positive axillary LN post-NAC, divided by all node-positive pts with an identified SLNB pre-NAC
[d]The IR was defined as the number of pts with a successfully identified SLN divided by the total number of pts in whom an SLNB was attempted.
[e]The FNR was defined as the proportion of patients with a negative SLNB but ≥1 positive non-SLN, divided by all pts with an identified SLNB and ≥1 positive lymph node after NAC.
[f]The three trials were GeparTrio, GeparQuattro, and GeparQuinto): Huober J, Fasching PA, Hanusch C, et al. Neoadjuvant chemotherapy with paclitaxel and everolimus in breast cancer patients with non-responsive tumours to epirubicin/cyclophosphamide (EC) ± bevacizumab—results of the randomized GeparQuinto study (GBG 44). Eur J Cancer. 2013;49(10):2284–293.
gClinical negativity was defined as absence of palpable disease in the nodal basin, and the absence of abnormally appearing lymph nodes on ultrasound. If abnormal imaging, negativity was confirmed by fine needle aspiration. Sentinel nodes metastases ≤0.2 mm and isolated tumour cells were considered to be negative.
Untch M, Loibl S, Bischoff J, et al. Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline–taxane-based chemotherapy (GeparQuinto, GBG 44): a randomized phase 3 trial. Lancet Oncol. 2012;13(2):135–44.
Gerber B, Loibl S, Eidtmann H, et al. Neoadjuvant bevacizumab and anthracycline–taxane-based chemotherapy in 678 triplenegative primary breast cancers; results from the geparquinto study (GBG 44). Ann Oncol. 2013;24(12):2978–84.
Untch M, Rezai M, Loibl S, et al. Neoadjuvant treatment with trastuzumab in HER2-positive breast cancer: results from the GeparQuattro study. J Clin Oncol. 2010;28(12):2024–31.
von Minckwitz G, Eidtmann H, Rezai M, et al. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. N Engl J Med. 2012;366(4):299–309.
von Minckwitz G, Blohmer JU, Costa SD, et al. Response-guided neoadjuvant chemotherapy for breast cancer. J Clin Oncol. 2013;31(29):3623–30.
von Minckwitz G, Rezai M, Fasching PA, et al. Survival after adding capecitabine and trastuzumab to neoadjuvant anthracycline-taxane-based chemotherapy for primary breast cancer (GBG 40–GeparQuattro). Ann Oncol. 2013;25(1):81–9.
[h]The FNR was defined as the proportion of patients with a negative SN who do have nodal involvement in non-SNs
[i]FNR was defined as the ratio of the number of pts in whom histological & histochemical evaluation showed tumour infiltration although the SN identification had predicted a negative result to the number of pts with axillary lymph node metastases in percent
[j]FNR was defined as the ratio of the number of FN cases to the total number of patients with at least one lymph node involved, sentinel or not.

ABS = abstract; ALN = axillary lymph node; ALND = axillary lymph node dissection; ARFS = axillary recurrence-free survival; BC = breast cancer; BCS = breast-conserving surgery; chemo = chemotherapy; CI = confidence interval; cN0 = clinically node-negative; cN1 = disease in movable axillary nodes; cN2 = disease in fixed or matted axillary lymph nodes; CT = computed tomography; DDFS = distant disease-free survival; DFS = disease-free survival; DM = distant metastases; DRFI = distant recurrence-free interval; ds = days; DSS = disease-specific survival; FNR = false negative rate; GCSF = granulocyte colony stimulating factor; HER2 = Human epidermal growth factor receptor 2; IR = identification rate (number of patients with a successfully identified SLN divided by the total number of patients in whom an SLNB was attempted); LN(s) = lymph node(s); LRR = loco-regional recurrence rate; LRRFI = Loco-regional recurrence-free interval; LRRFS = loco-regional recurrence-free survival; mos = months; NA = not applicable; NAC = neoadjuvant chemotherapy; NCDB = National Cancer Database; *nr* = not reported; *NS* = not significant; OR = odd ratio; OS = overall survival; pCR = pathological complete response; PFS = progression-free survival; PMRT = post mastectomy radiotherapy; pN0 = pathologically negative; pts = patients; RCT = randomized controlled trial; RNI = regional nodal irradiation; RT = radiotherapy; SD = standard deviation; SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy; TAD = targeted axillary dissection; US = ultrasonography; WBI = whole breast irradiation; wks = weeks; ypN- = patients with negative SLN status undergoing further ALND; ypN+ = patients with positive or undetected SLNs undergoing further ALND; ypSLNB- = patients for whom SLNB revealed no residual axillary metastasis and no further dissection was performed; yrs = years; ypN0 = post-treatment negative axillary nodes

Table 4-18. Corollary publication of unique studies identified for Question 4.

Main study Comparison; Objectives	Companion publications; Objectives	Summary results of the companion publication
Question 4C. Timing of SLNB		
Kuehn, 2013 [46] SENTINA SLNB vs. ALND **Objectives:** To evaluate a specific algorithm for timing of a standardised SLNB procedure in pts who undergo NAC	Kolberg-Liedtke, 2019 ABS [189] **Objectives**: To identify predictors of sentinel lymph node status in cN0 pts undergoing SLNB before initiation of NAC; Arms A, and B of the SENTINA trial	N=1022 pts. Parameters relevant for analysis were available for 805 cN0 pts. 527 and 278 pts presented with negative and positive LNs upon SLNB. Univariate regression models identified largest tumour diameter (OR 1.016, p=0.0041), tumour type (ductal vs. lobular, OR 2.004, p=0.00234), tumour grading (low vs. high, OR 0.537, p<0.001), hormone receptor status (negative vs. positive, OR 2.668, p<0.001), HER2 status (negative vs. positive, OR 1.462, p 0.0158) as being associated with SLN status. Multivariate analysis resulted in tumour diameter, hormone receptor, HER2 status, and tumour type being independently associated. These parameters were combined using stepwise (backward and forward) selection into a prediction model. This model predicted SLN status with an area under the curve of only 0.65.
	Liedtke, 2018 ABS [190] **Objectives:** To analyze the association between clinical/pathological parameters and conversion from cN+ to ycN0 in Arm C of the Sentina trial (i.e., pts with true conversion)	N= 596 pts clinically and or sonographically suspicious ipsilateral axillary nodes. In 152 pts (96,8%), lymph node metastases were confirmed by biopsy, and in 5 pts (3,2%), no malignant cells were identified. In both groups, we found a significant association (p<0,05) between increased rate of axillary conversion and small tumour diameter after NAC, absence of multifocality, absence of lymphovascular invasion (LVI), ER and/or PR negativity, HER2 negativity, triple negative disease, and complete pathological response (pCR). No multiple testing corrections were performed due to an exploratory setting. However, only among pts with biopsy-proven involvement prior to NAC, we found grade-3-tumours to be significantly associated with reduced probability of residual axillary involvement (76.1 vs. 33.8%, compared to G1 and G2, p=0.0323)
	Kolberg, 2018 [191] **Objectives:** To assess the role of pathological complete remission in the breast and clinical/pathological parameters in the prediction of residual axillary involvement after NAC using data in Arm B of the SENTINA trial	Arm B of the SENTINA study contained 360 pts, 318 of which were evaluable. After NAC 71/318 (22.3%) pts had involved SLNs or non-SLNs; 71/318 (22.3%) had a pCR in the breast. A statistically significant association between pCR in the breast and negative ER status, negative PR status, positive HER2 status, triple negative (TN) status, tumour size before and after NAC, multifocality, lobular morphology and axillary involvement after NAC was noted. Regarding residual axillary burden only the associations with lobular morphology, extracapsular invasion, multifocality, positive HER2 status and pCR in the breast were statistically significant
	Kolberg, 2018 ABS [184] **Objectives:** To investigate the association of clinical/pathological parameters and residual axillary involvement after NAC in the subgroup of patients with limited involvement	Arm B of the SENTINA study contained 360 pts, 265 of which were evaluable. After NAC 66/265 (24.9%) pts had involved SLNs or non-SLNs after NAC; 71/265 (26.8%) achieved a pCR in the breast. A significant association between pCR in the breast and ER negativity (p<0.0001), PR negativity (p<0.0001) and TN status (p=0.001) was observed. However, no statistically significant association between residual axillary involvement after NAC and clinical/pathological parameters ER (p=0.381), PR (p=0.52), HER2 (p=0.771), TN status (p=0.937), grade (G) 1 (p=0.081), G 2 (p=0.335), G 3 (p=0.747), age (p=0.789), tumour size before NAC (p=0.761) and pCR in the breast (p=0.136) could be demonstrated. A subset of pts in this cohort for whom axillary surgery after NAC could be safely omitted could not be identified.
	Schwentner, 2016 [185] **Objectives:** Subgroup analysis of of formerly cN1 pts. To investigate the predictive value of palpation and axillary US pts following NAC	1240 pts from 103 institutions entered the trial. 715 (arm C n=592; arm D n=123) pts, who presented initially cN1 underwent clinical evaluation of LN status following NAC. Palpation alone demonstrated a sensitivity of 8.3% (95% CI, 5.8-11.6), specifity of 94.8% (95% CI, 91.7-96.9) and a NPV of 46.6%. US alone revealed a sensitivity of 23.9% (95% CI, 19.8-28.5), specificity 91.7% (95% CI, 88.2-94.5), and a NPV of 50.3%. The investigators combined classification (palpation and US) resulted in a sensitivity of 24.4% (95% CI, 20.2-29.0), specificity 91.4% (95% CI, 87.8-94.2), and a NPV of 50.3%. Investigators classified the axilla nodes as being unsuspicious (cN0) following NAC in 592/715 pts (82.8%); of those 298 (50.3%) were pN0, 151 (25.5%) had 1-2 histologically involved nodes and 143 (24.2%) had >2 histologically involved nodes.

Main study Comparison; Objectives	Companion publications; Objectives	Summary results of the companion publication
	Galimberti, 2015 ABS [186] **Objectives:** To retrospectively analyze outcomes after a median of 61 mos (IQR 38–82) in 396 pts who were cN0 or cN1/2 before NAC treatment, became or remained cN0 after, and received SLNB	Five-year OS was 90.7% (95% CI, 87.7 to 93.7%): 93.3% (95% CI, 90.0 to 96.6) in initially cN0 pts, and 86.3% (95% CI, 80.6–92.1) in those initially cN+ (p=0.12). In initially cN0 pts, and also initially cN+ pts who responded well to NAC (pT0/pTx), SN negativity was a significant predictor of good outcome, consistent with the known prognostic significance of axillary status, and suggesting that SN status accurately reflected axillary status (low FNR). In initially cN+ pts found to be pT1/pT2–3, SN status (and whether or not AD was performed) had no influence on survival and thus did not accurately reflect axillary status (high FNR).
Tausch, 2011 [48] SLNB vs. ALND **Objectives:** To investigate feasibility and sensitivity of SLNB after NAC with the goal to achieve a FNR comparable to SLNB without NAC	Tausch, 2008 [187] **Objectives:** Retrospective previous feasibility study to the main study; Aims were: 1) To evaluate of the IR and the sensitivity of SLNB after NAC. 1) Further investigation is targeted on clinical patient and tumour characteristics and their influence on the false-negative rate	≥1 SLN was identified in 144 pts (IR, 85%): in 86% by blue dye alone, in 65% by tracers alone, and in 88% by a combination of methods. The SLN was positive in 70 women (42%) and was the only positive node with otherwise negative axillary nodes in 39 pts (23%). In 6 cases, the SLN was diagnosed as negative although tumour infiltration was detected in an upper node of the axillary basin (FNR, 8%; 6 of 76 pts; sensitivity, 92%). ≥62 pts (37%) were free of tumour cells in the SLN and in the axillary nodes.

ABS = abstract; AD = axillary dissection; CI = confidence interval; DCIS = ductal carcinoma in situ; DFS = disease-free survival; FNR = false negative rate; IBC-RFI = invasive breast cancer recurrence free interval; IR = identification rate; IQR = interquartile range; LN = lymph node; LRRFI = loco-regional recurrence-free interval; mos = months; NAC = neoadjuvant chemotherapy; NPV = negative predictive value; OS = overall survival; pCR = pathologic complete response; PMRT = post mastectomy radiotherapy; pts = patients; RNI = regional nodal irradiation; RT = radiotherapy; TN = triple negative; SLNB = sentinel lymph node biopsy; SN = sentinel node; SPC = second primary cancer; US = ultrasound; WBI = whole breast irradiation,

Table 4-19. Ongoing randomized controlled trials that are still recruiting patients relative to Question 4.

Study number	Design Target sample	Study title	Outcomes	Start / Completion date	Intervention(s)/ comparison(s) or reference standard	Status	Location
NCT01901094 MAC.19 trial	RCT N=2918	A Randomized Phase III Trial Comparing Axillary Lymph Node Dissection to Axillary Radiation in Breast Cancer Patients (cT1-3 N1) Who Have Positive Sentinel Lymph Node Disease After Neoadjuvant Chemotherapy	Invasive breast cancer recurrence-free interval (IBC-RFI). Time Frame: Up to 5 years after completion of radiation therapy	Feb 2014 / Feb 2024	ALND (surgery) and RT to the cancer area vs. RT to the axillary lymph nodes and the cancer area	Recruiting	Canada
NCT01872975 NSABP-B-51 TRIAL	RCT N=1636	A randomized phase III clinical trial evaluating post-mastectomy chestwall irradiation and RNI and post-lumpectomy RNI in pts with positive axillary nodes before NAC who convert to pathologically negative axillary nodes after NAC Aim: to test whether a favourable pathologic response to NAC also represents a predictive factor influencing the relative benefits of PMRT or the addition of RNI to breast RT	Invasive breast cancer recurrence-free interval (IBC-RFI). Time Frame: Time from randomization until invasive local, regional, or distant recurrence, or death from breast cancer, assessed up to 10 years •OS •LRRFI •DRFI •DFS-DCIS •Time to SPC •Effect of radiation therapy on cosmetic outcome in mastectomy and lumpectomy patients as assessed by quality of life questionnaire •Frequencies of adverse events graded according to the Common Terminology Criteria for Adverse Events version 4.0 •Molecular predictors of recurrence	Jun 2013 /Jul 2028	Regional nodal RT vs. chestwall RT vs. WBI	Recruiting	US

ALND = axillary lymph node dissection; DFS-DCIS = disease-free survival in ductal carcinoma in situ; DRFI = distant recurrence-free interval; LRRFI = loco-regional recurrence-free interval; NAC = neoadjuvant chemotherapy; OS = overall survival; PMRT = post mastectomy radiotherapy; RCT = randomized controlled trial; RNI = regional nodal irradiation; RT = radiotherapy; SPC= second primary cancer; WBI = whole breast irradiation.

Outcomes

A) Patients who were pathologically node negative at diagnosis

No studies were identified at this time

B) Patients who are pathologically node positive at diagnosis

SLNB compared with ALND, and ALND compared with no treatment (surgical trials)

OS/mortality

Kim et al. [44] did not detect any statistical significant difference in OS when comparing the four groups.

DFS

At 19.5 months of follow-up in the Kim et al. [44] study, patients in group 1 (n=31) had a worse DFS than those in group 2 (n=20) (77.1% vs. 85.4%, p=0.031). No statistically significant difference was noted when comparing patients who received SLNB, and for whom SLNB revealed no residual axillary metastasis and no further dissection was performed (group 1, n=31) with those who received complete ALND, and had no residual axillary metastasis on pathology (group 4, n=79).

Recurrence

Kim et al. [44] reported no statistically significant difference in axillary recurrence rate when comparing initially cytologically proven positive patients treated with NAC who received SLNB, and for whom SLNB revealed no residual axillary metastasis and no further dissection was performed (group 1, n=31) with those who received SLNB, had negative sentinel node status, and undergoing further ALND (group 2, n=20), and with those who received complete ALND, and had no residual axillary metastasis on pathology (group 4, n=79).

Quality of life

No data were available for this outcome

Adverse events

No data were available for this outcome

Radiotherapy compared with ALND, and Radiotherapy and ALND compared with no treatment to the axilla (Radiotherapy trials)

OS/mortality

Rusthoven et al. [45] showed, using a propensity score-matched analysis, that patients treated with mastectomy after NAC had a statistically significantly better OS if they received PMRT (with or without loco-regional node irradiation) compared with no PMRT, irrespective of their nodal status after NAC. Among patients who were node negative after NAC, 92% of those who received PMRT survived compared with 90% of those treated without radiotherapy (HR, 0.695; 95% CI, 0.518 to 0.929, p=0.014). Among patients who were node positive after NAC, 80% of those treated with PMRT survived compared with 76% of those treated without radiotherapy (HR, 0.845; 95% CI, 0.738 to 0.968, p=0.015). In patients treated with breast-conserving surgery, no statistically significant advantage was shown with the addition of loco-regional node irradiation to radiotherapy of the breast or chest wall, irrespective of the pathological stage after NAC (patients who were node-negative after NAC: HR, 1.028; 95% CI, 0.716 to 1.477,

p=0.880; and patients who were node-positive after NAC: HR, 0.962; 95% CI, 0.785 to 1.175, p=0.704 (see Table 4-6).

DFS and Recurrence

In multivariate analysis, Krug et al. [43] reported that radiotherapy was not a statistically significant predictor of outcomes such as DFS (HR, 1.14; 95% CI, 0.75 to 1.73, p=0.55) and loco-regional recurrence (HR, 0.51; 95% CI, 0.27 to 1.0, p=0.05). PMRT did not improve outcomes for the subgroup of patients with clinical stage T1 and T2 (n=441, PMRT vs. no PMRT: HR, 0.94; 95% CI, 0.45 to1.95], p=0.86). However, it did improve results for patients with clinical stage T3 and T4 tumours (loco-regional recurrence: HR, 0.4; 95% CI, 0.17 to 0.94, p=0.04), but these patients are not focus of this report. Similarly, radiotherapy improved outcomes for patients who were node positive at diagnosis (loco-regional recurrence: HR, 2.14; 95% CI, 1.19 to 3.87, p=0.01, and DFS: HR, 1.87; 95% CI, 1.35 to 2.60, p<0.01), but this group may have included patients with stage T3-4 tumours. No statistically significant difference was shown between radiotherapy or no radiotherapy groups for patients who were node positive at diagnosis and converted to node negative after NAC.

Patients with pathological N0 after neoadjuvant chemotherapy did significantly better with radiotherapy (HR, 0.2; 95% CI, 0.06 to 0.62, p=0.01), while patients who were node positive after NAC did not.

Other outcomes

No other outcomes were reported.

C) Timing: SLNB before versus after NAC

Survival

No data on this outcome were reported.

Recurrence

Fernandez-Gonzalez et al. [168] reported no significant difference in recurrence rate for SLNB before compared with SLNB after NAC at 16 months follow-up (11.5% vs. 0%, p=0.85). As well, Hunt et al. [53] reported no statistically significance difference in local, regional and distant recurrence at 47 months follow-up after adjusting for clinical stage (Table 4-17).

PFS

Fernandez-Gonzalez et al. [168] found no statistically significant difference in the probability of PFS at 60 months follow-up between patients who received SLNB before and those who received it after NAC (8.4% vs. 1% p=0.85).

Response

Papa et al. [173] reported no statistically significant difference in response rate between patients who received SLNB after NAC (12.9% [group 1, n= 31]) and those who received it before NAC (13.8% [group 2, n=58] , and 14% [group 3, n=28]).

Quality of life

No data on this outcome were reported.

Adverse events

No data on this outcome were reported.

Ability to map

None of the studies reported on this outcome for the comparison of interest. Hunt et al. [53] reported mapping success by single or dual tracer, and this will be reported in Question 5 section.

Identification rate

In patients who were pathologically positive identification rate ranged from 77.9% [171] to 100% [170]. In patients who were pathologically negative identification rate was not reported in the studies that met our inclusion criteria.

False negative rate

In patients that were pathologically positive false negative rate ranged from 11.9% [169] to 51.6% [46].

Literature Search Results for Primary Studies
Question 5: Mapping modalities for patients who are appropriate for axillary staging

The flow diagram for primary studies is reported in Appendix 4B. Three comparisons are relevant for this question:

A) Single tracer compared with dual tracer
B) US-guided SLNB compared with traditional SLNB, and
C) US compared with SLNB

No existing guidelines provided recommendations relevant to this question. Three systematic reviews met our inclusion criteria [49,117,118], and they provided evidence for comparisons A) Single versus dual tracer, and B) US–guided biopsy versus traditional SLNB. For the remaining comparison (US vs. SLNB), we included primary studies with a randomized or an observational comparative design published from 2007 to 2020. Table 4-20 describes the evidence that forms the basis for this recommendation.

The systematic reviews by Geng et al., 2016 [49], Houssami et al. [118] and its updates [192,193], and van Wely et al. [117] provided evidence for accuracy outcomes. Geng et al. compared single versus dual tracer [49], and van Wely et al. [117] and Houssami et al. [118,192,193] reported on US-guided versus traditional staging [117].

Ninety-two primary studies met our inclusion criteria. Sixty-five of these [194-256] did not control for baseline confounders; therefore, we considered them at critical risk of bias, and we did not extract data from them. Two studies [53,55] reported on direct patient outcomes, and 15 studies [46-48,50-60,257] reported on test accuracy outcomes. Two of these studies were also included for question 4 [48,53]. Three studies reported both on direct patient outcomes and diagnostic outcomes [46,53,59]. Details of these trials are reported in Table 4-21. We did not combine the results of the studies in meta-analysis because the trials were heterogeneous.

Companion studies

Eleven were corollary publications of the main studies [185,187,258-266]; Table 4-22 presents the objectives and summary results of the studies relative to Question 5 with their main publications. Two of the corollary publications were also included in question 4 [185,187] (see Table 4-18 for objectives and summary results).

Table 4-20. Literature search results for question 5

Comparisons in Question 5		Endorsed guidelines	Included, high quality SRs	Included RCTs	Included Observational comparative trials	Ongoing trials
Intervention	Control					
Single tracer	Dual tracer	NA	Geng, 2016 [49] (accuracy outcomes, patients treated with NAC)	**Direct patient outcomes:**		NA
				NA	Hunt, 2009 [53]	
				Diagnostic outcomes:		
				O'Reilly, 2015 [47], Jung, 2019 [257]	Kuehn, 2013 [46]*, Boughey, 2013 [51], Boileau, 2015 [52], Kang, 2010 [60], Nathanson, 2007 [50], Tausch, 2011 [48], Hunt, 2009 [53]*, Gimbergues, 2008 [54]	
US-guided SLNB	Traditional SLNB	NA	Van Wely 2014 [117] Houssami et al. [118,192,193]	**Direct patient outcomes:**		CK19B (NCT03280134)
				NA	Verheuvel, 2017 [55]	
				Diagnostic outcomes:		
				NA	Kramer, 2016 [56], Kim, 2016 [57], Cools-Lartigue, 2013 [58], Stachs, 2013 [59]*	
US	SLNB	NA	NA	**Direct patient outcomes:**		CK19B (NCT03280134)
				NA	NA	
				Diagnostic outcomes:		
				NA	Stachs, 2013 [59]*, Kuehn, 2013 [46]*	

*Studies that report both diagnostic and patient relevant outcomes
NA = not applicable; NAC = neoadjuvant chemotherapy; SLNB = sentinel lymph node biopsy; SRs = systematic reviews; US = ultrasound

Ongoing, Unpublished, or Incomplete Studies

We identified the CK19B ongoing trial (NCT03280134) that uses cytokeratin 19 (CK19) combined with contrast enhanced US for predicting nonsentinel lymph node status in early breast cancer. This study was expected to be completed in June 2020 but is ongoing.

Table 4-21. General characteristics and summary results of primary studies included for Question 5

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Intervention / Comparison	Outcomes	Intervention Methods/ Adjuvant treatment	Summary results
Patients treated with NAC						
Single vs. Dual dye						
STUDIES OF DIRECT PATIENT OUTCOMES						
Hunt, 2009 [53] **Country:** US **Funding:** *nr*	Retrospective study. **Accrual period** 1994 to 2007 **Aim:** 1) To evaluate the accuracy of SLNB for pts undergoing NAC first versus pts undergoing surgery first. 2) To evaluate the impact of NAC on the incidence of positive SLNs after chemotherapy and the need for completion ALND in pts with large primary tumours **Follow-up (median):** 47 mos	**N**=3746 clinically negative pts **Age (median):** SLNB before NAC: 57.4 yrs SLNB after NAC: 51.7 yrs, p<0.0001 **Stage**: SLNB before NAC: T1: 81.2% T2: 17.7% T3: 1.1% SLNB after NAC: T1: 12.7% T2: 75% T3: 12.3%	SLNB after NAC **n**=575 (15.3%) vs. SLNB before NAC **n**=3171 (84.7%)	*Technical success rate in identifying and removing a SLN in pts in whom surgery was attempted (mapping success). Number of ALND performed	Methods of SLNB: Blue dye with or without radiocolloid Adjuvant treatment: *nr*	**Mapping success**: With 1 agent: 1209 of 1240 pts: 97.5% vs. Combination of two agents: 2481 of 2506 pts: 99%, p<0.0001
STUDIES OF DIAGNOSTIC OUTCOMES						
Jung, 2019 [257] **Country:** Korea **Funding:** Republic of Korea government	RCT phase II **Accrual period** Apr 2015 to Oct 2017 **Aim:** To compare the rates for SLN identification between single dye (SD, i.e.,radiocolloid) vs. dual dye (DD, i.e., radiocolloid + indocyanine green fluorescence) in BC pts after NAC **Follow-up:** *nr*	N=130 pts treated with NAC (122 in analysis). 92.6% of pts were node positive before NAC **Age (mean ± SD)**: 48.8±9.95 **Stage**: T0-2: 69.7% T3,4: 30.3% N0,1: 54.1% N2,3: 45.9%	DD: n=58 vs. SD (n=64) ALND was performed when SLNs had positive malignant cells	IR* Number of SLNs Time to detection AE	Methods of SLNB: radiocolloid with or without indocyanine green fluorescence **Adjuvant treatment:** BCS: 74.59%; Mastectomy: 25.41%	IR: DD vs. SD: 98.3% vs. 93.8%, p=0.14 Number of SLNs: NS Time to detection: NS Subgroup: Initially node positive pts IR: NS AE: none reported
Boileau, 2015 [52]	Prospective multicentre (10 centres) phase II cohort – Bayesian design. This was a twin study of trial Z1071	N=145 pts with stage II to IIIa biopsy-proven node positive BC selected to receive NAC	n=127 SLNB vs. n=127 ALND; Reference standard: central	IR FNR	Methods of SLNB: at surgeon's discretion, isotope only (n=35, 28%) or dual tracer (n=92,	FNR with dual tracer: 5.2% (3 of 58 pts)

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Intervention / Comparison	Outcomes	Intervention Methods/ Adjuvant treatment	Summary results
SN FNAC (Sentinel Node biopsy following Neoadjuvant Chemotherapy) Country: Canada and USA Funding: Quebec Breast Cancer Foundation, Cancer Research Society, Week-end to End Women's Cancers, and Montreal Jewish General Segal Cancer Centre	[51] **Accrual period** Mar 2009 to Dec 2012, **Aim** 1) to evaluate the accuracy of SLNB after NAC in pts with biopsy-proven node-positive BC. It was hypothesized that the FNR would be ≤10%, similar to the rate reported in the NSABP B-32 trial. 2) to evaluate the IR of SLNB (estimated at ≥90%). 3) to evaluate and compare the accuracy of clinical examination, axillary US, and SLNB in identifying pts with axillary pCR after NAC **Follow-up**: stopped early at an unplanned interim analysis because results and methods were similar to ALLIANCE Z1071	**Age (median):** 50 yrs (range 26 to 75) **Stage**: T-stage T0: 3% T1: 5% T2: 50% T3: 40% N0: 17% N1: 74% N2: 6% Size: >5 cm: 40% Receptor status: Triple negative: 15% HER2-+: 28%	review of pathology after ALND		72%). All pts received ALND. **Adjuvant treatment**: *nr*	FNR with isotope only: 16.0% (4 of 25 pts), p=0.190
Tausch, 2011 [48] Sub-protocol of the ABCSG-Trial 14 **Country:** Austria, Switzerland **Funding:** *nr*	Prospective subprotocol of the Austrian Breast and Colorectal Cancer Study Group, (ABCSG)-14 RCT in which pts were randomized to two groups receiving either 3 cycles (control group) or 6 cycles (experimental group) of a preoperative epirubicin 75 mg/m^2 and docetaxel 75 mg/m^2 combination combined with GCSF. **Accrual period** *nr* **Aim** To investigate feasibility and sensitivity of SLNB after NAC	**N**=111, 98 eligible (all 111 pts in analysis) clinically negative and pathologically positive pts **Age (mean):** 48.4 yrs (range 28 to 70 trs) **Stage**: All M0 tumour sizes and stages, except for T4d (inflammatory BC)	**Index test:** SLNB; **Reference standard:** ALND	IR FNR Sensitivity Number of LN removed	Methods of SLNB: Only BD was used in 28 (25%) cases, radionuclide was used as a single method in 13 (12%), and the combination of both methods was applied in 70 (63%) cases. Injection site and methods were at the discretion of the surgeon. **Adjuvant treatment:** endocrine and/or cytotoxic therapy according to the histologic results of this initial staging of primary and axilla	IR with only BD: 82% (23 of 28) Radiosisotope alone: 85% (11 of 13) Radioisotope + BD combined: 94% (66 of 70), p=*nr*

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Intervention / Comparison	Outcomes	Intervention Methods/ Adjuvant treatment	Summary results
	with the goal to achieve a FNR comparable to SLNB without NAC **Follow-up:** *nr*					
Kuehn, 2013 [46] SENTinel NeoAdjuvant (SENTINA) trial **Country:** Germany, Austria **Funding:** Arbeitsgemeinschaft für Gynäkologische Onkologie-Breast, the German Breast Group, and Brustkrebs Deutschland	Four-arm prospective multicentre (103 institutions) cohort study **Accrual Period:** Sept 2009 to May 2012 **Aim** To evaluate a specific algorithm for timing of a standardised SLNB procedure in pts who undergo NAC **Follow-up:** *nr*	**N**=2234 Initially clinically positive pts who are downstaged after NAC **Age: median (range)** **Arm A:** 48 (20–75) **Arm B:** 48 (26–78) **Arm C:** 49 (22–98) **Arm D:** 50 (29–87) **Stage**: cN0, cN1, and cN2 Tumour size >20mm to ≤50mm: **Arm A:** 75% **Arm B:** 71% **Arm C:** 80% **Arm D**: 76%	**Arm A: n**=662 **Arm B: n**=360 **Arm C: n**=592 **Arm D: n**=123 **Arm A:** Clinically node-negative pts (cN0) who had SLNB before NAC and received no further axillary surgery if they had a pathologically negative sentinel node $pN0_{sn}$. **Arm B**: cN0 pts with a pathologically positive SN ($pN1_{sn}$) before NAC who underwent a second SLNB followed by ALND **Arm C:** Initially cN1 or cN2 pts who had NAC and then had SLNB and ALND if they converted to a clinically negative axillary status (ycN0). **Arm D:** Pts with suspicious nodes before and after NAC (ycN1) and	*FNR in Arm C Detection rate of SLNB before and after NAC in pts in arms B and C Detection rate and FNR of a second SLNB procedure after identification and removal of a positive SLN before NAC in pts in arm B **FNR defined as: the ratio of the number of pts with a negative SLN and one or more positive non-SLN to the number of pts with ≥1* involved LN among people in whom ≥1 SN was detected	Methods of SLNB: radiocolloid alone: **A&B before NAC:** 57% **B, after NAC:** 66% **C, after NAC:** 66% blue tracer alone: **A&B before NAC:** 1% **B, after NAC:** 1% **C, after NAC:** 1% Combined: **A&B before NAC:** 39% **B, after NAC:** 29% **C, after NAC:** 28% Adjuvant treatment: NAC consisted of ≥6 cycles of an anthracycline-based treatment	**Detection rate between radiocolloid and BD combined vs. radiocolloid alone:** **Arms A&B, SLNB before NAC:** 99.5% (399 of 401 pts; [95% CI, 98.2 to 99.9]), p=NS **Arm B:** 76.2% (80 of 105 pts vs. 52.9% (126 of 238 pts) **Arm C:** 87.8% (144 of 164 pts) vs. 77.4% (301 of 389 pts) **Arm C**: In multivariate regression analysis: Factors having an impact on detection rate: BD and radiocolloid combination: OR, 2.13 (95% CI, 1.01 to 4.46), p=0.046 Factors having an impact on FNR: FNR was consistently <10% for pts who had ≥3 SLN removed Number of SNs (per 1 SN): OR, 0.487 (95% CI, 0.287 to 0.825), p=0.008 FNR for radiocolloid and BD vs. radiocolloid alone in Arm C: 8.6% (6 of 70 pts) vs. 16% (23 of 144 pts); in multivariate analysis: OR, 0.353 (95% CI, 0.087 to 1.43), p=0.145

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Intervention / Comparison	Outcomes	Intervention Methods/ Adjuvant treatment	Summary results
			who received ALND **Reference standard:** ALND			**FNR Arms B and C:** B: 51.6% [33 of 64 pts]; (95% CI, 38.7 to 64.2) C: 14·2% [32 of 226]; (95% CI, 9.9 to 19.4) FNR according to technique: Radiocolloid alone: Arm B: 46.2% (14 of 25 pts) vs. Arm C 16% (23 of 144 pts) Radiocolloid and blue dye: Arm B 60.9% (15 of 25 pts) vs. Arm C 8.6% (6 of 70 pts) p=NS **FNR according to number of SNs removed (arms B and C)** 1 node removed: B: 66.7% (16 / 24), C: 24.3% (17/70) 2 nodes removed: B: 53.8% (7 / 13), C: 18.5% (10/54) 3 nodes removed: B: 50% (5 / 10), C: 7.3% (3/41) 4 nodes removed: B: 50% (3 / 6), C 0% (0/28) 5 nodes removed: B:18.2% (2 / 11), C: 6.1% (2/33)
Boughey, 2013 [51] **American College of Surgeons Oncology Group ACOSOG Z1071 (ALLIANCE)** **Country:** US **Funding:** National Cancer	Prospective multi-institutional (136 institutions) phase 2 trial **Accrual Period:** Jul 2009 to June 2011 **Aim** 1) To determine the FNR for SLN surgery after NAC when ≥2 SLN were excised, in women initially presenting with biopsy-proven cN1 breast cancer.	N=756 adult women with cN1 (n=663 evaluable), cN2 (n=38 evaluable), biopsy proven node-positive BC who had been treated with NAC and were T0-T4, N1-N2, M0 **Age** (mean ± SD): 50.2±11.0 yrs **Stage:** T0 or Tis: 1% T1: 13%	**SLNB and ALND n**= 687 (98%); cN1: n= 525 (76.4%) **SLNB only: n** = 2 (0.3%) **ALND only: n**=12 (1.7%) Index test vs. **Reference standard**: ALND or histopathology	IR FNR of SLNB after NAC	Methods of SLNB (n= 689): BD only (4.1%); radiocolloid only (16.8%); BD + radiocolloid (79.1%); ≥2 SLN resected. **Adjuvant treatment:** NAC: various chemo regimens: Anthracycline and taxane (74.6%) for a median of 4 mos Surgery:	**IR:** ≥1 SLN detected in 639 of 689 pts: 92.7% (95% CI, 90.5% to 94.6%) **Subgroups:** cN1: 605 of 663 pts: 92.9% (95% CI, 90.7% to 94.8%) cN2: 34 of 38 pts: 89.5% (95% CI, 75.2% to 97.1%) **FNR:** **Pts with ≥2 SLNs and cN1**: **FNR:**

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Intervention / Comparison	Outcomes	Intervention Methods/ Adjuvant treatment	Summary results
Institute of the National Institutes of Health	2) To determine the pathologic complete nodal response (pCR) rate where in a nodal pCR is pathologically node-negative (pN0) on the basis of SLN surgery and ALND. A Bayesian clinical trial design was chosen to determine whether the FNR was greater than 10% **Follow-up:** *nr*	T2: 54.9% T3: 26.4% T4: 4.7%			partial mastectomy: cN1: 40.1%; cN2: 28.9% Total mastectomy: cN1: 59.6%; cN265.8% No surgery: cN1: 0.3%; cN2: 5.3% Breast cancer surgery was performed within 84 ds after the completion of NAC. After NAC, and within 4 wks before surgery, pts underwent a physical examination and axillary US. At surgery, pts had appropriate treatment of the primary tumour and underwent SLE and then ALND. All SLNs were excised and submitted before the ALND was performed **Cut offs**: Each SLN was examined with hematoxylin-eosin staining, and SLNs + were defined as those with metastases >0.2 mm	cN1 pts: 7.1% cN2 pts: 12.6% (90% Bayesian credible interval 9.85%-16.05%) On multivariable analysis: FNR: BD 10.8%, and single tracer: 20.3%, p=0.05 By examination of number of SLN detected: ≥3 vs. 2: FNR, 9.1% for ≥3 SLNs vs. 21.1% for 2, p=0.007; no other factors made a significant contribution in explaining the variability in likelihood of a false-negative SLN finding. **Pts with ≥2 SLNs and cN2 (26 SLNB + ALND):** 12 pts no residual nodal disease **pCR:** 46.1% (95% CI, 26.6% to 66.6%) Residual disease detected by SLNB only 6 pts Residual disease detected by both ALND and SLNB: 8 pts **FNR:** 0% (95% CI, 0% to 23.2%)
Hunt, 2009 [53] **Country:** US **Funding:** *nr*	Retrospective study. **Accrual period** March 1994 to 2007 **Aim:** 1) To evaluate the accuracy of SLNB for pts undergoing NAC first versus pts undergoing surgery first. 2) To evaluate the impact of NAC on the incidence of positive SLNs after chemotherapy and the need	**N**=3746 clinically negative pts **Age (median):** SLNB before NAC: 57 yrs (range 22-92 yrs) SLNB after NAC: 51 yrs (range 25-84 yrs), p<0.0001 **Stage**: SLNB before NAC: T1: 81.2% T2: 17.7% T3: 1.1% SLNB after NAC:	SLNB after NAC **n**=575 (15.3%) vs. SLNB before NAC **n**=3171 (84.7%) Reference standard: ALND (conducted on 542 pts [27.1% vs. 28.9%, p=0.38])	*Technical success rate in identifying and removing a SLN in pts in whom surgery was attempted. False negative rate of SLN surgery in patients who were found to have >1	Methods of SLNB: Blue dye with or without radiocolloid Adjuvant treatment: *nr*	In multivariate analysis: **False negative rate by mapping techniques**: Mapping with blue dye vs. mapping with BD plus radiocolloid: OR 2.61 (95% CI, 0.78 to 8.76), p<0.0001 *A false-negative event was defined as a case where the SLN(s) was negative but an axillary (non-SLN) node was positive on pathologic examination.*

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Intervention / Comparison	Outcomes	Intervention Methods/ Adjuvant treatment	Summary results
	for completion ALND in pts with large primary tumours **Follow-up (median):** 47 mos	T1: 12.7% T2: 75% T3: 12.3%		positive SLN or non-SLN Number of ALND performed Loco-regional and distant recurrence IR		
Gimbergues, 2008 [54] **Country:** France **Funding:** *nr*	Prospective cohort study. **Accrual period** Mar 2001 to Dec 2006 **Aim** To determine clinicopathological factors that may influence the accuracy of SLN biopsy after NAC **Follow-up (median):** 35.64 mos	**N**=129 pts with infiltrating BC who were treated with NAC **Age (median range):** 53 yrs, 25 to 84 yrs **Stage**: T1: 1.6% T2: 71.3% T3: 27.1%	**Index test:** SLNB; **Reference standard:** ALND of level I and II	IR FNR	Methods of SLNB: radioisotope Adjuvant treatment: NAC: 5-fluorouracil, epirubicin, and cyclophosphamide, or docetaxel and epirubicin, or docetaxel alone.	IR: 93.8% Factors impacting IR: Age ≥60 yrs vs. aged <60 yrs: 82.1% vs. 97.9%, p=0.0063 FNR: 14.3% (all pts) Factors impacting FNR: Larger tumour size before NAC: 5.7% for T1-T2 vs. 28.5% for T3 cases, p=0.045 Positive clinical lymph node status before NAC: 0% for N0 vs. 29.6% for N1-N2 cases; p=0.003.
Patients who did not receive NAC						
A) Single vs. Dual dye						
STUDIES OF DIRECT PATIENT OUTCOMES						
No studies met our inclusion criteria						
STUDIES OF DIAGNOSTIC OUTCOMES						
O'Reilly, 2015 [47] **Country:** Ireland **Funding:** *nr*	RCT, single centre (tertiary referral cancer centre) Study of a diagnostic test used as replacement **Accrual period:** Mar 2010 to Sept 2012 **Aim:** To determine if the addition of BD to radioisotope	N=667 clinically and US node-negative BC women with 1-3 positive nodes at preoperative lymphoscintigram. Histologically proven node positive pts were excluded. Node negatives is undefined	n=342 Isosulfan BD + radioisotope vs. n=325 radioisotope alone **Reference standard:** dual tracer	IR Number of nodes retrieved Identification of metastatic disease Adverse events (only BD)	Radioisotope injection was given on the day of surgery. Three hours after isotope injection surgery was performed. Pts randomized to the BD arm received an intradermal injection of isosulfan BD (1 mL) over the tumour after induction of anesthesia.	Dual tracer group vs. Radioisotope only: IR: 100% vs. 100%, p=0.86 Number of nodes retrieved (mean): 1.5 (range 1-9, median: 1) vs. 1.4 (range: 1-8, median – 1), p=0.86 IR: The addition of BD increased the IR by 1.5%.

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Intervention / Comparison	Outcomes	Intervention Methods/ Adjuvant treatment	Summary results
	improves the accuracy of SLN detection **Follow-up:** *nr*	**Age**: Mean 48 yrs, SD: 10.6 (range 19 – 83 yrs) (48.3 vs. 47.7 yrs; p=0.47) **Stage:** Tumour size: mean 24.2 mm (24.3 mm vs. 24.1 mm; p=0.7).			All hot and blue nodes were removed during surgery.	Identification of metastatic disease: p=0.64 AE with BD: Anaphylaxis rate: 0.3% Skin tattooing rate: 0.6%
Kang, 2010 [60] **Country:** US **Funding:** *nr*	Retrospective cohort study of prospectively collected data **Accrual period:** 2002 to 2006 **Aim:** to evaluate the utilization of BD in addition to radioisotope and its relative contribution to SLN mapping **Follow-up:** *nr*	**N**=3402 clinically node negative pts who underwent lymphatic mapping with radiocolloid Dual tracer vs. radiocolloid: **Age (median, range):** 56 (23–91) yrs vs. 54 (22–99) yrs **Stage**: **Tis:** 13.1% vs. 19.9% **T1:** 59.5% vs. 58.7% **T2:** 23.9% vs. 19.3% **T3:** 2.5% vs. 1.8% **T4:** 1% vs. 0.3%	**n**=2049 (dual tracer) vs. **n**=1353 (radiocolloid only)	IR Number of nodes removed	Lymphatic mapping was performed with technetium Tc99 m-labeled sulfur colloid, at dose of 2.5 mCi for pts scheduled for operation the following day and 0.5 mCi for pts having same-day surgery. Intraoperative lymphatic mapping was performed with radiocolloid, with or without 1% isosulfan blue dye at the discretion of the operating surgeon.	Dual tracer vs. radiocolloid only: IR: 98% vs. 98%, p=0.8 Mean number of lymph nodes removed: 2.7 vs. 2.9, p=0.03
Nathanson, 2007 [50] **Country:** USA **Funding:** Rands Chair for Breast Cancer Research	Prospective non-randomized analysis **Accrual period** Apr 1995 to Dec 2005 **Aim** To determine whether high volume surgeons identify more SLN than low volume surgeons **Follow-up:** *nr*	**N**=1187 clinically node negative pts undergoing 1995 SLNB procedures **Age:** *nr* **Stage**: *nr*	**Group 1: High volume surgeons (performed >100 procedures) n**=4 (877 surgeries) vs. **Group 2: Low volume surgeons** (performed <100 procedures) **n**=17 (322 surgeries)	Ability to map IR: (only on 300 cases where SLNB and ALND were performed IR by surgeon group **Reference standard:** ALND	Group 1: blue dye and/or radiocolloid Group 2: blue dye only Radiocolloid: A total of 500 µCi was injected in three intradermal injections superficial to the breast lesion (or, if nonpalpable, in the periareolar region of the quadrant containing the lesion) on the day of the surgical procedure BD: injection of 5 mL of 1% isosulfan blue into the breast parenchyma adjacent to the breast cancer and into the subareolar plexus in the	The odds of finding SLNs was 2.6 times greater among surgeon group 1 compared with surgeon group 2 (95% CI, 1.7 to 4.1; p<0.0001). IR (300 cases): 90% FNR: 2.6% IR by surgeon group (from generalized estimating equations logistic regression model): Group 1 vs. Group 2: 94.6% vs.89.0%, p<0.0001; OR, 2.63 (95% CI, 1.70 to 4.07) In multivariable analysis: Dual tracer vs. BD only:

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Intervention / Comparison	Outcomes	Intervention Methods/ Adjuvant treatment	Summary results
					''clock'' position of the tumour **Adjuvant treatment:** mastectomy or BCT Pathologic Evaluation: standard hematoxylin and eosin staining. Cytokeratin immunohistochemistry was deliberately avoided	OR of detecting the SLN 2.9 (95% CI, 1.8 to 4.7; p<0.001). Surgeons in Group 1 vs. surgeons in Group 2: Surgeon group 1 was 2.7 times more likely than surgeon group 2 to find the SLN (95% CI, 1.7 to 4.3; p<0.001).
B) US-guided vs. Traditional SLNB						
STUDIES OF DIRECT PATIENT OUTCOMES						
Verheuvel, 2017 [55] **Country:** The Netherlands **Funding:** *nr*	Retrospective population study (data prospectively collected from the Netherlands Cancer Registry) **Accrual period** Jan 2008 to Dec 2014 **Aim** To examine whether the conclusions of the ACOSOG Z0011 trial are applicable to US-guided SLNB positive patients. **Follow-up (median):** 60 mos	**N**=11820 node positive BC pts *Pts with stage IV BC, with clinical stage T3-T4 tumour according to the TNM classification, those receiving NAC, those with palpable axillary nodes (cN C1), and those who did not undergo an ALND were excluded.* **Age (Median, range yrs):** 59 yrs (range 21 to 97 yrs) US-guided: 63 yrs (range 23 to 97 yrs) SLNB: 58 yrs (range 21 to 95 yrs) **Stage (pathological)**: **US-G** **SLNB** pT1a 1.9% 1.0% pT1b 9.2% 8.8% pT1c 40.5% 46.1% pT2 48.3% 44.1%	**US-guided biopsy n**=2671 vs. **SLNB n**=9149	OS	*nr*	US-guided vs. traditional SLNB: OS rate at 5 yrs: 81.6% vs. 89.6%, p<0.001 In multivariate analysis, adjusting for age at diagnosis, year of diagnosis, type of surgery, hormone receptor status, tumour morphology, tumour size, tumour grade, multifocality, number of positive lymph nodes, radiation therapy, and adjuvant systemic therapy, US-guided SLNB had a worse OS than traditional SLNB: HR=1.38; (95% CI, 1.23 to 1.56), p<0.001 **Sensitivity analysis:**When excluding pts >70 yrs of age, in multivariate analysis, the method of staging was no longer significant: HR, 1.13; 95% CI, 0.94 to 1.35, p=NS

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Intervention / Comparison	Outcomes	Intervention Methods/ Adjuvant treatment	Summary results
STUDIES OF DIAGNOSTIC OUTCOMES						
Caudle, 2016 [61] **Country:** USA **Funding:** grants from the National Institutes of Health, the PH and Fay Eta Robinson Distinguished Professorship in Research Endowment, and from from the Mike Hogg Foundation and MD Anderson	Prospective registry study of clinically positive pts after NAC **Accrual period** 2011 to 2015 **Aim** 1) to determine if pathologic changes in clipped nodes after NAC reflect the response of the nodal basin 2) to determine if TAD, which includes SLNB and selective localization and removal of clipped nodes, improves the FNR compared with SLNB alone **Follow-up:** *nr*	**N**= 208 pts with biopsy-confirmed nodal local or regional metastases with a clip placed in the sampled node, treated with NAC **Age (median):** 49 yrs, (range 23-84 yrs) **Stage:** T0: 0.5% T1: 9% T2: 65% T3: 23% T4: 2%	1) **n**=120 pathologically + of 191 evaluated: Clipped node vs. ALND (reference standard); 2) **n**=74 pathologically + of 118 evaluated a) SLNB alone and b) SLNB + Clipped node; both vs. ALND (reference standard) 3) **n** = 50 patologically + of 85 evaluated	FNR IR *FN event was defined as a case where the node (the clipped or the SLN) did not show metastasis even though residual disease was seen in other axillary nodes. The FNR was calculated as the number of FN events divided by the total number of pathologically node+ pts.* **Reference standard:** Histopathology (after ALND)	**Methods of SLNB:** An iodine-125 seed was placed in the clipped node under US guidance 1 to 5 ds before surgery. Mapping agents, including radiocolloid and/or BD, were injected before or at the time of surgery. During surgery, a gamma probe was used to identify SLNs. All nodes containing BD radioactivity, or which were palpable were removed and labeled as SLNs. **Adjuvant treatment:** (NAC): anthracycline and/or taxane based. in pts with HER2+ metastases: (HER2)– targeted therapy Five pts received neoadjuvant endocrine therapy as a component of clinical trials.	1) Clipped node to predict nodal status after NAC (191 pts who underwent ALND): FNR in the clipped nodes (in 5 of 120 pts pathologically + the clipped node did not show metastases): 4.2% (95% CI, 1.4 to 9.5) 2a) SLNB alone to predict nodal status: 7 false negative events in 118 pts: FNR for SLNB alone (dual tracer: 55%): 10.1% (95% CI, 4.2 to 19.8) 2b) SLNB + evaluation of the clipped node: FNR: 1.4% (95% CI, 0.03 to 7.3) Companing 2a) and 2b), p=0.03 3) TAD to predict nodal response after NAC (85 pts underwent both TAD and ALND): FNR for TAD (i.e., SLNB + clipped nodes removal) 2.0% (95% CI, 0.2 to 10.7) SLNB alone: FNR 10.6% (95% CI, 3.6 to 23.1), TAD vs. SLNB alone: p=0.13
Kramer, 2016 [56] **Country:** The Netherlands **Funding:** None	Retrospective analysis of prospectively maintained histopathological database **Accrual period** Jan 2004 to Dec 2014 **Aim** To investigate the accuracy of preoperative US/FNAC to detect ≥3 positive aLNs	**N**=2130 pts with invasive breast cancer not treated with NAC **Age:** Mean: 60 yrs (range 26 to 91 yrs) **Stage**: **T1**: 66.2% **T2**: 31.2%	US-guided FNAC **Reference standard:** Histological outcome (SLNB and/or ALND) was used for definitive axillary staging	FNR	Method of US: aUS with FNAC of the sonographically most suspicious LNs (US/FNAC) was performed. FNAC was indicated if LN cortex thickness of ≥2.3 mm, focal cortical thickening or a replaced or anomalous hilum	FNR on 137 of 2130 pts: 6.4%

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Intervention / Comparison	Outcomes	Intervention Methods/ Adjuvant treatment	Summary results
	Follow-up: *nr*	**T3**: 2.3%				
Kim, 2016 [57] **Country:** Korea **Funding:** Grant from the Basic Science Research Program of the National Research Foundation of Korea	Retrospective cohort **Accrual period** Jul 2007 to Jan 2014 **Aim** To investigate the diagnostic performance of pre-operative aUS and US-FNA and to evaluate the clinicopathologic and US features associated with LN metastasis in invasive lobular carcinoma **Follow-up:** *nr*	**N**=142 pts: 7 clinically positive, and 135 clinically negative **Age** Mean ± SD: 50.7±8.9 yrs **Stage (pathological)**: **T1:** 65.5% **T2:** 32.4% **T3**: 2.1% **N0:** 69.0% **N1**: 21.1% **N2**: 6.3% **N3**: 3.5%	US followed by US-guided FNA Surgery was the reference standard	FNR	Pre-operative US was conducted by 1 of 11 radiologists	FNR: on 8 of 23 pts 34.8%
Cools-Lartigue, 2013 [58] **Country:** Canada **Funding:** *nr*	Retrospective study of prospectively collected data **Accrual period** 2005 to 2007 **Aim** To determine the sensitivity, specificity, and accuracy of aUS in the detection of nodal metastases with or without the addition of FNAB. To characterize the axillary disease burden in pts with nodal metastasis identified by US and FNAB versus SLNB and determine the proportion of pts who can be spared an unnecessary SLNB and proceed directly to ALND **Follow-up:** *nr*	**N**=235 clinically node negative pts with invasive BC undergoing aUS **Age (mean ± SD, range):** 57.8±13.1 yrs, 22-97 yrs **Stage**: **T1:** 51.1% **T2:** 48.9%	aUS and FNAB **Reference standard:** histopathology after SLNB or ALND	FNR (undefined)	Abnormal LNs had absence of a fatty nodal hilum, eccentric cortical thickening, and a round hypoechoic node	FNR for all US: 17.4% (41/235) FNR with FNAB: 40.8% (20/49)

Study, date, country, study name, Funding	Design, Accrual period Aim Follow-up	Population	Intervention / Comparison	Outcomes	Intervention Methods/ Adjuvant treatment	Summary results
C) US vs. SLNB						
STUDIES OF DIRECT PATIENT OUTCOMES						
No studies were identified for this comparison						
STUDIES OF DIAGNOSTIC OUTCOMES						
Stachs, 2013 [59] **Country:** Germany **Funding:** *nr*	Retrospective cohort (1 institution) **Accrual period** Feb 2008 toJan 2010 **Aim** To identify factors influencing accuracy of aUS in preoperative BC assessment **Follow-up (median):** 95.6 mos	**N**=470 pts with primary BC **Age:** ≤50 yrs of age: 15.7% >50 yrs of age: 84.3% Mean age of pts who underwent SLNB (N=360): 63 yrs, (range 29-90 yrs) **Stage:** **pT1:** 59.1% **pT2:** 34.9% **pT3&T4:** 6%	US confirmed by FNB vs. SLNB **Reference standard:** histology (SLNB or ALND)	FNR (undefined)	Lymph nodes were identified as abnormal according to sonographic criteria including absence of a fatty nodal hilum, or a round hypoechoic node	FNR: 87 of 378 pts: 23% **NOTE**: in multivariate logistic regression analysis pathological size of nodal metastases was the only significant parameter associated with false negative US findings: size of nodal metastases ≤10 mm vs. >10 mm OR: 2.66 (95% CI, 1.81 to 3.91), p=0.001

AE = adverse events; ALND = axillary lymph node dissection; aUS = axillary ultrasound; BC = breast cancer; BCT = breast conserving therapy; BD = blue dye; chemo = chemotherapy; CI = confidence interval; CNB = core needle biopsy; ds = days; FN = false negative; FNA = fine needle aspiration; FNAB = fine needle aspiration biopsy; FNAC = fine needle aspiration cytology; FNR = false negative rate; GCSF = Granulocyte-colony stimulating factor; hs = hours; HER2 = human epidermal growth factor receptor; HR = hazard ratio; IHC = immunohistochemical; IR = identification rate; LN(s) = lymph node(s); LSG = lymphoscintigraphy; mCi = millicurie; min = minutes; mos = months; NAC = neoadjuvant chemotherapy; NS = not significant; *nr* = not reported; OR = odds ratio; OS = overall survival; pCR = pathological complete response; pts = patients; RCT = randomized control trial; RNI = regional nodal irradiation; SD = standard deviation; SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy; SN = sentinel node; TAD = targeted axillary dissection; US = ultrasonography; yrs = years; ypN0 = post-treatment negative axillary nodes; wks = weeks; µCi= microcuries

Table 4-22. Corollary publications of the main trials included for question 5.

Main study; Comparison; Objectives	Companion publications; Objectives	Summary results of the companion publication
Boughey, 2013 [51] ACOSOG Z1071 (ALLIANCE) SLNB+ALND vs. SLNB alone **Objectives:** To determine the FNR for SLN surgery following chemotherapy in women initially presenting with biopsy-proven cN1 breast cancer	Le-Petross, 2018 [258] **Objectives:** To determine lymph node characteristics on aUS images after NAC associated with residual nodal disease in pts with initial biopsy-proven node-positive breast cancer clinical T0–T4, N1–N2, M0 disease	Residual nodal disease was present in 373 of 611 pts (61.0%), and 238 (39.0%) had a complete nodal pathologic response. Increased cortical thickness (mean, 3.5 mm for node-positive disease vs 2.5 mm for node-negative disease) was associated with residual nodal disease. Lymph node short-axis and long-axis diameters were significantly associated with pathologic findings. Pts with nodal morphologic type I or II had the lowest rate of residual nodal disease (51 of 91 pts [56.0%] and 138 of 246 patients [56.1%], respectively), whereas those with nodal morphologic type VI had the highest rate (44 of 55 patients [80.0%]) (p=0.004). The presence of fatty hilum was significantly associated with node-negative disease (p = 0.0013)
	Boughey, 2015 [259] **Objectives:** To determine whether aUS (after NAC) and FNAC can identify abnormal nodes and guide pt selection for SLN surgery	Postchemotherapy aUS images were reviewed for 611 pts. 130 (71.8%, 95% CI, 64.7% to 78.3%) of 181 aUS-suspicious pts were node + at surgery compared with 243 (56.5%, 95% CI, 51.6% to 61.2%)of 430 aUS-normal pts (p<0.001). Pts with aUS-suspicious nodes had a greater number of positive nodes and greater metastasis size (p<0.001). The SLN FNR was not different based on aUS results; however, using a strategy where only pts with normal aUS undergo SLNB would potentially reduce the FNR in Z1071 pts with two SLNs removed from 12.6% to 9.8% when preoperative aUS results are considered as part of SLN surgery
	Wallace, 2017 ABS [260] **Objectives:** To analyze how the findings of ACOSOG Z1071 influenced clinical practice and whether surgeons followed appropriate techniques	When analyzed by half-year increments, and as a function of continuous time the increase in rate of adoption of Z1071 was statistically significant (p=0.0003). Statistically significant differences in approach to implementation of Z1071 existed among surgeons (p<0.0001), between University and County hospital facilities (p<0.0001), according to race (p=0.0095) and according to insurance status (p=0.0002). Of 86 pts undergoing SLNB, appropriate technique for minimizing FNR was performed in 94.2%. Positive axillary LNs were clipped in 39.5% of pts undergoing SLNB. Of these, retrieval was confirmed in 73.5%.
	Vriens, 2017 [261] **Objectives:** To assess the impact of timing of SLN procedure, pre- versus post-NAC, on final pathologic node-negative rate (pN0) in pts with clinically node-negative (cN0) breast cancer. Secondary endpoint: the usability of the SN procedure in pts with clinically node + disease that converted to cN0 after neoadjuvant chemotherapy	In total 439 pts were included, of whom 230 (52%) had pretreatment cN0. In this group, pN0 status was seen in 58% (N=23) of pts with a sentinel node biopsy post-NAC compared to 51% (N=83) pre-NAC, including ALND whenever performed. In multivariable analysis, timing of sentinel node procedure (pre- versus post- NAC) was, however, not significantly associated with final pN0/pN0(i+) status, with an OR of 1.18 (95% CI, 0.64 to 2.18) after correction for age, clinical tumour status, histology, grade, hormone- and HER2 receptor. Of pts with clinically node-positive disease only 15% had a final pN0 status, with a FNR of the sentinel node of 30%.
	Boughey, 2016 [262] **Objectives:** To evaluate the clip location at surgery (SLNB or ALND)	A clip was placed at initial node biopsy in 203 pts. In the 170 (83.7%) pts with cN1 disease and ≥2 SLNs resected, clip location was confirmed in 141 cases. In 107 (75.9%) pts where the clipped node was within the SLN specimen, the FNR was 6.8% (CI, 1.9 to 16.5%). In 34 (24.1%) cases where the clipped node was in the ALND specimen, the FNR was 19.0% (CI,5.4 to 41.9%). In cases without a clip placed (n=355) and those where clipped node location was not confirmed at surgery (n=29), the FNR was 13.4% and 14.3%, respectively.

	Boughey, 2015 [263] **Objectives:** To evaluate factors affecting SLN identification after NAC in pts with initial node-positive breast cancer	Of 756 pts enrolled, 34 pts withdrew, 21 were ineligible, 12 underwent ALND only, and 689 had SLN surgery attempted. ≥1 SLN was identified in 639 pts (92.7%: 95% CI, 90.5 to 94.6%). Among factors evaluated, mapping technique was the only factor found to impact SLN identification; with use of BD alone increasing the likelihood of failure to identify the SLN relative to using radiolabelled colloid ± BD (p=0.006; OR 3.82 [95% CI, 1.47 to 9.92]). The SLN identification rate was 78.6% with BD alone; 91.4% with radiolabelled colloid and 93.8% with dual mapping agents. Pt factors (age, BMI), tumour factors (clinical T or N stage), pathologic nodal response to chemotherapy, site of tracer injection and length of chemotherapy treatment did not significantly affect the SLN identification rate.
	Boughey, 2014 [264] **Objectives:** To determine the impact of tumour biology on rates of breast-conserving surgery and pathologic complete response (pCR) after NAC	Of the 756 pts enrolled on Z1071, 694 had findings available from pathologic review of breast and axillary specimens from surgery after chemotherapy. 170 (24.5%) pts were TN, 207 pts were (29.8%) HER2-positive, and 317 (45.7%) were HER2-negative. Age, clinical tumour and nodal stage at presentation did not differ across subtypes. Rates of breast-conserving surgery were significantly higher in pts with triple-negative (46.8%) and HER2-positive tumours (43.0%) than in those with hormone-receptor-positive, HER2-negative tumours (34.5%) (p=0.019). Rates of pCR in both the breast and axilla were 38.2% in TN, 45.4% in HER2-positive, and 11.4% in hormone-receptor-positive, HER2-negative disease (p<0.0001). Rates of pCR in the breast only and the axilla only exhibited similar differences across tumour subtypes.
Gill 26650 Sentinel Node biopsy versus Axillary Clearance (SNAC) TRIAL SLNB (+ ALND if node + or not detected) vs. ALND **Objectives:** To determine whether management of the axilla by SLNB for negative nodes with ALND if nodes were positive was better than routine ALND in terms of morbidity and cancer-related outcomes.	Elmadahm, 2015 [265] **Objectives:** To determine the effect of clinical factors on SLN identification in the SNAC trial	SLNs were identified in 1024 of 1088 women (94%), localized with LSG in 779 (81.4%), and were identified by gamma probe in 879 (91.8%). The BD identified SLNs in 890 of 1073 (82%) women. Three pts had allergic reactions. BD detected the SLNs in 141 of 178 women with negative LSG mapping and in 44 of 79 women with no hot SLNs detected intraoperatively. Age, BMI and tumour presentation (screen detected versus symptomatic) were significantly related to the identification of the SLN. For BD, the primary tumour location was significantly related to identification rate. The detection of blue SLN was significantly lower in women with inner quadrant tumours.
Verheuvel, 2017 [55] **Objectives:** To examine whether the conclusions of the ACOSOG Z0011 trial are applicable to US-guided SLNB positive patients.	Verheuvel, 2015 [266] **Objectives:** To evaluate potential differences in pt and tumour characteristics and survival between US axillary node positive pts vs. SLNB axillary node positive pts This is the same as the main study on a smaller scale	*DFS rate at 5 yrs: US vs. SLNB* 72.6% (95% CI, 71.8 to 73.4) vs. 87.7% (95% CI, 87.2 to 88.2), p=0.001 , HR: 2.71 (95% CI, 1.49 to 4.92) *OS rate at 5 yrs: US vs. SLNB* 73.0% (95% CI, 72.3 to 73.8) vs. 82.4% (95% CI, 81.7 to 83.1), p<0.001 HR: 2.67 (95% CI, 1.48 to 4.84)

ABS = abstract; ALND = axillary lymph node dissection; aUS = axillary ultrasound; BD = blue dye; BMI = body mass index; CI = confidence interval; cN0 = clinically node negative; DFS = disease-free survival; FNAC = fine needle aspiration cytology; FNR = false negative rate; HER2 = human epidermal growth factor receptor; LN – lymph node; LSG =

lymphoscintigraphy; NAC = neoadjuvant chemotherapy; nN0 = pathologic node negative rate; OR = odds ratio; pCR = pathological complete response; pts = patients; SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy; SN = sentinel node; TN = triple negative; US = ultrasonography; yrs = years

Study Design, Risk of Bias, AND Certainty of the Evidence

We identified trials reporting both on direct patient outcomes and diagnostic outcomes. Among all the trials identified, five reported on the operator expertise [48,50,57,59,257]. The expertise of the operators was described by reporting the number of years of experience, number of cases treated, as "experienced surgeons/examiners", or "institutions had performed ≥50 procedures with a sensitivity of ≥95% to avoid including learning curves".

A) Single tracer compared with dual tracer

Direct patient outcomes:

Ability to map

Hunt et al. [53] reported mapping success by single or dual tracer: mapping success was statistically significantly better with blue dye and radiocolloid than with blue dye alone ($p<0.0001$, see Table 4-21 for detailed results).

Diagnostic outcomes

We considered the systematic review by Geng et al. [49] at low risk of bias as assessed with the ROBIS tool [76] (Tables 4-1 and 4-2). However, Geng et al. [49] review had slightly different inclusion criteria than the present review, making this evidence somewhat indirect. The authors included 16 studies published from 1993 to 2015, for a total of 1456 node negative patients at diagnosis, with stages T1 to T4 breast cancer who received NAC. This systematic review compared mapping performed with blue dye only, with radiocolloid only, or with a combination of blue dye and radiocolloid. The authors summarized identification rate for this comparison with a fixed-effects model from 13 out of the 16 studies because three studies used different mapping methods. Of the 13 included studies, five were published before our cut-off date of 2007 [267-271], one included a population of advanced-stage breast cancer [272], and four did not meet our sample size limit of 100 patients [273-276].

The evidence provided by this review, although partially indirect, is relevant for patients subgroups treated with NAC.

Nine primary studies identified through our own search met the inclusion criteria [46-48,50-54,60]. One of the studies was an RCT [47]; the others were observational studies, and all but one [60] had a prospective design. The characteristics of the studies are reported in Table 4-21.

We considered the risk of bias of studies of single versus dual tracer [46,47,50-52,60] unclear [46,50] or high [47,51,52,60], as assessed with the QUADAS-2 [79], because the results of the index test and of the reference standard were not, or it was unclear whether they were, interpreted in a blind fashion (Table 2, Appendix 6). One potential confounder that is inconsistently reported by the trials is the expertise of the surgeon. We did not conduct a meta-analysis because the studies were heterogeneous.

For outcomes such as survival, disease control, and quality of life, the certainty of the evidence was low for both patients treated with NAC or not for this comparison.

The certainty of the evidence for patients treated with NAC for identification rate and false negative rate can be considered moderate: the studies for these outcomes are at unclear or high risk of bias; a small portion of the patients included in the studies had T3-T4 disease; therefore, the evidence is indirect to a certain extent. The studies had generally a large sample size, but when calculating the false negative rate, the event rate could be very small (e.g., false negative rate with dual tracer: 5.2% (3 of 58 patients) [52], false negative rate with isotope only: 16.0% (4 of 25 patients) [46], giving way to imprecision.

The included studies consistently indicated 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 identification rate with a single tracer.

The certainty of the evidence for patients not treated with NAC was moderate to low. The studies included were of high [47,60] or unclear [50] risk of bias. The studies reported inconsistent results: Nathanson et al. [50] reported a higher identification rate for dual tracer, while Kang et al. [60] reported no difference by adding blue dye to radiocolloid. None of the studies reported on surgeons' expertise. The studies included a portion of patients with stage T3 and T4, or the stage was not reported, and therefore this evidence can be considered partially indirect.

B) Ultrasound-guided staging compared with traditional SLNB

Direct patient outcomes:

Our search for primary studies identified one very large population-based retrospective trial [55] including 11,820 node-positive patients. This study compared US-guided biopsy with traditional SLNB procedure in terms of OS. The characteristics of the study are reported in Table 4-21. When evaluated with the ROBINS-I tool [78], this study presented several major flaws, which made its risk of bias to appear critical (Table 1, Appendix 6). For this reason we will not discuss it any longer.

Diagnostic outcomes:

We identified the systematic reviews by van Wely et al. [117] and by Houssami et al. [118] with its updates [192,193], and four retrospective trials reporting on diagnostic outcomes of axillary US-guided fine needle aspiration biopsy [56-59].

At the first step of the ROBIS tool [76] we decided not to include the Houssami et al. [118] systematic review, and its updates [192,193] because this systematic review does not align with the scope of ours: its selection criteria differ from ours, the quality of the studies was not evaluated or considered for study selection, the included studies had sample sizes often much smaller than what we required (the authors excluded studies with samples smaller <20 patients, while we excluded studies with samples <100 patients), and the population was not limited to early stage breast cancer, therefore we will not discuss it any further.

Patients of the studies in the systematic reviews by van Wely et al. [117] had breast cancer not limited to early stage. Therefore the evidence provided is partially indirect. The intervention was US-guided biopsy, and the reference standard was ALND. The outcome was the number of positive nodes identified. No randomized trials were identified for this question. Van Wely et al. [117] searched the literature up to September 2013. Therefore we updated the search for this topic for nonrandomized trials. After full evaluation with the ROBIS tool [76], we considered the van Wely et al. systematic review [117] at unclear risk of bias (Tables 4-1 and 4-2, and Tables 1 to 7 in Appendix 5).

In node-positive patients treated with NAC, Caudle et al. [61] reported a prospective evaluation of the use of clipped nodes for selective localization and removal of positive axillary nodes. The evaluation of this study with QUADAS-2 [79] revealed an unclear risk of bias. It was unclear whether the index test (i.e., targeted axillary dissection) and the reference standard (i.e., histopathology) were interpreted independently from each other. This study included 25% of patients with stage T3-4 disease, which makes the evidence partially indirect.

Three retrospective trials [56-58] evaluated patients who did not receive NAC. The risk of bias of these studies was unclear to high because it was unclear whether the index test and

the reference standard were interpreted in a blind fashion [56-58], and because of bias in the selection of patients [58].

The certainty of this evidence is low. Risk of bias is critical for direct patient outcomes, and high to unclear for diagnostic outcomes. The studies included a portion of patients with breast cancer stage T3-4, so the evidence is partially indirect. The study reporting on direct patient outcomes [55] was considered at critical risk of bias. The other studies [56-58,61] reported on accuracy outcomes, which are indirect measures. The three studies that reported on false negative rate [57,58,61] had very small samples; we did not pool the results into a meta-analysis because the studies were heterogeneous. False negative rates were higher in studies with smaller sample size. Inconsistency may be partly due to different definitions of this outcome used in each study. It is not possible to exclude publication bias.

C) Ultrasound compared with SLNB

We did not identify any systematic review for this comparison.

Direct patient outcomes:

No studies reported on direct patient outcomes for this comparison.

Diagnostic outcomes:

One retrospective study [59] reported on false negative rate of preoperative US. We considered the risk of bias of this study unclear because the authors did not report whether the reference standard was interpreted without knowledge of the results of the index test. The general characteristics of this study are presented in Table 4-21, and the quality, evaluated with the QUADAS-2 tool [79], in Table 2, Appendix 6.

The SENTINA trial [46] used specific criteria for patients with US-negative axilla in whom SLNB was then performed. This trial gives us an estimate of the false negative rate of US by their criteria.

The Stachs et al. trial [59] was at unclear risk of bias: it was unclear whether the reference standard and the index test were interpreted in a blind fashion. This evidence is indirect as we do not have any direct patient outcome. The Stachs et al trial [59] was a single study; therefore, this body of evidence can be considered imprecise. It is not possible to exclude publication bias.

OUTCOMES

A) Single tracer compared with dual tracer

We included studies of patients who did and did not received NAC. A detailed summary of the results is reported in Table 4-21.

a) Patients treated with NAC:

Direct patient outcomes

No evidence was available on survival, disease control, and quality of life.

Ability to map

Hunt et al. [53] reported a better technical success rate in identifying and removing involved sentinel nodes with a combination of blue dye and radiocolloid compared with blue dye alone (99% vs. 97.5%, respectively, p<0.0001)

Adverse events

O'Reilly et al. [47] reported an anaphylaxis rate of 0.3%, and a skin tattooing rate of 0.6% with blue dye.

Diagnostic outcomes

Identification rate

In 13 studies of patients with breast cancer at stages T1-T4 who received SLNB, Geng et al. [49] reported no statistically significant difference in identification rate between 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%) mapping methods, p=0.180 (Table 4-2).

The SENTinel NeoAdjuvant (SENTINA) trial [46] reported that, when SLNB was performed before NAC, no difference was observed between the combination radiocolloid and blue dye (dual tracer) and radiocolloid alone (single tracer) (99.5% [399 of 401] vs. 98.8% [573 of 580], p value:not reported*)*. When SLNB was done after NAC, the addition of blue dye was associated with a significant increase in detection rate (76.2% [80 of 105] vs. 52.9% [126 of 238] in clinically negative patients who had a pathologically positive sentinel node before NAC and received a second SLNB followed by ALND [arm B of the trial], and 87.8% [144 of 164] vs. 77.4% [301 of 389] 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], p values: not reported). In arm C dual tracer was identified by the authors as one of the factors affecting increased detection rate in multivariate analysis: OR, 2.13; 95% CI, 1.01 to 4.46, p=0.046. This study included about 30% of patients with stage T3-T4 disease, making this evidence partially indirect. Tausch et al. [48] reported an identification rate of 82% with blue dye alone, 85% with radioisotope alone, and 94% with the combination, (p=not reported*)*.

False negative rate

The SENTINA trial [46] reported no statistically significant difference in false negative rate for single compared with dual tracer. The American College of Surgeons Oncology Group (ACOSOG) Z1071 trial [51] reported no statistically significant difference in false negative rate for dual tracer (10.8%) compared with single tracer (20.3%), p=0.05. The SN-FNAC trial [52] also reported no statistically significant difference between dual tracer (5.2%) and isotope only (16%), p=0.190.

Hunt et al. [53] showed a statistically significant lower false negative rate with blue dye combined with radiocolloid compared with blue dye alone (OR, 2.61; (95% CI, 0.78 to 8.76), p<0.0001).

Gimbergues et al. [54] reported that factors impacting false negative rate when radiocolloid alone was used were larger tumour size (5.7% for T1-T2 vs. 28.5% for T3 cases, p=0.045) and positive clinical lymph node status before NAC.

b) Patients who were initially node negative and did not receive NAC

Direct patient outcomes

We did not identify any study that reported on direct patient outcomes for this group of patients.

Diagnostic outcomes

Identification rate

O'Reilly, et al. [47] reported no statistically significant difference in identification rate between single (radioisotope) versus dual tracer (radioisotope and blue dye combination).

Kang et al. [60] reported no difference in identification rate between radiocolloid and combination radiocolloid and blue dye (98.4% vs. 98.4%, p=0.8)

Nathanson et al. [50] reported that identification rate 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<0.0001). Identification rate was 96.5% for more experienced surgeons using dual tracer (radioisotope and blue dye combined) and 78.5% for less-experienced surgeons using single tracer (blue dye). When dual tracer was used, and junior surgeons were mentored and a protocol was in place, the difference between more versus less-experienced surgeons was not statistically significant (96.5% vs. 94.2, p=0.277).

False negative rate

None of the included trials on this population reported data on false negative rate by single or dual dye.

B) US-guided SLNB compared with traditional SLNB

Direct patient outcomes

OS

Verheuvel et al. population study [55] reported a worse OS for US-guided SLNB compared with traditional SLNB. OS rate was 81.6% vs. 89.6% at 5-year, p<0.001, and in multivariate analysis HR, 1.38; 95% CI, 1.23 to 1.56, p<0.001. In a sensitivity analysis, excluding patients 70 years old or older, the method of staging was no longer significant.

Disease control, quality of life, adverse events or complication rate, ability to map, and procedure completion rate

No data are available at this time.

Diagnostic outcomes

Van Wely et al. [117] compared with each other three groups of patients: those who had ALND after a positive biopsy (US+/biopsy+), those who had ALND after a negative biopsy and a positive SLNB (US+/biopsy-/SLNB+), and those with no suspicious nodes at US, but who had a positive SLNB (US-/SLNB+). Patients with a positive biopsy had a greater likelihood of having

more positive nodes than those with a negative biopsy (RR, 0.57; 95% CI, 0.49 to 0.67, p<0.001), and the authors concluded that this group of patients is most likely to benefit from further axillary treatment (i.e., ALND). Conversely, due to the low probability of >3 nodes involved in patients with negative biopsy (RR, 0.69; 95% CI, 0.43 to 1.12), or negative US (RR, 0.99; 95% CI, 0.89 to 1.10), the authors suggested that these patients can forego further axillary treatment (Table 4-2). In patient treated with NAC, Caudle et al. [61] showed a false negative rate of 4.2% (95% CI, 1.4 to 9.5) for the clipped node: of 191 patients who underwent ALND (reference standard), residual disease was identified in 120 (63%), and the clipped node revealed metastases in 115 patients. When SLNB alone predicted nodal status: seven false negative events were detected in 118 pts: false negative rate for SLNB alone (dual tracer: 55%): 10.1% (95% CI, 4.2 to 19.8). When SLNB combined with the evaluation of the clipped nodes false negative rate was significantly better for than for SLNB alone: 1.4% (95% CI, 0.03 to 7.3) vs. 10.1% (95% CI, 4.2 to 19.8), p=0.03.

Kramer et al. (2016) [56], Kim et al. (2016) [57], and Cools-Lartigue et al. (2013) [58] reported variable false negative rates, (false negative rate: 6.4% [137 of 2130 patients], 4.8% [8 of 23 patients] for invasive lobular carcinoma, and 40.8% [20 of 49 patients], respectively.

C) Ultrasound compared with SLNB

Direct patient outcomes

No data are available at this time.

Diagnostic outcomes

Identification rate

No data are available at this time.

False-negative rate

The Stachs et al. trial [59] examined what factors are associated with a false negative result of axillary US as a staging procedure. When histopathology after ALND or SLNB was the reference standard the false negative rate of axillary US was 23% (87 of 378 pts). Size of nodal metastases ≤10 mm was an independent predictor for false negative axillary US (OR, 2.66; 95% CI, 1.81 to 3.91, p=0,001).

DISCUSSION AND CONCLUSIONS

Recommendation 1

For Recommendation 1 we recognized the recent Society of Surgical Oncology's Choosing Wisely statement, and considered in the context of our goals of preventing morbidity from additional staging interventions when these do not impact on patient survival, of respecting individual patient's preferences and clinical circumstances, and of avoiding increased morbidity from overtreatment.

This recommendation was based on studies [5,6,8] that compared SLNB with ALND, and did not report on quality of life, adverse events, and complication rates. The results of the upcoming trials [9-11,123,124] that compare SLNB with no staging may change this recommendation.

We stated that SLNB as a first-line axillary staging procedure can be offered to patients who are clinically node negative on physical examination and/or US, or are found to be sonographically abnormal on imaging without confirmatory biopsy. This statement aligns with exisiting clinical guidelines as described in the National Comprehensive Cancer Network (NCCN) pathway [277].

Recommendation 2

Surgical interventions

For surgical trials we endorsed the ASCO 2017 recommendation since SLNB is the current standard of practice for node-negative patients.

Radiotherapy interventions

No existing guidelines provide recommendations on radiotherapy interventions.

We gave a weak recommendation for loco-regional irradiation in selected patients. Consistent with Recommendation 1, we underlined the importance of discussing with the patients the advantages and disadvantages of this treatment, as well as of considering each situation individually. The evidence base for this recommendation is composed of four unique fully published RCTs [23-25,86] and several of their corollary studies. The meta-analysis of individual patient data [86] reported data on 700 women who were pathologically node negative, and were treated with breast surgery, ALND, and loco-regional nodal irradiation compared with no loco-regional irradiation. We decided not to use this trial because, after discussion with the internal review panel, we realized that treatment modalities have changed so much since the included patients were treated, over 20 years ago, that the collected data are not valid any longer today.

In general, patients with early-stage disease and fewer than three positive nodes can safely undergo axillary radiation using standard tangents or two-field radiation instead of a completion ALND. There is general consensus that loco-regional nodal irradiation should be reserved for high-risk patients for whom the determination of high risk is based on patient and tumour location/features and not whether the patient undergoes an ALND, and that loco-regional nodal radiation should not simply be applied to patients with one or two positive nodes because they did not undergo an ALND. However, there may be high-risk characteristics that increase concern for the radiation oncologist that would expand the use of axillary radiation beyond our recommendations. These may include: young age, triple negative disease, human epidermal growth factor receptor 2 (HER2)/neu-positive disease, high-grade primary or possibly gross, extranodal extension.

Recommendation 3

In this guideline we did not provide any recommendations for patients with DCIS, because of our definition of early-stage breast cancer.

We endorsed the ASCO 2017 recommendation 2.1 for women who have two positive nodes or less; for women who have three positive nodes at SLNB, or for those who would have been excluded from the trials on which this recommendation is based (i.e., the Z0011 [26-28], and the IBCSG 23-01 [29,30]). We recommend avoiding an ALND after careful consideration of the clinical circumstances and patient values and preferences in the choice of treatment.

ASCO also issued a recommendation for women who had mastectomy. ASCO Recommendation 2.2 for these patients reads: *"Women with early breast cancer who are node positive and are receiving mastectomy: Clinicians may offer ALND for women with early-stage breast cancer with nodal metastases found in SNB specimens who will receive mastectomy (Type: evidence based; benefits outweigh harms. Evidence quality: low. Strength of recommendation: weak) (ASCO 2017 guideline [3,4])"*. This recommendation was based on an unplanned subgroup analysis of 86 patients from the IBCGS 23-01 trial who experienced nine events: HR, 0.52; 95% CI, 0.09 to 3.10. Because of the small number of patients in this unplanned subgroup, we decided not to endorse the ASCO recommendation. Rather, the way we phrased our recommendations for patients who did not fit the inclusion criteria of the included trials takes into account ASCO recommendations 3.1, and 3.3, and 3.4.

Our recommendations for post-mastectomy patients with one to two positive lymph nodes fits with the treatment algorithm outlined by NCCN guideline version 3.2019 (available at: https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf), as these patients should be considered based on ACOSOG Z0011 [3,4] criteria. In these patients, ALND can be safely avoided in favour of radiation to the axilla similar to what would be offered to breast-conserving surgery patients (chest wall radiation overlapping axilla or limited to axilla without extending to loco-regional radiation other than in specific circumstances).

Limited data to drive these recommendations are supported by expert opinion given that early-stage breast cancer with one to two positive nodes is expected to behave biologically in a similar way to disease excised by breast-conserving surgery. Therefore, these post-mastectomy patients should be treated similarly to breast conserving patients using ACOSOG Z0011 [3,4] which determined that they can safely avoid ALND. Patients with three or more positive nodes should undergo axillary dissection.

The NCCN Version 3.2019 guideline [277], which was excluded from this review because it was not based on a systematic review of the evidence, similar to our recommendation, supports the option to avoid ALND in patients whose positive sentinel nodes contain *only* micrometastases (0.2 mm to 2 mm). Patients with a combination of micro- and macrometastases should be treated according to the number of positive nodes.

Several ongoing trials will clarify issues that are still undefined: the POSNOC trial (NCT02401685) is looking at the role of axillary treatment in patients with one or two sentinel nodes with macrometastases. The INSEMA trial (NCT02466737), SENOMAC (NCT02240472, NCT03083314, NCT01468883), and SERC trials (NCT01717131) aim to show that less axillary surgery is better with patients experiencing less surgical complications; the MA39 (NCT03488693, NCT00005957) trial is testing the need of loco-regional irradiation in low risk ER+, HER2- breast cancer patients with one to three involved nodes; and the OPTIMAL trial (NCT02335957) is investigating whole breast radiation compared with loco-regional irradiation. The final publication of these further studies will possibly strengthen or change our recommendation.

Recommendation 4

The lack of relevant evidence reporting on direct patient outcomes for patients who are clinically lymph node negative at diagnosis prompted us to issue a recommendation based on the Working Group members' expertise. For patients who were lymph node positive at diagnosis, although the evidence base is of moderate to low certainty, the Working Group issued strong recommendations based on its members experience.

This recommendation was drafted in an effort to follow the patient flow through NAC, typically done to downsize primary tumours from operable by mastectomy to operable by breast-conserving surgery. For clinically node-negative patients, where the value of neoadjuvant systemic therapy is clear based on surgical downsizing or tumour subtype, the recommendation to time SLNB with definitive surgery will reduce additional resource utilization, and will avoid patients with pathologically positive nodes having to undergo a completion axillary dissection after NAC.

Recommendations for patients with clinically positive lymph nodes were based on a paradigm shift in treatment decision making from diagnostic staging to post-NAC restaging of the axilla with SLNB for clinical responders. This new recommendation should avoid unnecessary ALND for those rendered node negative by NAC who are then recommended to receive axillary radiation instead. We gave this strong recommendation despite the lack of long-term data on clinical outcomes in patients treated in this way because many emerging studies have supported re-staging patients after NAC and avoidance of morbidity from ALND is a relevant survivorship concern for patients and clinicians. Additionally, among breast experts, this approach to patient care is being routinely done.

We did however recommend ALND and loco-regional radiation for patients who remained clinically node positive after NAC or had residual positive lymph nodes based on surgical pathology.

When the trials that are now ongoing come to completion, this recommendation may be revised.

Recommendation 5

A) Single tracer compared with dual tracer

We recommended not adding blue dye to radiocolloid on a regular basis for sentinel lymph node identification. The evidence base for this comparison is not strong, and the success of this procedure depends from the operator's expertise, a factor that was not regularly mentioned in the included trials, as well as from the techinques used. There are indications of risk of anaphylactic reactions with blue dye. A meta-analysis published in 2006 [278], before our cut-off date and therefore not included here, suggests that single tracer identification may be acceptable, and indeed the marginal benefit with the addition of blue dye seems to decrease with increasing surgical experience.

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

We recommended not screening the axilla of patients who are clinically lymph node negative, and those with smaller tumours (i.e., T1 to T2) with US, and to screen with US and core biopsy only those patients who have larger tumours (i.e., >5 cm in diameter) or those extending through skin or deep chest wall structures (T4), although these fall outside of the scope of this guideline for early-stage disease. In both the adjuvant and neoadjuvant setting, recent clinical practice is for radiologists to screen the axilla in clinically node-negative patients with US and to perform core biopsy. This shift in standard practice will avoid completion axillary dissection in the majority of patients with clinically node-negative early stage resectable tumours who would be deemed lymph node positive by US plus or minus biopsy confirmation, as most of them will have two or fewer positive nodes. Avoiding preoperative detection of positive axillary lymph nodes in patients planning to go for primary surgery rather than NAC will

minimize morbidity from the surgery without conferring clear clinical benefit. For this reason, we recommended avoiding axillary US in clinically node-negative patients going to primary surgery. In contrast, using axillary ultrasound plus US-guided core biopsy to confirm nodal positivity in clinically node positive patients will permit clinicians to determine whether NAC has resulted in a clinical response in the axilla. Treatment decisions should be based on response to NAC in these patients, where patients rendered clinically node negative by NAC should have definitive axillary staging by SLNB at the time of surgery. Those who remain clinically node positive and do not demonstrate a significant response to NAC should undergo ALND as axillary staging and regional control, followed by loco-regional radiation.

C) Ultrasound staging versus surgical staging

No evidence was available at this time for using imaging modalities such as axillary US as the definitive staging procedure instead of SLNB, and therefore, we could not recommend it.

We comprehensively summarized the evidence and provided recommendations for the management of the axilla in female patients with early-stage breast cancer; we covered both surgical and radiotherapy interventions, for which evidence-based guidelines are presently lacking.

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. Having said that, we support the generalization of these guidelines to male patients with breast cancer. Other potential limitations of this work include the lack of focus on new/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-centred outcomes such as morbidity from interventions, such as lymphedema rates in patients treated by axillary radiation rather than ALND. Hopefully, these gaps will be filled with future updates to this document. The recommendations are based on clinical trials that generally excluded, or had a minimal representation of patients with lobular carcinoma. Very few studies specifically address lobular carcinoma, making this evidence insufficient to make specific recommendations for these patients. However, we support generalizing these recommendations to patients with lobular cancer until future data changes our understanding of how to manage the axilla in these patients.

We hope that this guideline standardizes treatment decisions in managing the axilla for early-stage breast cancer patients while minimizing morbidity from overtreatment without clear clinical benefit.

Management of the axilla in early-stage breast cancer

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC Report Approval Panel (RAP) (Appendix 1). The results of these evaluations and the Working Group's responses are described below. The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2. The comments of patient representatives and the Working Group responses are summarized in Table 5-3. The main comments from the ASCO reviewers, and the Working Group's responses are summarized in Table 5-4.

Expert Panel Review and Approval

Of the 11 members of the GDG Expert Panel, ten members cast votes and one abstained, for a total of 90.9% response in May 2020. Of those that cast votes, 90.9% approved the document.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
Figure 1 Algorithm 1) No radiotherapy for breast-conserving therapy with one to two nodes? 2)In node positive scenario (≥3), I would recommend presentation as standard whole breast or chest wall plus regional radiotherapy instead of regional radiotherapy only. Those patients with breast-conserving therapy T1a and three or more lymph nodes—why not a ALND? You mention that in the discussion that those with three or more positive lymph nodes should have a ALND but do not mention T1A as an exception. I would suggest putting this in the discussion as a possible option to skip radiation and ALND in those with small tumours if they are having systemic therapy. Are you recommending no ALND for the breast-conserving therapy with T1a and one to three positive nodes ?	Figure 1 was edited; the node positive box after SLNB has now only three arms A note was added (note e) to arm 1 of the three arms to explain that in some rare circumstances it is possible to avoid radiation. Regional radiotherapy was changed to loco-regional radiotherapy throughout, and a definition was added for it in the list of definitions.
Figure 1. Note a This will be confusing if include biopsy-positive in cN-	No change was made, as it is important to keep this definition
Figure 1 Note c Data for removing clipped node does not always state you have to have three nodes if clipped node removed	We do not know how many lymph nodes to include if using clip, but we know that the dual tracer and three nodes harvested achieve best false positive rate. There are insufficient data on to how many nodes are clipped; therefore, we are not mandating a specific number of nodes
Definitions 2) Clinical versus pathological positivity You should clarify that pathologic positivity does not include lymph nodes with only isolated tumour cells.	We added at the end of the paragraph: *We do not consider lymph nodes to be pathologically positive if they only contain isolated tumour cells.*
Recommendation 1: Qualifying statement. Should we not put in a statement that if SLNB is being considered to be omitted that a consultation with a medical oncologist to discuss anti-hormonal therapy should have been completed before surgery? Otherwise how will the surgeon know that the patient will be treated with hormonal therapy?	We added at the end of the paragraph: *If omission of SLNB is considered, a consultation with a medical oncologist can be considered before surgery, to discuss hormonal therapy.*
Recommendation 2 You should include definition of high-risk feature – it is not clear in the qualifying statements portion for this recommendation but is outlined well in the Recommendation 3 statement. Key evidence section: Consider leading this section with description of the EORTC and MA20 node-negative patients and then describing impact on outcomes in both these trials, and toxicities in both of these trials. As below, I would consider dropping the EBCTCG portions because the women included were treated before 2000, and effects of treatment are not comparable today.	Definition #6 has been added for high-risk features Data on the EBCTCG trial [86] have been deleted from the key evidence section. A note has been made in Section 4, as well.

Comments	Responses
Recommendation 3 D) Radiotherapy compared with no treatment It is not clear if a patient has T1a and three or more positive lymph nodes that radiation can be omitted and the patient also does not need an ALND. Above you indicate that patients with three or more positive lymph nodes, then ALND or regional radiation is recommended.	We deleted the paragraph: "Clinicians may offer the option of omitting radiotherapy of the regional nodes in addition to chemotherapy or hormonal therapy being given to patients with unilateral invasive cancers of small size (i.e., T1a), and none to three positive nodes with favourable tumour features (e.g., such as ER+ undergoing hormonal therapy) and clear margins." And we modified the sentence: "In patients with unilateral invasive cancer of small size (i.e., T1a), favourable tumour features (e.g., ER+ undergoing hormonal therapy), clear margins, and one to three positive nodes, treated with chemotherapy or hormonal therapy, clinicians may offer the option of omitting radiotherapy of the regional nodes." Into: "In patients with unilateral invasive cancer of small size (i.e., T1a), favourable tumour features (e.g., ER+ undergoing hormonal therapy), clear margins, and one to three positive nodes, treated with chemotherapy or hormonal therapy, clinicians might offer the option of omitting radiotherapy of the regional nodes.". In recognition that the Killander et al. studies [40,41] included patients recruited a long time ago, we added a note in the patient values section in regard to the qualifying statement that says we suggest to omit radiotherapy in older women as to say that these studies used older techniques.
Recommendation 4B initially node-positive patients: "For patients who were initially clinically and biopsy proven node positive, and became node negative after NAC the Working Group members recommend SLNB to restage the axilla, either using clipping of the positive node at diagnosis, or using dual tracer and at least three sentinel nodes in order to minimize the false negative rate and optimize accuracy of the procedure." 1) This situation is not addressed in radiotherapy recommendation. 2) Should we not also include something about the need for radiological assessment of nodes for clinical nodal staging if considering NAC so as to accurately identify patients with suspicious nodes upfront given that this may impact the radiation therapy offered? There are patients that present with non-palpable positive nodes with early-stage breast cancer but the way the recommendation is currently written – the only patients who should have radiological and potential biopsy are those that initially present with palpable lymph nodes. Radiological axillary staging currently happens regularly at some institutions in those being considered for NAC but not all. I would feel this is especially important given we are recommending against SLNB prior to NAC (which I agree with). I see that we have put in axillary US pre-NAC for staging in the Figure 1 algorithm but this should also be addressed in body of this recommendation as well. 3) Recommendation 4 Justification section, Desirable, Undesirable Effects, and Balance Of Effects:	1, and 2) We added the sentence at the end of the paragraph: "At this time, we also recommend loco-regional radiation for these patients, regardless of pathologic status of sentinel lymph nodes." 3) We added the sentence at the end of the paragraph: "In patients who receive NAC and remain node positive, the current standard is to recommend ALND with loco-regional radiotherapy. Data from ongoing studies may change this practice."

Comments	Responses
"For patients who are initially clinically and biopsy-proven node positive, given the absence of data to guide management, the Working Group members consider loco-regional nodal irradiation the safest approach." Surgical recommendations for this group (ALND for initially clinically node positive with residual node positive disease or sentinel lymph node for -) are not discussed here?	
Recommendation 5, qualifying statement B) "Lymph nodes which are biopsied under ultrasound guidance and are positive at diagnosis need to be clipped, such that the node containing the clip can be localized to make sure it is excised at surgery. 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." This would cause a practice change within imaging, but would conform to your recommendation. If you feel this change is not accurate or necessary, that is fine with me.	We are not actually recommending that every biopsied node be clipped because this is practice-changing and may not be affordable. We leave this to institutional practices. All we are saying is that if your institution is clipping the nodes, they need to be localized at surgery. We rephrased: *If a clip is used to identify a biopsied lymph node at diagnosis, the node containing the clip needs to be localized to make sure it is excised. If dual tracer is used, three or more sentinel nodes have to be identified. If three or more sentinel nodes are not identified in a patient who has had NAC according to standard sentinel lymph node techniques, an axillary dissection is recommended.*

RAP Review and Approval

Three RAP members, including the PEBC Director, reviewed this document in April 2020. The RAP conditionally approved the document on June 1st, 2020.

Table 5-2. Summary of the Working Group's responses to comments from RAP.

Comments	Responses
1. This is a massive and very detailed document. I have offered some edits to help make it easier for the reader. I also think that some simple techniques such as breaking up large paragraphs, ensuring appropriate punctuation and avoiding run-on sentences would help the reader to digest this information more easily. Hopefully the edits I have suggested will be helpful in this regard. The final recommendations need to be stated very clearly and succinctly if any of this document is to be read by busy clinicians, especially surgeons. The broad objectives are clearly stated at the beginning of Section 2 but it would be helpful if there were specific objectives that corresponded to the recommendations and that these objectives were stated at the beginning of the presentation of the detailed data supporting each of the recommendations Conditionally approve.	We introduced all the suggested in-text changes to improve style and readability. In Section 2, we added Specific objectives before each recommendation to orient the readers. We also revised the recommendations to make them an easier/faster read for busy clinicians (e.g., we eliminated the subtitles Radiotherapy interventions and Surgical interventions from Recommendation 2)
2. Minor editorial corrections suggested	We made the suggested in-text chages
3. A large and well written document. A few minor suggestions.	We implemented the suggested changes from in-text comments.

Table 5-3. Summary of the Working Group's responses to comments from the patients representatives Consultation Group.

Comments	Responses
Several in-text editorial changes were suggested in the PATIENT VALUES sub-section in the Justification and interpretation of Recommendations 3, 4, and 5 to highlight patients points of view.	We made all the suggested editorial changes.
All recommendations are clear and unambiguous; however, Recommendations 1 and 2 seem a bit less clear than Recommendations 3, 4, and 5. Not a critical point, but for Recommendations 1 and 2 radiotherapy interventions were presented first, and then surgical interventions. For 3 and 4, the order was reversed. Recommendation 1. The generalizability statement adds to the recommendation, i.e. it applies to all women with early-stage breast cancer and likely to men. Recommendation 2. Looking at radiotherapy interventions, benefits are moderate. It was noted that the Working Group identified this as a weak recommendation for this treatment. Did the Working Group have difficulty reaching consensus or is it that the data are so weak? The Working Group cannot recommend regional node irradiation for node-negative patients. Should be case by case, but again includes using a patient centred approach. Recommendation 3. There are clear conditions to be met in the patient's condition for each treatment option, but again discussion with the patients and a case-by-case basis. Recommendation 4. As before, the parameters for the treatments are well spelled out. Clearly stated e.g. the working group members is to time the SLNB after NAC and not before in clinically node negative patients who will receive NAC. Are the parameters too specific and/or limited so they may not consider all cases? Recommendation 5. This one was clearly delineated.	The order of the interventions has been changed to match with surgical interventions first and radiotherapy interventions second for all recommendations. An overall statement has been added to make clear that for all recommendations a patient-centred approach is required. The word "women" has been changed throughout to "patients". A generalizability statement has been added to Recommendation 1, and referred to in the other recommendations to clarify what the management of this condition in male patients is. To clarify Recommendation 2, the type of patient that are suitable for radiotherapy interventions have been specified. To further clarify the text, the "Justification" has been moved together with the "Interpretation of the evidence".
Section 2 was easy to follow and understand. Lots of evidence, not enough shown from ongoing trials. Recommendation 1. It seems a good support for SLNB A Choosing Wisely. While omitting SLNB has no impact on survival, there is a risk of recurrence. While there are limited studies, they seem strong enough. In the justification, one of the studies reported on quality of life (pain or restriction in movement of arm). In the interpretation for Recommendation 1, considered OS, DFS, and local control as critical outcomes and quality of life as an important outcome. The section on Certainty of the	No reponse needed.

Comments	Responses
evidence was good. The differentiation is meaningful: for example, Recommendation 1 support by Working Group was moderate to high. Recommendation 2. Qualifying statements for the surgical interventions (identifies a good list of studies on which the Recommendation 2 is based that excluded categories of patients). Again, this helps the specialist accept, reject or modify this recommendation. For patients in the list, the decisions should be made after discussion between patients and clinicians. For the Radiotherapy subsection, the certainty of the body of evidence that supports radiotherapy interventions is moderate. No current clinical trials, but examined the results of clinical trials and there was some discussion of mortality rates after 20 years, some treatments done, had a worse mortality rate for those that had radiotherapy. None of the included radiotherapy three studies reported on quality of life and one was at a high risk of bias. There was a very low quality of evidence supporting the use of radiotherapy in addition to chemotherapy for post-mastectomy women. For the surgical interventions, used eight studies with one more added, and no new evidence that would change the 2014 ASCO recommendations. For the surgical interventions, I like the certainty as moderate to high for survival outcomes, low for quality of life, and moderate for recurrence and adverse events outcomes. Recommendation 3. The qualifying statements clarify the recommendations, I like that the Working Group cites that for exactly 3 positive lymph nodes, there is not enough evidence to make a recommendation, however, the working group members recommend proceeding with ALND and considering regional radiation. That does provide some direction to the clinician. When the evidence is not present, they state that it is not available and recommend an alternative plan. (Page 12 – At this time, evidence from randomized trials is not available to support the recommendation … we believe that clinicians and patients should discuss advantages and disadvantages of all options depending on the characteristic of the tumour, other clinical circumstances, and patient preferences. I thought the analysis of the key evidence was well detailed. The Working Group clearly stated pros and cons from the studies. Recommendation 4 There are not much supporting data for A and B in Recommendation 4, but use the expertise of the Working Group. This raises the question about clinicians not in the Working Group. Do they have a chance to offer alternatives or question the rationale?	

Comments	Responses
I like that the Working Group identified two randomized trials due in 2024 and 2028. This will make the clinicians watch the formative data as they are released (assuming some data may be released over the trial). Recommendation 5 There was extensive discussion on this recommendation and it appears extensive studies support the recommendation. I like the sections on certainty of the evidence. They establish low, medium, etc. on various conditions.	
Although about the age of women, what is the age of older or younger? Recommendation 1. The Working Group noted that some patients may experience axillary recurrence and suggested this possibility to be discussed and evaluated, according to individual patient's values and preferences. I appreciated at almost every stage the patient had the opportunity to be part of the decision. There are patients who want the specialists to make the decision and that is fine, but the opportunity has to be present.	The age of older or younger women has been spelled out throughout.
All treatments seemed acceptable; shared decision making, quite refreshing patient preferences taken into account. Page 15 – Some patients may consider radiotherapy interventions acceptable, and others less so.	No responses needed.

Table 5-4. Comments from ASCO reviewers, and Working Group's responses.

Questions	Reviewer 1 – Round 1: October 18, 2020	Reviewer 2 – Round 1: October 18, 2020	Reviewer 2 – Round 2: December 14, 2020	Reviewer 2 – Round 3: February 16, 2021
1. Does the introduction provide the reader with a reasonable background and rationale for the development of this guideline? Is it clearly explained why—and for what purpose—this particular guideline is needed?	Yes *If not, please describe what you feel the shortcomings are, and suggest ways that the introduction could be improved:* Adequate and easy to read.	Yes	NA	NA
Authors' Response to Reviewers' Comments relative to Question 1:	No response required	No response required	NA	NA

Questions	Reviewer 1 – Round 1: October 18, 2020	Reviewer 2 – Round 1: October 18, 2020	Reviewer 2 – Round 2: December 14, 2020	Reviewer 2 – Round 3: February 16, 2021
2. Does the evidence review identify and describe the most important and/or relevant studies?	Yes *Comments:* Authors provided the rationale for the recommendations and their limitations -as well as the pertinent limitation for the studies- in the guideline and a more extensive review in the data supplement.	Yes	NA	NA
Authors' Response to Reviewers' Comments relative to Question 2:	No response required	No response required	NA	NA
3. Were important studies given enough discussion in the text?	Yes *Comments:* Yes, however, some sections talk about the results first and then about the study population, would start with the study population to provide context to the readers.	Yes	NA	NA
Authors' Response to Reviewers' Comments relative to Question 3:	Change made, page 15 and 16 of the manuscript – we added populations for each objective.	No response required	NA	NA
4. Are any important studies (particularly, RCTs or meta-analyses / systematic reviews) not identified or cited?	No	No	NA	NA
Authors' Response to Reviewers' Comments relative to Question 4:	No response required	No response required	NA	NA
5. Is the evidence/literature review section comprehensive yet concise?	Yes	Yes	NA	NA
Authors' Response to Reviewers' Comments relative to Question 5:	No response required	No response required	NA	NA
6. Does the information in Data Supplement provide sufficient background/rationale	Yes	Yes	NA	NA

Questions	Reviewer 1 – Round 1: October 18, 2020	Reviewer 2 – Round 1: October 18, 2020	Reviewer 2 – Round 2: December 14, 2020	Reviewer 2 – Round 3: February 16, 2021
and additional information?				
Authors' Response to Reviewers' Comments relative to Question 6:	No response required	No response required	NA	NA
7. Are the recommendations supported by the evidence? If any assumptions are made in formulating the recommendations or in linking the evidence to the recommendations, are these assumptions reasonable and clearly articulated?	Yes *Comments:* Assumptions -generalizations from RCT- and expert recommendations are clearly articulated otherwise clear evidence is provided for each recommendation.	No Unless stated below, I agree with the substance of the recommendations from the authors. I will use this box to detail the portions of the recommendations that I do not think are supported by the literature or in direct conflict with what the authors state: **Recommendation 1** · SLNB should be considered for staging selected low-risk patients with clinically node-negative (T1N0) early-stage breast cancer who do not have significant competing comorbidities. The authors provide no guidance for the elderly breast cancer patient. A global recommendation for ALL T1N0 ER+HER2- breast cancer patients to be considered for a SN without mentioning age is ignoring multiple prospective trials. The authors present a qualifying statement, but this do not give true guidance and leaves the user of this guideline perplexed as to what to actually do. Qualifying statement for **Recommendation 1:** "We are aware of the Choosing Wisely statement released on July 12, 2016, and updated on June 20, 2019 by the Society of Surgical Oncology (SSO) available at: http://www.choosingwisely.org/clinician lists/sso-sentinel-node-biopsy-in-node-negative-women-70-and-over/ that stated: "Don't routinely use sentinel node biopsy in clinically node negative women ≥70 years of age with early stage hormone receptor positive, HER2 negative invasive breast cancer" if they will be treated with hormonal therapy. If	**Recommendation 1:** This reviewer does not feel that the authors have had given credence to the previous critique to Recommendation 1. For older patients (over 70 years of age) sentinel lymph node biopsy for low risk T1 N0 ER+ HER2neu-negative breast cancer patients less than 3 cm in size and ER+ HER2 negative there is good evidence in the literature (Hughes KS, 2004, Rudenstam CM 2006, Martelli G 2012) to omit any axillary staging procedure including a sentinel node in this patient population. This is both supported by three clinical trials (cited above, with additional follow-up publications verifying the initial conclusions with longer follow-up) as well as choosing a wisely statement of the Society of Surgical Oncology. Until the authors of the guideline incorporate a phenotype and age approach to Recommendation 1, this reviewer cannot accept their revision of Recommendation 1. I would agree that all clinically node negative low risk T1 N0 ER-, PR- HER2+ and all triple negative breast cancer patients should be considered for a sentinel node. I would also concur that all T1, small T2, low risk ER+, HER2- patients less than 70 years of age should be considered for a sentinel node procedure.	**Recommendation 1** 1. This reviewer again does not feel that the authors have had a thorough literature review nor properly cite relevant articles. In their supplemental table they have included references from 2006, 2012 and 2014 but neglect Hughes KS et al., seminal work in NEJM 2004 and long-term CALGB9343 follow-up in Journal of Clinical Oncology in 2013. The omission of this work leaves this reviewer thinking the authors have not done a diligent and thorough literature review. Is this a bias? Is this an oversight? 2. Their verbiage still is not strong enough for this reviewer to feel that they properly have investigated and made appropriate recommendations for patients with T1, ER+, clinically node negative breast cancer (over the age of 70).

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		omission of SLNB is considered, a consultation with a medical oncologist can be considered before surgery, to discuss hormonal therapy." Furthermore, the crux of omitting SN AND whole breast radiation therapy is under the assumption that the patient WILL take anti-estrogen therapy. **Recommendation 4, B)** Initially node-positive patients. For patients who were initially clinically and biopsy proven node positive, and became node negative after NAC, we recommend SLNB to restage the axilla, either using clipping of the positive node at diagnosis, or using dual tracer and at least three sentinel nodes in order to minimize the false negative rate and optimize accuracy of the procedure. This is an extremely controversial topic and the authors seem to make the case that this is very straight forward. They reference the data from ACOSOG Z1071 but the authors neglect to state that the false-negative rate for Z1071 was 12.6% (above the pre-determined false negative rate). The actual finding in Z1071 (besides improved accuracy of dual tracer, three nodes removed) that has led to an actual promising possibility is removal of the "clipped" node (Caudle AS et al.,) The authors would be bettered served to acknowledge this area of controversy as opposed to let the reader think this area has a clear solution. Furthermore, the "sentinel" node is not always the "clipped" node. The authors need to be very clear about the difference between these two terms.	To be a useful guideline in 2020 and beyond, the authors must acknowledge the different behaviors of the various phenotypes of breast cancer (Perou CM, Nature 2000). To recommend a blanket for all phenotypes where clear differences exist, is not providing a useful guideline. **Recommendation 4:** The authors write this Recommendation as if the controversy in axillary management following neoadjuvant systemic therapy is clear, straight-forward and supported by level 1 evidence. This reviewer cannot accept that the literature is clear on how to handle an axilla following neoadjuvant systemic chemotherapy and is supported by the myriad of talks at San Antonio Breast Conference 2020 attempting to shed clarity on this topic. For patients that started node positive, there is conflicting data regarding how the axilla should be managed. The authors choose to cite a post hoc, unplanned analysis that demonstrated that the false negative rate in ACOSOG Z1071 (Boughey JC 2013) was 9.1% when dual tracer was used and at least 3 lymph nodes were identified. However, this was a post hoc, unplanned analysis. The original planned analysis demonstrated a false-negative rate of 12.6%. Furthermore, the exciting post hoc findings in ACOSOG Z1017 is the removal of the “clipped” node where the false-negative rate was 6.8%. Trying to verify this approach, MD Anderson (Caudle AS 2016) embarked upon a prospective trial of removal of the sentinel node and the “clipped	**Recommendation 4:** Management of the axilla post-neoadjuvant therapy 1. The guideline and this reviewer seem to be more aligned that management of the axilla post-neoadjuvant therapy. However, this reviewer is mystified why the guideline is trying to balance supporting clinicians who have access to clips and clinicians who do not. Personally, I do not know of any breast surgeon who does not have access to clips in the breast. Are the reviewers insinuating that have access to clips but have mammographers that aren’t willing to place them in axillary node? For context, as an American Board of Surgery Complex General Surgical Oncology Certifying Exam examiner, failure to place a clip following in a breast core would be viewed as a critical fail. Again, I completely agree that the level 1 evidence for what to do with the clipped node is a separate issue, but to imply that there is lack of access to clips that can be placed in the breast or the axilla is not congruent with modern 2020/2021 medicine.

Questions	Reviewer 1 – Round 1: October 18, 2020	Reviewer 2 – Round 1: October 18, 2020	Reviewer 2 – Round 2: December 14, 2020	Reviewer 2 – Round 3: February 16, 2021
			node". They identified a false-negative rate of 12.5% if only the sentinel node was removed, almost identical to the false-negative rate on ACOSOG Z1071. However, if the sentinel node AND the clipped node were removed, the false-negative rate was 2.3%. Thus, the key to a low false-negative in the axilla appears to be the "clipped" node. However, this needs to be verified in other centers. As such, this reviewer cannot accept a Recommendation for a management guideline of the post neoadjuvant axilla as written by the authors when the axilla started node positive. **Recommendation 5** The authors choose to cite ACOSOG Z1071 when the recommendation should be for sentinel node following neoadjuvant therapy with dual-tracer technique. However, now in recommendation 5, the authors choose to omit Z1071 as basis for promoting dual tracer. The sentinel node technique is obviously a more technically challenging procedure postneoadjuvent chemotherapy; nonetheless, dual tracer has clearly been shown to have higher accuracy rates. The authors seem to think that there is a large literature recommending and have seemingly arbitrarily chosen dual tracer should be performed in centers that do less than 100 sentinel node procedures per year. I am unsure where this reference is since no data are provided to document this. Recommendation 6: I concur with changing from multiple tumors to multifocal tumors for recommendation 3a.	
		Recommendation 5 A) Single versus dual tracer. We recommend not to add blue dye on a regular basis for SLNB if the radiocolloid signal identifies the sentinel lymph node in the axilla. There must be a bias amongst the review panel. Time and time again in the literature, dual tracer agent technique has superior accuracy and identification rates as compared to single tracer agent technique. The authors must recognize this. In Qualifying Statement (C) for Recommendation 5 the authors state "If dual tracer is used, three or more sentinel nodes have to be identified." This is the exact finding in ACOSOG Z1071. This is a correct reference for the data, but is in direct conflict with Recommendation 5 A. The authors have a large body of literature to overcome to recommend AGAINST dual tracer technique.		**Recommendation 5**: Dual vs Single Tracer. Again, the authors seem to try to build arguments about strong level 1 evidence and cite a single 2015 reference that states that patients have single versus dual dye in patients with primary breast surgery goes against the overwhelming majority of level 1 evidence demonstrates dual agent tracer is superior (ACOSOG Z10, ACOSOG Z11, NSABP B32, AMAROS just to name a few trials). It is still very confusing to this reviewer why the guideline would continue to propose single agent approach based on a single clinical trial when the majority of clinical trial supports the superiority of dual tracer agent.

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Authors' Response to Reviewers' Comments relative to Question 7:	No Response required	**Round 1** **Recommendation 1:** We changed the statement "We are aware of the Choosing Wisely…" to: "We are supportive of the Choosing Wisely…". We moved this Qualifying Statement statement: "*We are supportive of the Choosing Wisely statement released on July 12, 2016, and updated on June 20, 2019 by the Society of Surgical Oncology (SSO) available at: http://www.choosingwisely.org/clinician-lists/sso-sentinel-node-biopsy-in-node-negative-women-70-and-over/ that stated: "Don't routinely use sentinel node biopsy in clinically node negative women ≥70 years of age with early stage hormone receptor positive, HER2 negative invasive breast cancer" if they will be treated with hormonal therapy. If omission of SLNB is considered, a consultation with a medical oncologist can be considered before surgery, to discuss hormonal therapy*." to be part of the recommendation proper. We agree that the crux of omitting SLN is under the assumption that the patient will take anti-estrogen therapy because it is clear from Choosing Wisely guideline that it was in patients taking hormonal therapy with early-stage ER- disease that avoiding SLN was not associated with any impact on survival or loco-regional recurrence, which is why we felt it was important to contextualize the recommendation within this guideline. **Recommendation 4B** We agree that this is a very controversial topic. We moved the statement: "•Shared decision-making processes should be put in place ~~and a decision aid developed~~ while we await mature	**Round 2** **Recommendation 1:** We added to the first bullet point: "For adult patients <70 years of age …" We added to the second bullet point: "For patients ≥70 years of age with early-stage hormone receptor positive, HER2 negative invasive breast cancer" This makes the age and phenotype approach more visible. The phenotype is repeated within the Choosing Wisely statement as well. As mentioned, this statement was updated by Choosing Wisely in 2019. We had included the Rudenstam 2006, and the Martelli 2012 trials in our review. The Hughes 2004 was published prior to our cut off date of 2007. **Recommendation 4B** We clarified recommendations 4, 2nd bullet point by rephrasing to state: •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 at least three sentinel nodes to minimize the false negative rate and optimize accuracy of the procedure. At this time, we also recommend LRNI for these patients, regardless of pathologic status of sentinel lymph nodes. Before this change it read:	**Recommendation 1:** For Recommendation 1, we understand that the reviewer felt we had not cited key articles in the literature regarding the omission of sentinel node biopsy in patients over 70 and that our verbiage supporting this omission was still not strong enough. In response to the last round of reviews, we had revised this Recommendation 1, putting this recommendation to omit sentinel node biopsy in patients over 70 as the first bullet point, and simplifying the language. Thus, we were initially surprised by this comment, but upon further review realized that the version we had submitted back to the reviewer at the last round did not include these changes. We apologize to the reviewer for this error, and we have ensured that those changes were included in this latest resubmission. Additionally, we believe that the reviewer is making an important point. The CCO-PEBC guideline methodology is quite structured in order to avoid the potential for bias, precisely to avoid this possibility raised by the reviewer. As a result, the CALGB 9343 (Hughes et al, 2013) study was excluded because its outcomes were evaluating radiation-tamoxifen versus radiation to the breast, as opposed to the axilla as required by our inclusion criteria, in early-stage disease. However, we now realize that this study was instrumental in speaking to the safety of avoiding axillary dissection (and now sentinel node biopsy procedures) in these older low risk patients since 2/3 of the patients had no axillary

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		clinical trial data, to enable patient value-based decision making." from the Qualifying Statement to the body of the recommendation. However, we did not advocate for the creation of a decision aid in the recommendation (strikthrough). In the Interpretation of the Evidence section for Recommendation 4, we added the statement reported here in in italics: "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 this potential increased morbidity from ALND." We recommended clipping the node (Recommendation 4B2) because clipping the node and localizing it will provide the lowest false negative rate. However, it remains unknown whether harvesting the biopsied node or not in cases where 3 or more nodes are harvested by SLNB will result in any change in nodal status provided by the three node dual tracer technique, since as the reviewer has mentioned, the clipped node is not the SLN in approximately 25% of the time. Our guideline provides support for both institutions who clip nodes at diagnosis and those who do not (hospitals may find the cost of adding a clip to every nodal biopsy to be outside current budgetary constraints). We reference ACOSOG Z1071 in support of this recommendation because while the overall FNR was 12.6%, there was a statistically significantly lower FNR of 9.1% when dual tracer and at least 3	•For patients who were initially clinically and biopsy-proven node positive, and became node negative after NAC, we recommend SLNB to restage the axilla, either using clipping of the positive node at diagnosis, or using dual tracer and at least three sentinel nodes in order to minimize the false negative rate and optimize accuracy of the procedure. At this time, we also recommend LRNI for these patients, regardless of pathologic status of sentinel lymph nodes. In the Interpretation of the evidence for rec 4 section (page 39): 2nd bullet point, page 39, we added: "We recognize that this area is 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 this potential increased morbidity from ALND", We also added a 3rd bullet point specifically about restaging the axilla after NAC and about clips: "•We recognize that restaging the axilla after NAC as well as the role of clips remain controversial. Further work is ongoing in this area that may help clarify this in the future". We identified the Caudle AS, et al. study, and we included it our systematic review (Question 5). We added the evidence tables for all the studies, including the Caudle AS et al. study, to the online supplementary material. **Recommendation 5**	staging. The low risk of recurrence in these patients therefore informed statements about the safety of avoiding sentinel node procedures. As a result, we appreciate this comment by the reviewer and have navigated the challenges of a structured systematic review by citing this reference in the 'Interpretation of the Evidence for Recommendation 1' section, where we reference the long-term follow-up publication for this study by Hughes et al, 2013, where the authors present sustained low rates of locoregional recurrence, and also discuss avoidance of sentinel node biopsy, even though the study did not meet our inclusion criteria for the systematic review. We believe that this will provide further support for this recommendation, reference key seminal work, while maintaining the systematic review methodology. We hope that this will address the concerns raised by the reviewer. **Recommendation 4:** In Recommendation 4, the reviewer expressed concerns regarding the recommendations being provided for both institutions that use biopsy clips in the axilla and those that do not. We agree with the reviewer regarding the comment about use of biopsy clips in the breast, but we do recognize that there is not a consistent standard regarding use of clips in the axilla, which is why we wanted to provide direction for institutions who do as well as those who do not currently clip the axillary node at biopsy. This collaborative ASCO/Ontario Health (Cancer Care Ontario) initiative is intended to guide practice in both Canada and the US. In response to this

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		nodes were identified (p=0.007), which falls within what we would consider **Recommendation 5A** While the older literature did support dual dye to increase accuracy and identification rates, the largest, more recent, and highest quality studies (i.e., Kang, 2010 [60] O'Reilly, 2015 [47]) showed no difference in identification rate between single and dual dye. It is possible that the differences seen in older trials were reflecting a learning curve at the level of the surgeon or institution. We agree with the comment from the reviewer that for situations where the identification rate will be lower (i.e., lower volume centers or newer surgeons), dual tracer should be used. Therefore, we changed the Qualifying statement of Recommendation 5 from: "Dual tracer should be used in low-volume centers (<100 SLNB procedures per year)" To: "*Dual tracer should be used in settings where it is expected to be a learning curve for the operators performing the procedure (e.g., low volume centers, surgeons in training/post training)"* We strove to clarify for readers that patients undergoing primary surgery for early stage breast cancer (NOT undergoing neoadjuvant chemotherapy), single tracer that identifies a node in the axilla is sufficient for staging the axilla based on the above data. This should not be confused with SLN following neoadjuvant chemotherapy, where the ID rate is lower and FNR is higher and in that setting, which is the ACOSOG Z1071 study cohort, dual tracer and more than	The primary comparison of the included studies was dual versus single tracer; therefore, we restricted our search, and included studies with this comparison. This excluded the Z1071 because this was not the primary comparison in this study. We changed Recommendation 5 (A) Single versus dual tracer to: "•For patients having primary surgery, we recommend using a sentinel node tracer (i.e., it is not necessary to add blue dye on a regular basis for SLNB if the radiocolloid signal successfully identifies the sentinel node(s) in the axilla). In cases of non-identification, blue dye can be added. Screening for radiocolloid signal prior to incision is recommended, and blue dye can be added prior to making the incision. In patients who receive NAC, we recommend either placing a biopsy clip into the positive node at diagnosis and localizing at time of surgery as well as using dual tracer (radiocolloid plus blue dye)." Before the change it was: "•We recommend not to add blue dye on a regular basis for SLNB if the radiocolloid signal identifies the sentinel lymph node in the axilla. In case of non-identification, blue dye can be added. Screening for radiocolloid signal prior to incision is recommended, and blue dye can be added prior to making the incision. In patients who receive NAC, we consider reasonable either clipping of an abnormal lymph node at the time of diagnostic node biopsy or using radiocolloid plus blue dye." It is clearer in the algorithm; therefore, we clearly recommend, in	reviewer comment, Dr. Brackstone polled the Surgical Leads at the major academic institutions across Canada and 95% do not routinely place clips in the axilla of biopsied lymph nodes at the time of biopsy (citing cost concerns as well as clip migration, retrieval, and localization challenges). While we can appreciate that there will be variability in practice across larger US institutions with different cost reimbursement opportunities, this reflects the Canadian landscape. While this may change in the future, we wanted to provide current recommendations. At this time, we discussed how best to address this with ASCO-affiliated co-authors Drs. Tari King and Mariana Chavez-MacGregor to provide useful recommendations to clinicians in the US and Canada, and together we determined that it was best to provide direction for both options. We, therefore, did not change the recommendation, but we appreciate the comments raised by the reviewer and hope that we have sufficiently addressed them here. **Recommendation 5:** In Recommendation 5, the reviewer raises the concern regarding the recommendation that single tracer can be used for sentinel node biopsy procedures being performed at upfront surgery, and the evidence base that we presented. We had discussed this concern at the second round of reviews, but likely did not sufficiently clarify this point and our rationale for this recommendation and we hope that these comments will fully address these concerns.

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		three nodes are essential. Z1071 does not apply to early stage primary surgery. A reference to the online CCO guideline provides access to all the evidence tables with results and quality assessment for interested readers.	the algorithm, that for primary surgery the sentinel node procedure can be performed with single or dual tracer. But for NAC patients, dual tracer achieves the lowest possible false negative rate, as it was discussed in Recommendation 4. The sentence "100 sentinel node procedures per year" had already been changed in round 1. We updated the algorithm.	Similar to the literature, we divided the discussion around the technique for sentinel node procedure after neoadjuvant chemotherapy (within Recommendation 4) from the technique for sentinel node procedure during upfront surgery (within Recommendation 5). The reviewer is correct in describing many landmark trials where sentinel node biopsy was validated and subsequently used in large RCT trials. We felt it might be best to address each one listed to explain how it influenced our guideline draft. NSABP-B32 was the landmark trial upon which the sentinel node procedure was validated, and in this study, dual dye was mandated, and so we are unable to determine from this study whether in fact both are required or not. Neither ACOSOG Z10 (using sentinel node biopsy and bone marrow biopsy to predict risk of recurrence), AMOROS (the only of the three to mention sentinel node technique, "sentinel node procedure had to be done with a radioactive isotope, preferably combined with blue dye") or ACOSOG Z11 (randomizing node positive patients to completion dissection versus none in breast conservation) mandated whether surgeons should use dual versus single tracer. It was left to surgeon preference, so this evidence is not useful to decide whether single or dual dye should be used. To ensure that we properly and fully addressed the Reviewer's concern, we also consulted a world-renown expert in this area, Dr. Monica Morrow, and asked her if she was aware of any additional studies to help us decide whether single or dual tracer should be used. Dr. Morrow directed us to a

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				2005 publication arising from Z10 data by Posther et al.,[279] which she co-authored, and which we had not been included in our systematic review because it was published before 2007, our cut-off date. In the Posther et al. study 79% of patients had dual tracer, 15% had blue dye only and 6% had radiocolloid only; the authors showed that use of single versus dual dye did not significantly predict for sentinel lymph node failure rate, whereas surgeon volume did. We found the quote from Dr. Armando Giuliano in the discussion at the end of Posther's publication to be helpful for this current discussion: "This trial showed overwhelmingly that the combination of radioisotope and blue dye is how most investigators learn to do the procedure. There is no advantage in my mind of 1 technique over the other in experienced hands except that the preoperative lymphoscintigram may identify extra axillary drainage. The only randomized trial comparing the 2 methods showed no advantage of one technique over the other." While we did not intend to be prescriptive, we did want to look for any level 1 (randomized trials with the outcome in question as primary outcome) evidence to guide whether it is necessary to use dual tracer or not. The trials we provided were the only identified through systematic review, demonstrating no significant difference with single versus dual tracer. We made the recommendation in support of single tracer as per surgeon preference for patients undergoing sentinel node biopsy at

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				the time of upfront surgery based on the RCT trials evaluating dual versus single tracer. We suspect that the current recommendations for methods for performing sentinel node biopsy following neoadjuvant chemotherapy, based on lower false negative rates identified in trials where subgroup analyses were done post-hoc, may also change over time as the longer-term data from these studies demonstrate sustained low rates of axillary failure and/or prospective randomized trials are completed to tell us that we do not need 'dual dye, 3+ nodes etc.'. Because we do not have that data yet, we stayed with the recommendations of the current studies and expert consensus to date for the neoadjuvant cohort but made mention that this recommendation is pending future higher-level data on the subject. In summary, we very much appreciate the opportunity to respond to the thoughtful comments made by the reviewer in this third round of revisions, and we hope very much that we have been able to sufficiently address these concerns as we look forward to being able to complete this guideline process successfully.
8. Do you agree with the substance of the recommendations?	Yes *If not, please list the reason(s) why:* I agree with the substance of the recommendations. Would add strength of recommendations (in summary and throughout the document) per #10. Some comments: Qualifying statement for recommendation 2: multi centric breast cancer and multiple tumors are	No	NA	

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	mentioned. Do you mean ipsilateral tumors only? should it say multicentric and multifocal disease instead? Recommendation 3A: would add a line about patients that undergo mastectomy (and the lack of data). The authors are covering the data for breast conservation therapy but not for mastectomy.			
Authors' Response to Reviewers' Comments relative to Question 8:	See #10 below for strength of the recommendations. We changed in the Qualifying statement of Recommendation 2: from "multiple tumors" to "multifocal tumors" Recommendation 3A: In the Interpretation of the evidence for Recommendation 3A, it is in the second bullet point that we discuss the evidence that exists at this time for patients with mastectomy. A small subgroup of patients the IBCGS 23-01 trial[29,30] received mastectomy. This is the only evidence for this population, and it is our opinion that is reasonable to extrapolate the breast conserving data to the mastectomy patients with early-stage breast cancer in specific patient circumstances that need to be carefully considered. Therefore, in the qualifying statement we recommended that decisions be taken on a case-by-case basis after discussion between patients and clinicians, taking into account the limited data specific to mastectomy and considering that these recommendations represent an extrapolation from trials designed for patients undergoing breast conserving surgery based on expert opinion.	No response required	No response required	NA
9. Were areas of uncertainty / areas	No *Comments:*	No	NA	NA

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lacking strong evidence appropriately identified?	The authors did mention some areas of uncertainty for which there are ongoing clinical trials and provided references however there is still a lot of uncertainty and I think adding strength of recommendation for each section would be useful for the readers			
Authors' Response to Reviewers' Comments relative to Question 9:	We added strength of the recommendation statements for each recommendation, in the format that ASCO uses, to all recommendations (e.g., Type: evidence based; benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong).	No response required	NA	NA
10. Are the limitations of the literature and any assumptions that were made in the formulations of the recommendations adequately described?	Yes	Yes	NA	NA
Authors' Response to Reviewers' Comments relative to Question 10:	No response required	No response required	NA	NA
11. Are the tables and figures helpful in interpreting the text?	Yes *Comments:* Figure 1 in particular, provides a very clear summary of the recommendations	Yes	NA	NA
Authors' Response to Reviewers' Comments relative to Question 11:	No response required	No response required	NA	NA
12. Are any tables or figures unnecessary or redundant with the text?	No	No	NA	NA
Authors' Response to Reviewers' Comments relative to Question 12:	No response required	No response required	NA	NA
13. Would additional tables or figures be helpful? If you suggest additional tables, please	No	No	NA	NA

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give specifics regarding what you would like to see in the table(s), and indicate which text should be removed or shortened in the main body of the guideline.				
Authors' Response to Reviewers' Comments relative to Question 13:	No response required	No response required	NA	NA
14. Please provide any additional comments you may have that were not addressed above.	*Minor comments:* Make sure the abbreviations are written correctly and that the words are written once Refer to the receptor status (ER, PR, HER2) consistently throughout the guideline Page 27: prior to D) appears to be a line missing ("please") Page 46: typo in external review "would b"	No	NA	NA
Authors' Response to Reviewers' Comments relative to Question 14:	Abbreviations have been checked and corrected when necessary. Receptor status has been checked and corrected when necessary. "Please" was there in error – it has been deleted The typo on page 46 has been corrected	No response required	NA	NA

EXTERNAL REVIEW
External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Three targeted peer reviewers from Ontario and Alberta who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. All three agreed to be the reviewers (Appendix 1). Two responses were received. Results of the feedback survey are summarized in Table 5-5. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-6.

Table 5-5. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=2)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				1	1
2. Rate the guideline presentation.				1	1
3. Rate the guideline recommendations.			1		1
4. Rate the completeness of reporting.			1		1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			1		1
6. What are the barriers or enablers to the implementation of this guideline report?	This guideline is very practical and widely applicable to practice across centres (rural, community and academic). As the guideline states, implementation would not require significant changes or costs in the current system. Well written and straightforward algorithm that should be reasonable to follow, but does not really address the patient groups where there is uncertainty (primarily because of insufficient evidence to guide practice) and therefore defaults to previous practise.				
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. Rate the overall quality of the guideline report				1	1
8. I would make use of this guideline in my professional decisions.				1	1
9. I would recommend this guideline for use in practice					2

Table 5-6. Responses to comments from targeted peer reviewers.

Comments	Responses
1. Recommendation 1 is rather vague; it does not specify what factors should be taken into account when considering SLNB. It references a document that suggests it is feasible to avoid SLNB in patients older than 70 suggesting	• Suggested change in Qualifying statement: If omission of SLNB is considered, a consultation with a medical oncologist can be considered before surgery, to discuss hormonal therapy, and

discussion with medical oncology (no reference is made of radiation or referral to radiation oncology), however there is not good evidence to support this and there is no discussion under this point regarding the role for or the omission of adjuvant radiation and how this would impact the decision for SLNB. The patients age should NOT be used as a deciding factor but rather the probable life expectancy. There has to date been clear descriminants found to identify a group of patients in whom radiation can safely be omitted.	with a radiation oncologist to discuss radiotherapy. We agree that not all patients 70 years old or older are the same; in some cases the Choosing wisely statement would apply, while in other cases it would be less appropriate or it would not meet the patient's requirements. This depends on the characteristics and circumstances of the patients, including their values and preferences. That is why we recommended that patients should be evaluated on a case-by-case basis.
• Recommendation 2 is very reasonable	
• Recommendation 3 avoidance of ALND in patients with <3 nodes is very reasonable. The evidence to support ALND in the population with >3 nodes is not discussed in details and is assumed because this has been standard practise although there is little evidence (no proven survival advantage, possible improved local control in population who are clinically node positive). The statement that women >65 years of age may benefit less from radiation is incorrect! There is less benefit to the group as a whole as the risk is lower yet the benefit to the individual patient may actually be greater! Unfortunately the group of patients where the most controversy regarding decision-making exists were not included in the evidence (lack of data on these groups).	No response is needed. This was based on the Killander (2009) studies (loco-regional recurrence rate: 5.3% radiotherapy + tamoxifen vs. 18.5% tamoxifen, p<0.001; recurrence rate of systemic disease: 40% vs. 50% respectively, p=0.047), with no difference shown for OS.
2. Does not provide evidence for ALND in population group excluded from omission of ALND, the assumption is made that there is benefit (default) but there is not strong evidence to support this. Radiation and systemic therapy may confer equivalent benefit.	No evidence is available at this time for radiation and systemic therapy compared with ALND (standard of practice).
3. The key stakeholders were appropriate and very knowledgeable in their respective fields. The literature review is thorough and balanced with clear consideration of risks, benefits, alternatives and patient-related factors. Where evidence is not available, the expert opinion provided is balanced, rationale and justified.	No response is needed.
The guideline is well-organized and easy to navigate. Clinicians looking for direction in individual situations would be able to easily identify the recommendation and evidence supporting it.	No response is needed.

The guidelines are well-supported and sound. I particularly appreciate the statement for Recommendation 1 where consultation with a medical oncologist is proposed prior to omission of SLNB for women older than 70. Despite the evidence in this area, there are many contributing factors to this decision (patient fitness, tumour subtype, treatment options, etc). The qualifying statement is balanced and well done.	No response is needed.
The literature review and guideline development is thorough and transparent. The authors clearly state areas where data are lacking or studies are currently ongoing. Each recommendation is supported by sufficient evidence at present.	No response is needed.
This guideline is very practical and widely applicable to practice across centres (rural, community and academic). As the guideline states, implementation would not require significant changes or costs in the current system.	No response is needed.
This guideline collates and evaluates extensive existing guidelines and evidence in the management of the axilla for early stage breast cancer. It will provide a framework for discussions around individual patient management and allow for consistent, evidence-based decision making in patient care.	No response is needed.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All surgical oncologists, radiation oncologists, medical oncologists, and general surgeons, in the PEBC database were contacted by email to inform them of the survey. Additionally, three individuals representing the American Society of Radiation Oncology (ASTRO) participated. Two hundred and 12 professionals were contacted and 34 participated in the survey; 31 practicing in Ontario, and three practicing in California, Florida, and Illinois (USA). Forty-six (22%) responses were received. Twelve stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from 34 people are summarized in Table 5-6. The main comments from the consultation and the Working Group's responses are summarized in Table 5-7.

Table 5-6. Responses to four items on the professional consultation survey.

	Number 34 (16%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	1	1	2	14	16
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	1	2	3	12	16
3. I would recommend this guideline for use in practice.	1	2	0	12	19

4. What are the barriers or enablers to the implementation of this guideline report?	There are sections that are a little confusing....and perhaps could be laid out better with less conflicting information in the same paragraph. For example , the definition of early breast cancer is well laid out and upon first read it is hard to catch the exclusions. Perhaps writing it as found later in the guidelines (not including DCIS and IIIA) is more clear? The diagram/algorithm is fabulous, clear and easy to follow....a pin-up! Promoting and accepting of the guideline in breast centres. Preparing a easy to follow algorithm or the available flow diagram would help implementation. Discussing and popularizing the details with stake holders or breast management team. Engaging residents and fellows to understand and use it. I am not aware of any barriers. Publication in a high-impact clinical oncology journal would be an enabler to implementation. It is quite detailed in its recommendations, and the authors emphasize the evaluation of patients on a case-by-case basis. this speaks to the widespread variability that does exist in clinical practice, and therefore will help guide care but there will still be huge variation in what actually happens to these patients. Dissemination to the appropriate clinicians. Enablers are being PEBC/OH (CCO) and expert panel. Specific algorithm is also an enabler. Management of the axilla has changed dramatically in a short time, and I think dissemination of information and challenging traditional surgical dogma are barriers to implementation. This guideline is very complex and should be simplified, it should be concise and simple and contain practical use scenarios. Extrapolating subgroup analysis for high-risk node-negative patients treated with mastectomy to have postmastectomy radiation should have a stronger qualifying statement. Our centre routinely wants to radiate most patients and for 84-year-old patients (a recent example) with a T2 NO triple negative cancer being recommended no chemotherapy due to comorbidities but strong recommendation for postmastectomy radiation, has concern for overtreatment. Therefore, changing the guideline to state in selected high-risk node-negative triple negative patients younger than 50 treated with mastectomy, radiation therapy can be considered or enrollment in a clinical trial. More radiation oncology consensus statements are needed. I think this is a very important topic. In fact, I have recently read an excellent paper on the difficulty of de-implementing procedures, and this was used as a prime example. Some barriers: for leaders in breast surgery, certainly in teaching hospitals, increasingly these people are doing nothing but breast surgery and the surgery itself is becoming more and more minimal, many of us would be concerned that the end result will be 20 years of training to do a lumpectomy. In the absence of challenges being added to the field like primary responsibility for plastics/reconstruction, it is going to prove very difficult to recruit quality leaders for the future. There are obvious economic problems, these of course should not be a consideration but again, unless there is a move to salary for instance, removing a large number of sentinel node biopsies will be a real deterrent to recruiting breast surgeons. Last comment is that if we do not have the node information, we are still running a pretty high risk of having the patient sent back having been convinced that it is necessary, and I for one 8-second operations. So the recommendations have to be absolutely standard and not leave us in the position

	of having to rebook a second procedure, as we were prior to the original trial switch remove the obligation for completion dissections. Everyone has to be on board with these recommendations. Poorly written. Not precise. Language not transferable to average reader. One small example: "medial/central" tumours. Does this include tumours in the central part of breast or are the writers referring to medial breast tumours that are in the central chest. One section describes SLNB for T1 tumours specifically – what about T2 tumours? Critical review of the papers is poor. The inclusion of radiation guidelines and alternatives as well as patient exclusions makes almost every case one for 'shared decision making'. It will be used as a reference document by most surgeons because of the length and detail but not read completely; therefore, some important points could be missed. A shorter compact version would be most useful for most surgeons. None, should be standard of practice. Potential barrier would be lack of uptake, or some not reading the entire document. The flow diagram and a summary page will be very useful with a link to the full document and encouragement for clinicians to discuss with their local colleagues. 'Potential' Barriers- ensure standard approach for placement of clips in clinically or imaging-detected nodes prior to NAC as per MCC discussion of selected patients in this category prior to commencing treatment. Enablers: our Regional Program has a cohesive multidisciplinary team of physicians that allows for consistent approach to follow the recommendations in this guideline. Current practice is essentially consistent with the guideline and can proceed with required adoption of those components that require changes in practice. Thank you for the opportunity of reviewing this guideline report. Much of the report is excellent and currently how we practice clinically. The major problem with the report is in Recommendation 5, B and C. Current recommendations from the 2012 Canadian Association of Radiologists Breast Imaging guidelines are to evaluate the axilla when performing a breast biopsy. (ref CAR https://car.ca/book/breast-imaging-guidelines/ page 12). This means that most patients will have had the axilla evaluated before the diagnosis of breast cancer is established. The guideline as written will generate a great deal of controversy. For example, there are several surveys about the standard approach to the axilla among breast radiologists in both the US and Canada. One survey of this topic will be presented at an international meeting in the USA at the Radiological Society of North American in 2020 (Mansi et al, Mass. Gen Hospital, RSNA 2020). The results of this survey indicate that 70% of respondents perform routine axillary ultrasound for any breast lesion that will be biopsied. The OH (CCO) guideline would be strengthened by providing guidance to how to manage the axilla once if imaging has been performed. Instead of saying not to look at the axilla, which will be highly controversial, it would be more prudent to provide guidance on what to do if or when nodes are identified, for example, one single abnormal lymph node, or two or more. Providing clear guidelines on indications to when to recommend axillary lymph node biopsy, e.g,. if Z011 criteria are not, for example, three nodes that appear highly suspicious, as well as the requirement to perform targeted axillary dissection (TAD) after biopsy-proven axillary nodes, would be practical and useful. There is need for clear guidance on this as oncologists will often ask if the axilla has been imaged and will often request this post surgery. It is essential that radiologists be asked to document whether the axillary ultrasound was performed or not, and any nodes that are biopsied should be clipped to allow for TAD, if necessary. I am in strong support of the remainder of the guideline recommendations, which are strongly evidence based, and on which we base our clinical practice. Thank you for the opportunity to comment. I would be pleased to provide more details as necessary. I think getting the information out will be challenging especially to surgeons who do a low volume of breast cancer surgery Excellent and thorough. The guidelines are very well done, inclusive of the most up-to-date studies, and balanced between the role of surgery and radiotherapy. Guidelines are most effective if their presentation can be kept simple and straightforward. There are many other guidelineas and it is not back by a multinational society – i.e., it might be defined as limited to the Canadian population. None

	Barriers to implementation include the fact that it takes a lot of time and reading (by busy physicians and surgeons) to consider the nuances of the recommendations and the quality of evidence they rest on -- many of the recommendations rightly suggest taking patient factors into consideration, though the onus is on the provider to be able to recognize and identify the factors in question based on understanding of the voluminous version. Barriers to implementation also include practical considerations such as circumstances where there is not access to radionuclide injection, clipping of lesions/nodes, localization of nodes for retrieval, etc. The general messages of safe de-escalation of treatment to minimize morbidity to patients will certainly enable uptake of the guidelines. Suggest clarification of "prognostic groups" and "staging" where these terms appear, i.e., specify either anatomic stage or prognostic stage by AJCC 8th edition, p3, at end regarding benefit described for locoregional radiation as "modestly benefit <5%", I would suggest a benefit <5% should be described as minimally benefit - I would appreciate more discussion around criteria of three or more lymph nodes as minimum in post-NAC SLNB-eligible patients. SN-FNAC study identified that two yields an acceptable false negative rate if IHC performed. This would allow more centres to participate in successful downstaging if they have pathology expertise but don't have ability to clip and localize nodes. Pushing to achieve three or more lymph nodes on SLNB is in some cases resulting in surgeons performing what amounts to a 'limited axillary random node sampling' in order to try to keep a patient from recommendation of morbid ALND. This scenario has come up in the American Society of Breast Surgeons forums and conference talks. - More specifics regarding clipping of nodes would be helpful. For example, in centres where nodes cannot be localized, will it suffice to take intraoperative X-ray of nodes to confirm clipped node retrieved? How many nodes should be clipped and retrieved if there are more than one that seem abnormal pre-chemotherapy? If more than three nodes removed but clipped node not retrieved? Etcetera. I am not supportive of recommendation to omit vital blue dye injection (dual modality) in non-NAC cases. Regarding continuing its use in low volume centres <100 cases/year, this number of cases per centre does not reflect individual surgeon experience level or case number, and that surgeon-level of detail has not been quantified in the evidence cited. SLNB procedure using blue dye as an adjunct reflects technical skill of a surgeon that would not be expected to be different if the surgeon was moved to a low-volume centre from a high one and vice versa. It is rightly acknowledged and explored within the document in great detail that the false negative rate is lowest in the more challenging circumstance of the post-NAC axilla, so I do not understand the Working Group recommending AGAINST using this approach for all SLNB. I note as well there is no technical description of definition of a sentinel node from first principles of the method, i.e., to search for all palpable, blue and 'hot' nodes greater than 10% of the greatest 10-second count. The Geng et al. systematic review is in context of NAC, and Hunt et al. compares blue dye alone to dual modality, which is not useful for forming the conclusion of omitting blue dye. Furthermore, the risk of anaphylaxis with the use of intraoperative, intradermal vital blue dyes is vanishingly small in an updated systematic review and meta-analysis by Perenyei et al. in *Annals of Surgery* from this year (0.0068%). One of the studies included for question #5 [Kang et al., ref 257] is not looking at vital blue dye at all, but fluorescing indocyanine green, which is not at all relevant. I suggest that routine use of blue dye in the cN0 axilla of the chemo-naive patient should be left to individual surgeon preference and discretion. In the least, this can be a valuable teaching tool for precise sentinel node identification and dissection in centres with trainees – a very thorough review that unifies and consolidates much of the current controversy around these clinical scenarios, with sound methodology, sincere thanks and congratulations to the Working Group!

Additional Comments

This guideline is very helpful as there are many multidisciplinary options in choice and delivery of care.

Good work

On page 25, Recommendation 5B, US-guided staging versus standard guided (dye/isotope) staging', why is only a core biopsy of the axillary node recommended? Shouldn't the recommendation be for either a US-guided core biopsy or a US-guided FNA (fine needle aspirate)? Either sample could show metastasis.

I believe Recommendation 1 should be T1N0 AND T2N0?? The T2 is completely missing.

Clear guidance with limits given

None

Any role for commenting on isolated tumour cells and micromets especially in the NAC group.

It was not easy to read; too much repetition

Overall well-written guideline

Page 25. Qualifying statements for Recommendation 5. A) Dual tracer should be used in low-volume centres (<100 SLNB procedures per year).
I think the choice of dual tracer should be based on the competence and judgment of the individual surgeon and not on the volume of cases done at the centre (hospital). Although it still not very objective, the number of cases a surgeon does in a year is a better measure than the number at a centre by several surgeons.

Consent for lumpectomy with sentinel nodes
1. The complete name of the surgery is stated.
2. Most of the basics of the surgery are explained (e.g., day care surgery, nuclear medicine injection, general anesthesia, incision locations, scar, discharge care).
3. Most of the common material risks are stated (swelling, bleeding, pain, bruising, hematoma, infection)
4. Serious material risks are stated (re-operation for positive margin or >2 positive nodes, anesthesia risks)
5. There is no coercion of the patient
6. All the patient's questions are answered clearly and fully
7. Comprehension by the patient is confirmed e.g. by asking the patient to repeat what was stated
8. The course of the disease without surgery is explained
9. Alternatives to surgery are discussed
10. A second opinion or a return appointment for further discussion is offered if indicated.

Thanks for all the hard work!

As a medical oncologist, I grapple with the patient with clinical node negative T2 intermediate grade HR+ Her2 neg breast cancer referred for neoadjuvant chemo who is ambivalent about chemo. The review did not address whether there is any data from clinical trials or ongoing randomized trials looking at the role of oncotype as a predictor of response or non-response to chemotherapy. If there were such trials, these may suggest a role for determining pathologic axillary nodal status to determine whether oncotype would be useful to see if neoadjuvant chemotherapy is appropriate or not. This would be an important consideration for surgeons as an early oncotype determination would be required.

Very thorough and clear

Not sure where the data came from NOT to use blue dye as a dual tracer
gutsy move to recommend a sentinel node with a clinically suspicious node or a biopsy-proven node that is positive (in patients not getting NAC) in a patient clinically node negative - I agree with recommendation

Thank you for the opportunity to review the guidelines. I look forward to their publication.

Nice job

No comments

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP, and the ASCO reviewers.

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Appendix 1: Affiliations and Conflict of Interest Declarations

Name	Discipline	Affiliation	Declarations of interest
Working Group			
Dr. Muriel Brackstone	Surgical oncology	London Health Sciences Centre, London,Ontario, Canada	Declared no conflict of interest
Dr. Ian Dayes	Radiation oncology	Juravinski Cancer Centre, Hamilton, Ontario, Canada	Declared no conflict of interest
Dr. Andrea Eisen	Medical oncology	University of Toronto, Odette Cancer Centre, Toronto, Ontario, Canada	Declared no conflict of interest
Dr. Jay Engel	Surgical oncology	Cancer Center of Southeastern Ontario, Kingston General Hospital, Kingston, Ontario, Canada	Declared no conflict of interest
Dr. Sandip SenGupta	Pathology	Kingston General Hospital, Pathology Department, Kingston, Ontario, Canada	Declared no conflict of interest
Dr. Francisco Perera	Radiation oncology	London Health Sciences Centre, London,Ontario, Canada	Declared no conflict of interest
Dr. Ralph George	Surgical oncology	St. Michael's Hospital, CIBC Breast Centre, Division of General Surgery, Toronto, Ontario, Canada	Declared to have received financial support by Abbvie Pharmaceuticals
Dr. Anat Kornecki	Radiology	Western University, Division of Breast Imaging, London, Ontario, Canada	Declared no conflict of interest
Dr. Tulin Cil	Surgical oncology	University Health Network, Princess Margaret Hospital, Toronto, Ontario, Canada	Declared to be a consultant for the Canadian Breast Cancer Foundation
Ms. Fulvia Baldassarre	Heatlh research methodology	McMaster University, Cancer Care Ontario, Program in Evidence-based Care, Juravinski Hospital, Hamilton, Ontario, Canada	Declared no conflict of interest
Expert panel			
Dr. Kathleen Bell	Genetic Counselling, Diagnostic Assessment	Juravinski Cancer Centre, Hamilton, Ontario, Canada	Received grants and support ≥$500 in a single year by AstraZeneca for acting as a speaker and a consultant. Is the clinical manager for the genetics department at Juravinski Cancer Centre.
Dr. Glykeira Martou	Plastic surgery	Hotel Dieu Hospital, Department of Surgery, Kingston, Ontario, Canada	Declared no conflict of interest
Dr. Brian Pinchuk	Surgical oncology	North York General Hospital, Toronto, Ontario, Canada	Received ≥$500 in a single year by Medtronic
Dr. Derek Muradali	Radiology	Saint Michael's Hospital, Toronto, Ontario, Canada	Declared no conflict of interest
Dr. Leta Forbes	Medical oncology	Lakeridge Health Oshawa, Oshawa, Ontario, Canada	Declared no conflict of interest
Dr. Marcie McCune	General surgery	Stratford General Hospital, Stratford, Ontario, Canada	Declared no conflict of interest
Dr. Ghazaleh Kazemi	Medical oncology	Juravinski Cancer Centre, Hamilton, Ontario, Canada	Received ≥$500 in a single year by Pfizer as advisory board member for (Ibrance meeting) and Eisai (Halaven meeting).
Dr. Tari King	Surgical oncology (breast)	Brigham and Women's Hospital, Boston MA, USA	Is a breast surgeon and her professional income could increase or decrease by substantially more than $10,000 depending on the outcome of the guideline. Also provided advice or guidance regarding the objects of study in a public capacity (CME conferences)
Dr. Mariana Chavez Mac Gregor	Medical oncology	MD Anderson, Huston TX, USA	Earned ≥$500 in a single year acting as a consultant for Pfizer, Roche , Esai, and received grants from Novartis.
Dr. Janet Horton	Radiation oncology	Research Triangle Park NC, USA	Works at a pharmaceutical company called G1 Therapeutics. The company's drugs are oncology based but have no overlap with the focus of this guideline. Earned ≥$500 in a single year

Name	Discipline	Affiliation	Declarations of interest
			acting as a consultant for Qfix - speaker (radiation devices). Received travel funding to speak at Varian Training session (radiation devices). Owns G1 Therapeutics stocks. Received Varian Medical Systems - research grant for preoperative breast radiotherapy
Patty Spears	Patient representative	ASCO, USA	Declared no conflict of interest
Targeted Peer Reviewers			
Conrad Falkson	Radiation oncology	Cancer Centre of Southeastern Ontario, Kingston, Ontario	Declared no conflict of interest
May Lynn Quan	Surgical oncology	Arnie Carbonneau Cancer Institute, Calgary, Alberta	Declared no conflict of interest
Sara Rask	Medical oncology	Royal Victoria Hospital, Barrie, Ontario, Canada	Declared no conflict of interest

Name	Affiliation	Declarations of interest
Report approval panel		
William Evans	Oncosynthesis Consulting Inc, Hamilton, Ontario, Canada	Declared no conflict of interest
Laurie Elit	Juravinski Cancer Centre, Hamilton, Ontario, Canada	Declared no conflict of interest
Jonathan Sussman	McMaster University, Hamilton, Ontario, Canada	Declared no conflict of interest
Patients' representatives		
Patty Spears	Patient representative ASCO, USA	Declared no conflict of interest
Marissa Myers	Ontario Health, (CCO), Ontario, Canada	Declared no conflict of interest
Patricia Sevean	Ontario Health, (CCO), Ontario, Canada	Declared no conflict of interest
Laurie Petz	Ontario Health, (CCO), Ontario, Canada	Declared no conflict of interest
Lise Craig	Ontario Health, (CCO), Ontario, Canada	Declared no conflict of interest
Bob Tuck	Ontario Health, (CCO), Ontario, Canada	Declared no conflict of interest
Minna Allarakhia	Ontario Health, (CCO), Ontario, Canada	Declared no conflict of interest
Anne Newman	Ontario Health, (CCO), Ontario, Canada	Declared no conflict of interest

Appendix 2: Literature Search Strategy

A. Search strategies for systematic reviews

The Cochrane Library was searched with the text term: axilla

Database: OVID MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINEI Daily and Ovid MEDLINEI 1946 to June 8, 2017
Search Strategy:

1	Axilla/
2	(axill: adj25 breast).tw.
3	*Breast Neoplasms/di, dg, dt, pa, pp, rt, su, th [Diagnosis, Diagnostic Imaging, Drug Therapy, Pathology, Physiopathology, Radiotherapy, Surgery, Therapy]
4	*Breast/pa, re, su [Pathology, Radiation Effects, Surgery]
5	(breast adj25 (cancer or carcinoma or adenocarcinoma or neoplasm: or tumour or tumour)).tw.
6	*Lymphatic Metastasis/
7	Lymph Nodes/dg, pa, pp, re, su [Diagnostic Imaging, Pathology, Physiopathology, Radiation Effects, Surgery]
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	Sentinel Lymph Node Biopsy/
10	(sentinel lymph node excision or lymphadenectomy).tw.
11	axillary lymph node dissection.mp.
12	Antineoplastic Agents/dt, su, tu, th [Drug Therapy, Surgery, Therapeutic Use, Therapy]
13	Antineoplastic Combined Chemotherapy Protocols/tu [Therapeutic Use]
14	chemoradiotherapy/ or chemotherapy, adjuvant/ or neoadjuvant therapy/ or radioimmunotherapy/ or radiotherapy, adjuvant/
15	Radiotherapy/
16	Mastectomy, Segmental/
17	((breast adj conserving surgery) or BCS or lumpect:).tw.
18	ultrasonography, interventional/ or ultrasonography, mammary/
19	((ultras: or echograph: or US) adj21 stag:).tw.
20	((magnetic resonance imaging or MRI or positron emission tomography or PET) adj21 stag:).tw.
21	positron emission tomography.mp. or Positron-Emission Tomography/ or *coloring agents/ or radiopharmaceuticals/
22	Neoplasm Staging/
23	(axill: adj25 (manag: or completion or sentinel or SN or SNB or SLN or SLNB or ALND)).mp.
24	(axill: adj3 (surg: or sampl: or stag:)).mp.
25	((block or lymph node or axillary) adj (clear: or dissect:)).mp.
26	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27	(systematic adj (review: or overview:)).mp.
28	(meta-analy: or metaanaly:).mp.
29	(pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.
30	(exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
31	(medline or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.
32	(reference list: or unnfavourable: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
33	or/27-32
34	(selection criteria or data extract: or quality assess: or unnfav score or unnfav scale or methodologic: quality).ab.
35	(stud: adj1 select:).ab.
36	(34 or 35) and review.pt.
37	33 or 36
38	(guideline or practice guideline).pt.
39	exp consensus development conference/
40	consensus/
41	(guideline: or recommend: or consensus or standards).ti.
42	38 or 39 or 40 or 41
43	37 or 42
44	(comment or letter or editorial or note or erratum or short survey or news or newspaper article or case report or historical article).pt.
45	(animals not humans).sh.
46	8 and 26 and 43
47	46 not 44
48	47 not 45
49	limit 48 to English language
50	limit 49 to yr=”2011 –Current”

Database: Embase <1996 to 2017 June 08>
Search Strategy:

1	axilla/
2	(axill: adj25 breast).tw.
3	*breast tumour/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]
4	*breast/su [Surgery]
5	(breast adj25 (cancer or carcinoma or adenocarcinoma or neoplasm: or tumour or tumour)).tw.
6	*lymph node metastasis/
7	lymph node/
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	sentinel lymph node biopsy/
10	(sentinel lymph node excision or lymphadenectomy).tw.
11	axillary lymph node dissection.mp.
12	antineoplastic agent/dt [Drug Therapy]
13	chemoradiotherapy/
14	adjuvant chemotherapy/
15	radioimmunotherapy/
16	adjuvant radiotherapy/
17	radiotherapy/
18	partial mastectomy/
19	((breast adj conserving surgery) or BCS or lumpect:.tw.
20	interventional ultrasonography/
21	echomammography/
22	((ultras: or echograph: or US) adj21 stag:.tw.
23	((magnetic resonance imaging or MRI or positron emission tomography or PET) adj21 stag:).tw.
24	cancer staging/
25	positron emission tomography.mp.
26	positron emission tomography/
27	coloring agent/
28	radiopharmaceutical agent/
29	(axill: adj25 (manag: or completion or sentinel or SN or SNB or SLN or SLNB or ALND)).mp.
30	(axill: adj3 (surg: or sampl: or stag:).mp.
31	((block or lymph node or axillary) adj (clear: or dissect:).mp.
32	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33	(systematic adj (review: or overview:).mp.
34	(meta-analy: or metaanaly:.mp.
35	(pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:.mp.
36	(exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
37	unfavour or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.
38	(reference list: or unfavourable: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
39	(selection criteria or data extract: or quality assess: or unfav score or unfav scale or methodologic: quality).ab.
40	(stud: adj1 select:.ab.
41	(39 or 40) and review.pt.
42	33 or 34 or 35 or 36 or 37 or 38
43	41 or 42
44	consensus development conference/
45	practice guideline/
46	*consensus development/ or *consensus/
47	*standard/
48	(guideline: or recommend: or consensus or standards).kw,ti.
49	44 or 45 or 46 or 47 or 48
50	(editorial or note or letter or short survey).pt. or abstract report/ or letter/ or case study/
51	43 or 49
52	exp animal/ not human/
53	8 and 32 and 51
54	53 not 50
55	54 not 52
56	limit 55 to (English language and yr=”2011 –Current”)

A. Search strategies for randomized controlled trials

Database: OVID MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINEI Daily and Ovid MEDLINEI 2007 to January 12, 2018

1	Axilla/
2	(axill: adj25 breast).tw.
3	exp Breast neoplasms/
4	exp Breast/ or breast diseases/
5	((breast adj25 (cancer or carcinoma or adenocarcinoma or neoplasm: or tumo?r)) or (mammary adj25 (cancer or carcinoma or adenocarcinoma or neoplasm: or tumo?r))).tw.
6	*Lymphatic Metastasis/
7	Lymph Nodes/dg, pa, pp, re, su [Diagnostic Imaging, Pathology, Physiopathology, Radiation Effects, Surgery]
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	((breast adj milk) or (breast adj tender$)).ti,ab,sh.
10	8 not 9
11	Sentinel Lymph Node Biopsy/
12	(sentinel lymph node excision or lymphadenectomy).tw.
13	axillary lymph node dissection.mp.
14	Antineoplastic Agents/dt, su, tu, th [Drug Therapy, Surgery, Therapeutic Use, Therapy]
15	chemoradiotherapy/ or neoadjuvant therapy/ or radioimmunotherapy/ or radiotherapy, adjuvant/
16	Radiotherapy/
17	Mastectomy, Segmental/
18	((breast adj conserving surgery) or BCS or lumpect:.tw.
19	ultrasonography, interventional/ or ultrasonography, mammary/
20	((ultras: or echograph: or US) adj21 stag:.tw.
21	((magnetic resonance imaging or MRI or positron emission tomography or PET) adj21 stag:.tw.
22	*coloring agents/ or radiopharmaceuticals/
23	Neoplasm Staging/
24	(axill: adj25 (manag: or completion or sentinel or SN or SNB or SLN or SLNB or ALND)).mp.
25	(axill: adj3 (surg: or sampl: or stag:).mp.
26	((block or lymph node or axillary) adj (clear: or dissect:).mp.
27	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28	exp Randomized Controlled Trial/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/ or ((exp Clinical Trial/ or Prospective Study/ or Prospective Studies/) and Random$.tw.) or exp Randomized Controlled Trials as topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/ or exp “Randomized Controlled Trial (Topic)”/ or “Phase 3 Clinical Trial (Topic)”/ or “Phase 4 Clinical Trial (Topic)”/ or ((exp Clinical Trials as Topic/ or exp “Clinical Trial (Topic)”/) and random$.tw.) or Random Allocation/ or Randomization/ or Single-Blind Method/ or Double-Blind Method/ or Single Blind Procedure/ or Double Blind Procedure/ or Triple Blind Procedure/ or Placebos/ or Placebo/ or ((singl$ or doubl$ or tripl$) adj3 (blind$3 or mask$3 or dummy)).tw. or (random$ control$ trial? Or rct or phase III or phase IV or phase 3 or phase 4).tw. or (((phase II or phase 2 or clinic$) adj3 trial$) and random$).tw. or (placebo? Or (unfavour$ adj2 random$)).tw. or (random$ adj3 trial$).mp. or “clinicaltrials.gov”.mp.
29	10 and 27 and 28
30	29 not (exp “Animals”/ not “Humans”/)
31	limit 30 to (English language and yr=”2007 –Current”)

Database: Embase <2007 to 2018 January 11>

1	axilla/
2	(axill: adj25 breast).tw.
3	exp breast tumour/
4	exp breast/ or breast disease/
5	(breast adj25 (cancer or carcinoma or adenocarcinoma or neoplasm: or tumour or tumour)).tw.
6	*lymph node metastasis/
7	lymph node/
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	((breast adj milk) or (breast adj tender$)).tw.
10	8 not 9
11	sentinel lymph node biopsy/
12	(sentinel lymph node excision or lymphadenectomy).tw.
13	axillary lymph node dissection.mp.
14	antineoplastic agent/ or Neoadjuvant chemotherapy/
15	chemoradiotherapy/
16	radioimmunotherapy/
17	adjuvant radiotherapy/
18	radiotherapy/
19	mastectomy/
20	((breast adj conserving surgery) or BCS or lumpect:.tw.
21	interventional ultrasonography/
22	echomammography/

23	((ultras: or echograph: or US) adj21 stag:.tw.
24	((magnetic resonance imaging or MRI or positron emission tomography or PET) adj21 stag:.tw.
25	cancer staging/
26	coloring agent/
27	radiopharmaceutical agent/
28	(axill: adj25 (manag: or completion or sentinel or SN or SNB or SLN or SLNB or ALND)).mp.
29	(axill: adj3 (surg: or sampl: or stag:).mp.
30	((block or lymph node or axillary) adj (clear: or dissect:).mp.
31	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	exp Randomized Controlled Trial/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/ or ((exp Clinical Trial/ or Prospective Study/ or Prospective Studies/) and Random$.tw.) or exp Randomized Controlled Trials as topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/ or exp "Randomized Controlled Trial (Topic)"/ or "Phase 3 Clinical Trial (Topic)"/ or "Phase 4 Clinical Trial (Topic)"/ or ((exp Clinical Trials as Topic/ or exp "Clinical Trial (Topic)"/) and random$.tw.) or Random Allocation/ or Randomization/ or Single-Blind Method/ or Double-Blind Method/ or Single Blind Procedure/ or Double Blind Procedure/ or Triple Blind Procedure/ or Placebos/ or Placebo/ or ((singl$ or doubl$ or tripl$) adj3 (blind$3 or mask$3 or dummy)).tw. or (random$ control$ trial? Or rct or phase III or phase IV or phase 3 or phase 4).tw. or (((phase II or phase 2 or clinic$) adj3 trial$) and random$).tw. or (placebo? Or (unfavour$ adj2 random$)).tw. or (random$ adj3 trial$).mp. or "clinicaltrials.gov".mp.
33	10 and 31 and 32
34	33 not (exp "Animals"/ not "Humans"/)
35	limit 34 to (English language and yr="2007 –Current")
36	limit 35 to editorial
37	limit 35 to (erratum or letter or note)
38	limit 35 to (short survey or tombstone)
39	36 or 37 or 38
40	35 not 39

Database: EBM Reviews – Cochrane Central Register of Controlled Trials from 2007 to January 12, 2018
Search Strategy:

1	axilla/
2	(axill: adj25 breast).tw.
3	exp Breast Neoplasms/
4	((breast adj10 (cancer or carcinoma or adenocarcinoma or neoplasm: or tumo?r)) or (mammary adj10 (cancer or carcinoma or adenocarcinoma or neoplasm: or tumo?r))).tw.
5	Lymphatic Metastasis/
6	Lymph Nodes/de, pa, re, su [Drug Effects, Pathology, Radiation Effects, Surgery]
7	((breast adj milk) or (breast adj tender$)).ti,ab,sh.
8	Sentinel Lymph Node Biopsy/
9	(sentinel lymph node excision or lymphadenectomy).tw.
10	axillary lymph node dissection.mp.
11	Antineoplastic Agents/de, dt, tu, th [Drug Effects, Drug Therapy, Therapeutic Use, Therapy]
12	Chemoradiotherapy/
13	Neoadjuvant Therapy/
14	Radioimmunotherapy/
15	Radiotherapy, Adjuvant/
16	Radiotherapy/
17	Mastectomy/
18	((breast adj conserving surgery) or BCS or lumpect:.tw.
19	Ultrasonography, Interventional/
20	Ultrasonography, Mammary/
21	((ultras: or echograph: or US) adj21 stag:.tw
22	((magnetic resonance imaging or MRI or positron emission tomography or PET) adj21 stag:).tw.
23	*Coloring Agents/
24	Radiopharmaceuticals/
25	Neoplasm Staging/
26	(axill: adj25 (manag: or completion or sentinel or SN or SNB or SLN or SLNB or ALND)).mp.
27	(axill: adj3 (surg: or sampl: or stag:)).mp.
28	((block or lymph node or axillary) adj (clear: or dissect:)).mp.
29	1 or 2 or 3 or 4 or 5 or 6
30	29 not 7
31	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
32	30 and 31
33	limit 32 to (yr="2007 –Current" and English language)

C) Search strategies for the identification of nonrandomized evidence for Question 4

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to August 16, 2018>
Search Strategy:

1	AXILLA/dg, pa, su [Diagnostic Imaging, Pathology, Surgery]
2	(axill: adj25 breast).tw.
3	*Breast Neoplasms/di, dg, pa, su, th [Diagnosis, Diagnostic Imaging, Pathology, Surgery, Therapy]
4	*Lymph Nodes/dg, pa, su [Diagnostic Imaging, Pathology, Surgery]
5	*Lymphatic Metastasis/
6	1 or 2 or 3 or 4 or 5
7	((breast adj milk) or (breast adj tender$)).mp.
8	6 not 7
9	*Sentinel Lymph Node Biopsy/mt [Methods]
10	((sentinel lymph node adj3 (excision or biopsy)) or lymphadenectomy).tw.
11	Neoplasm Staging/
12	9 or 10 or 11
13	*Neoadjuvant Therapy/
14	*Time Factors/
15	(timing adj3 sentinel:).tw.
16	(neoadjuvant adj5 therapy).tw.
17	preoperative chemotherapy.mp.
18	((prior or before or after) adj5 neoadjuvant).tw.
19	13 or 14 or 15 or 16 or 17 or 18
20	12 and 19
21	8 and 20
22	exp animals/ not humans/
23	21 not 22
24	limit 23 to (english language and yr="2007 -Current")
25	limit 24 to (addresses or autobiography or bibliography or biography or case reports or classical article or comment or consensus development conference or consensus development conference, nih or dataset or dictionary or directory or duplicate publication or editorial or "expression of concern" or festschrift or guideline or historical article or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or letter or meta analysis or news or newspaper article or overall or patient education handout or periodical index or personal narratives or portraits or practice guideline or published erratum or retracted publication or "retraction of publication" or "review" or "scientific integrity review" or systematic reviews or twin study or validation studies or video-audio media or webcasts)
26	24 not 25

Database: Embase <1996 to 2019 January 10>
Search Strategy:

1	axilla/
2	(axill: adj7 breast).tw.
3	*breast cancer/di, dm, rt, su, th [Diagnosis, Disease Management, Radiotherapy, Surgery, Therapy]
4	*lymph node/
5	*lymph node metastasis/dm, rt, su, th [Disease Management, Radiotherapy, Surgery, Therapy]
6	1 or 2 or 3 or 4 or 5
7	((breast: adj milk) or (breast: adj tender$)).tw.
8	6 not 7
9	*sentinel lymph node biopsy/
10	((sentinel lymph node adj3 (excision or biopsy)) or lymphadenectomy).tw.
11	*cancer staging/
12	9 or 10 or 11
13	*neoadjuvant therapy/
14	*time factor/
15	(timing adj3 sentinel:).tw.
16	(neoadjuvant adj5 therapy).tw.
17	preoperative chemotherapy.tw.
18	((prior or before or after) adj5 neoadjuvant).tw.
19	13 or 14 or 15 or 16 or 17 or 18
20	12 and 19
21	8 and 20
22	exp animals/ not humans/
23	21 not 22
24	limit 23 to (english language and yr="2007 -Current")
25	limit 24 to (editorial or erratum or letter or note or short survey or tombstone
26	24 not 25

D) Search strategies for the identification of nonrandomized evidence for Question 5

Database: OVID MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Jan 17, 2019
Search Strategy:

1	AXILLA/dg, pa, su [Diagnostic Imaging, Pathology, Surgery]
2	(axill: adj25 breast).tw.
3	*Breast Neoplasms/di, dg, pa, su, th [Diagnosis, Diagnostic Imaging, Pathology, Surgery, Therapy]
4	*Lymph Nodes/dg, pa, su [Diagnostic Imaging, Pathology, Surgery]
5	*Lymphatic Metastasis/
6	1 or 2 or 3 or 4 or 5
7	((breast adj milk) or (breast adj tender$)).mp.
8	6 not 7
9	*Sentinel Lymph Node Biopsy/mt [Methods]
10	((sentinel lymph node adj3 (excision or biopsy)) or lymphadenectomy).tw.
11	Neoplasm Staging/
12	9 or 10 or 11
13	8 and 12
14	RADIOCOLLOID:.mp.
15	*Coloring Agents/
16	Coloring Agents/ad, ae, di, po, sd, tu, th, to [Administration & Dosage, Adverse Effects, Diagnosis, Poisoning, Supply & Distribution, Therapeutic Use, Therapy, Toxicity]
17	(BLUE adj2 DYE).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
18	*Radioisotopes/
19	RADIOISOTOPE:.mp.
20	Image-Guided Biopsy/
21	*Radioactive Tracers/
22	*Ultrasonography/
23	ULTRASO:.tw.
24	*RADIOPHARMACEUTICALS/
25	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26	13 and 25
27	limit 26 to english language
28	limit 27 to yr="2007 -Current"
29	limit 28 to (addresses or autobiography or bibliography or biography or case reports or classical article or comment or consensus development conference or consensus development conference, nih or dataset or dictionary or directory or duplicate publication or editorial or "expression of concern" or festschrift or guideline or historical article or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or letter or meta analysis or news or newspaper article or overall or patient education handout or periodical index or personal narratives or portraits or practice guideline or published erratum or retracted publication or "retraction of publication" or "review" or "scientific integrity review" or systematic reviews or twin study or validation studies or video-audio media or webcasts)
30	28 not 29

Database: Embase <1996 to 2019 January 16>
Search Strategy:

1	[AXILLA/dg, pa, su [Diagnostic Imaging, Pathology, Surgery]]
2	(axill: adj25 breast).tw.
3	[*Breast Neoplasms/di, dg, pa, su, th [Diagnosis, Diagnostic Imaging, Pathology, Surgery, Therapy]]
4	[*Lymph Nodes/dg, pa, su [Diagnostic Imaging, Pathology, Surgery]]
5	*Lymphatic Metastasis/
6	1 or 2 or 3 or 4 or 5
7	((breast adj milk) or (breast adj tender$)).mp.
8	6 not 7
9	[*Sentinel Lymph Node Biopsy/mt [Methods]]
10	((sentinel lymph node adj3 (excision or biopsy)) or lymphadenectomy).tw.
11	Neoplasm Staging/
12	9 or 10 or 11
13	8 and 12
14	RADIOCOLLOID:.mp.
15	*coloring agent/
16	(BLUE adj2 DYE).mp.
17	*radioisotope/
18	RADIOISOTOPE.mp.
19	image guided biopsy/
20	*tracer/

21	*echography/
22	ULTRASO:.tw.
23	*radiopharmaceutical agent/
24	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25	13 and 24
26	limit 25 to (english language and yr="2007 -Current")
27	exp ANIMALS/ not HUMANS/
28	26 not 27

Appendix 3: Selection criteria: Management of the axilla in early-stage breast cancer
Selection criteria: Management of the axilla in early-stage breast cancer

Research questions:

Q1. Which patients with early-stage breast cancer require axillary staging (i.e., sentinel node excision [SLNB], axillary lymph node dissection [ALND], or ultrasound [US])?

Q2. For women with early-stage breast cancer who did not receive neoadjuvant chemotherapy (NAC), and are sentinel lymph node negative at diagnosis:

a. Is further axillary treatment (i.e., radiation, or surgery) indicated?
b. What sentinel node negative patients subgroups are most likely to benefit from further axillary treatment with radiation therapy?

Q3. 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 patients subgroups are most likely to benefit from further axillary treatment either with radiation or with surgery or both?

Q4. For women who were treated with NAC:

a. If the lymph node is negative at diagnosis, what axillary treatment (i.e., radiation or surgery) is indicated after chemotherapy?
b. If the lymph node is positive at diagnosis, what axillary treatment (i.e., radiation or surgery) is indicated after chemotherapy?
c. When is the best timing for performing sentinel node excision: prior or following NAC?

Q5. Among patients with early breast cancer appropriate for axillary staging:

a. Is there a better identification rate with single or dual tracer?
b. Is there a better identification rate with US-guided SLNB or traditional SLNB?
c. Is there a better identification rate with US or SLNB?

Systematic reviews:
INCLUDED
Studies that:

- were published in or after 2011, and had a search strategy cut-off in or after 2010
- address at least one research question with similar inclusion and exclusion criteria than ours
- comprehensively searched at least one database
- include search date and search terms
- include an assessment of the quality of included evidence
- extracted relevant info from each study
- analyzed the data appropriately
- included patients (women and men) with early-stage breast cancer, (i.e., Stages I, IIA, and IIB; prognostic groups T1, T2, N0, N1mi, N1, M0), and tumour size ≤5 cm.
    - the patients can be node negative or positive at diagnosis or after NAC
- Examined interventions and comparisons such as:

- In all patients:
    i. axillary staging performed by surgery (axillary lymph node dissection [ALND] or sentinel node excision [SLNB] or imaging compared with no staging;
- In the subgroup of patients treated with NAC and who need staging:
    i. SLNB before NAC compared with SLNB after NAC
    ii. SLNB with single tracer compared with SLNB with dual tracer
    iii. US-guided SLNB compared with non-utrasound guided SLNB
    iv. US staging compared with SLNB
- In the subgroup of patients who are node negative at diagnosis or after NAC:
    i. further axillary treatment with radiation therapy compared with no further treatment to the axilla
- In the subgroup of patients who are node positive at diagnosis or after NAC:
    i. radiation therapy and surgery (ALND, SLNB) compared with no treatment
    ii. radiation therapy compared with surgery (ALND, SLNB)
    iii. radiation therapy compared with no treatment
    iv. surgery compared with no treatment

EXCLUDED

Studies that were:

- abstract of systematic reviews
- non-English-language reports
- published before 2011
- reports of results for patients with advanced-stage breast cancer
- reports of results for patients with early-stage breast cancer (as described above) that also included patients with more advanced stages, but did not present separate analyses
- reports that examined interventions that were other than those listed (e.g., radiotherapy dosage, whole breast radiotherapy)
- reports that focused on outcomes that were not of interest (e.g., cost)

Table 1. Research questions, comparisons and inclusion criteria, with relative area of interest for each question

Population*	Intervention	Comparison	Outcomes	Design	Cut-off dates	Area of interest
Q1. Which patients with early breast cancer require axillary staging (i.e., Sentinel Node Excision [SLNB], axillary dissection [ALND], or ultrasound [US])?						
Women or men with early-stage breast cancer: i.e., stage I, IIA, IIB; Prognostic groups: T1, T2, N0,N1mi, N1, M0, tumour size ≤5 cm	Axillary staging (performed by surgery or imaging)	No staging	Measures of: • survival, • disease control, • QOL, • adverse events, (e.g., lymphedema rate), • surgical complications rate, • ability to map • procedure completion rate.	• Guidelines • Systematic reviews • RCTs with a sample size = or > 100 • If no RCTs, comparative studies Primary studies with a sample size ≥100	*Guidelines*: 2014 to Dec 5, 2016 *Systematic reviews*: 2011 to Jun 9 2017 *Primary studies*: 2007 to February 18, 2020	Surgery

QOL = quality of life; RCT = randomized controlled trial

Q2. 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 (i.e., radiation, or surgery) indicated?** **b. What sentinel node-negative patients subgroups are most likely to benefit from further axillary treatment (e.g., with radiation therapy)?**						
Patients (as defined in Q1) who are negative at SLNB and have not received NAC	Further axillary treatment with: e.g., Radiation therapy	No further axillary treatment	Measures of: • survival, • disease control, (i.e., local, regional, distant recurrences), • QOL, • adverse events.	• Guidelines • Systematic reviews • RCTs • If no RCTs, comparative studies Primary studies with a sample size ≥100	*Guidelines*: 2014- to Dec 5, 2016 *Systematic reviews*: 2011 to Jun 9, 2017 *Primary studies*: 2007 to February 18, 2020	Radiation Oncology

QOL = quality of life; RCT = randomized controlled trial

Q3. 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 patients subgroups are most likely to benefit from further axillary treatment either with radiation or with surgery or both?						
Patients (as defined in Q1) who are positive at SLNB, and have not received NAC	SLNB and no further axillary surgery	ALND	Measures of: • survival, • disease control, (i.e., local, regional, distant recurrences), • QOL, • adverse events.	• Guidelines • Systematic reviews • RCTs • If no RCTs, comparative studies Primary studies with a sample size ≥100	*Guidelines*: 2014- to Dec 5, 2016 *Systematic reviews*: 2011 to Jun 9, 2017 *Primary studies*: 2007 to February 18, 2020]	Radiation Oncology or Surgery
	Radiation therapy of the axilla (regional node irradiation)	No radiation to the regional lymph nodes				
	Radiation therapy	Further surgery (ALND)				
	Radiation therapy	No treatment				

ALND = axillary lymph node dissection; QOL = quality of life; RCT = randomized controlled trail;

Q4. For women who were treated with NAC: **a. If the lymph node is negative at diagnosis, what axillary treatment (i.e., radiation or surgery) indicated after chemotherapy?** **b. If the lymph node is positive at diagnosis, what axillary treatment (i.e., radiation or surgery) indicated after chemotherapy?** **c. When is the best timing for performing sentinel node excision: prior or following NAC?**						
a. Initially node negative after NAC						
Patients (as defined in Q1) who received NAC and are negative at SLNB	Further axillary treatment with: e.g., Radiation therapy	No further axillary treatment	Measures of: • survival, • disease control, (i.e., local, regional, distant recurrences), • QOL, • adverse events.	• Guidelines • Systematic reviews • RCTs • If no RCTs, comparative studies Primary studies with a sample size ≥100	*Guidelines*: 2014 to Dec 5, 2016 *Systematic reviews*: 2011 to Jun 9, 2017 *Primary studies*: 2007 February 18, 2020	Radiation Oncology
b. Initially node positive after NAC						
Patients (as defined in Q1) who received NAC and are positive at SLNB	SLNB	ALND	Measures of: • survival, • disease control, (i.e., local, regional, distant recurrences), • QOL, • adverse events.	• Guidelines • Systematic reviews • RCTs • If no RCTs, comparative studies Primary studies with a sample size ≥100	*Guidelines*: 2014- to Dec 5, 2016 *Systematic reviews*: 2011 to Jun 9,2017 *Primary studies*: 2007 to February 18, 2020	Radiation Oncology or Surgery
	Radiation therapy and surgery (ALND)	No treatment to the axilla				
	Radiation therapy	Surgery (ALND)				
	Surgery (ALND)	No treatment to the axilla				
c. timing						
Patients (as defined in Q1) who have received NAC	SLNB before NAC	SLNB after NAC	Measures of: • survival, • disease control, • QOL, • false negative rate, • adverse events, (e.g., lymphedema rate), • surgical complications rate, • ability to map, procedure completion rate.	•Systematic reviews •RCTs with a sample size = or > than 100 •If no RCTs, comparative studies Primary studies with a sample size ≥100	*Guidelines:* 2014- to Dec 5, 2016 *Systematic reviews*: 2011 to Jun 9, 2017 *Primary studies*: 2007 to February 18, 2020	Medical Oncology or Surgery or Radiation Oncology or Imaging

ALND = axillary lymph node dissection; NAC = neoadjuvant chemotherapy; QOL = quality of life; RCT = randomized controlled trial; SLNB = sentinel lymph node biopsy

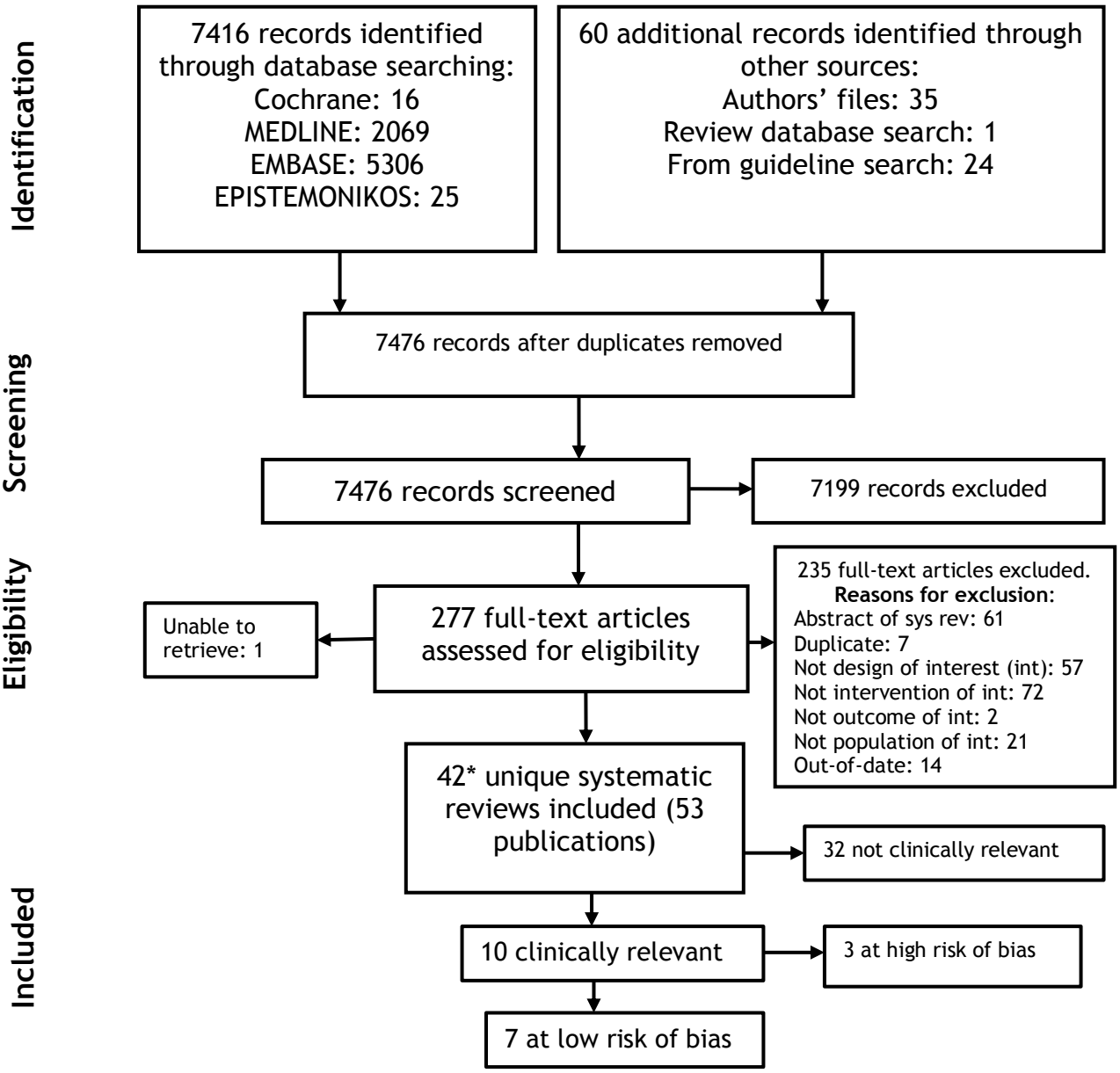
Q5. Among patients with early breast cancer appropriate for axillary staging:
a. **Is there a better identification rate with single or dual tracer ?**
b. **Is there a better identification rate with US-guided SLNB or traditional SLNB?**
c. **Is there a better identification rate with US or SLNB?**

Population	Intervention	Comparison	Reference standard	Outcomes	Design	Cut-off dates	Area of interest
The subgroup of patients with early-stage breast cancer who are treated with NAC	a. single tracer	a. dual tracer	Hystopathology	Measures of: • survival, • disease control, • QOL, • false negative rate, • adverse events, (e.g., lymphedema rate), • surgical complications rate, • ability to map, procedure completion rate. • Identification rate	• Systematic reviews • RCTs with a sample size = or > than 100 • If no RCTs, comparative studies Primary studies with a sample size ≥100	*Guidelines*: 2014- to Dec 5, 2016 *Systematic reviews*: 2011 to Jun 9, 2017 *Primary studies*: 2007 to February 18, 2020	Medical Oncology or Surgery or Radiation Oncology or Imaging
	b. US-guided SLNB	b. traditional SLNB					
	c. US	c. SLNB					

NOTES:
We excluded patients with ductal carcinoma in situ (DCIS) because they are stage zero and should not require staging since the cells can't spread beyond mild duct lining. We exclude patients with stage III cancer because it is covered in our locally advanced guideline.

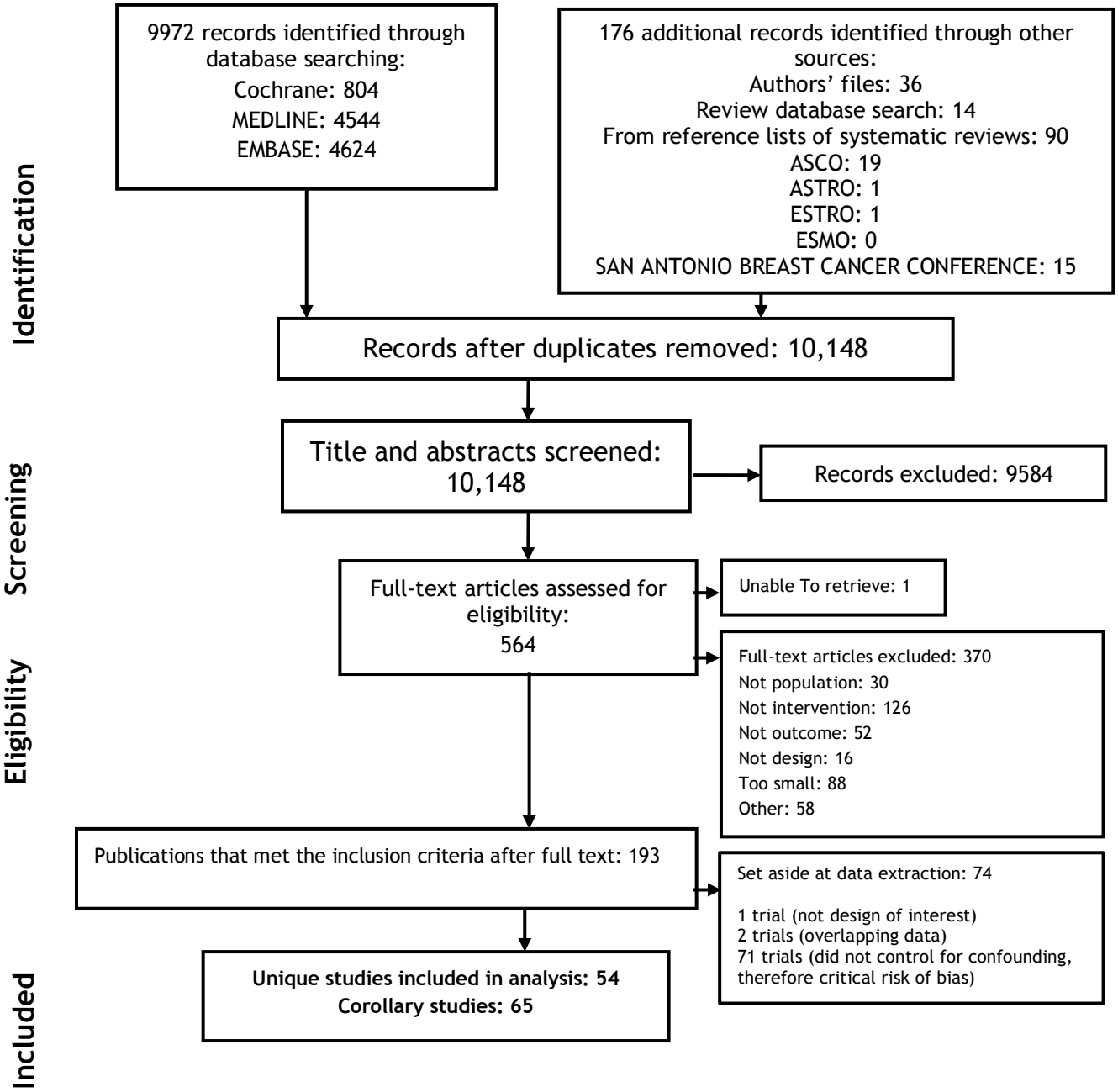
ALND = axillary lymph node dissection; NAC = neo-adjuvant chemotherapy; QOL = quality of life; RCT = randomized controlled trial; SLNB = sentinel lymph node biopsy; US = ultrasound.

Appendix 4: PRISMA Flow Diagram
APPENDIX 4A: Systematic reviews



* Three of these reviews were relevant for more than one question [84,88,104]

APPENDIX 4B: Primary studies



NOTES:

- Ongoing trials that were identified through a search of clinicaltrials.gov, and have not been otherwise published, are not counted in this diagram.
- Some trials were included in multiple questions, and they appear multiple times in the evidence tables, but they are counted only once here.

Appendix 5. Quality assessment of practice guidelines and systematic reviews

Appendix 5A Appraisal of the ASCO 2017 guideline [3] with AGREE II by two reviewers: (FB†, and NV‡)

DOMAIN 1. SCOPE AND PURPOSE

1) The overall objective(s) of the guideline is (are) specifically described.

1 Strongly Disagree	2	3	4	5	6x‡	7 x† Strongly Agree

Comments:
Overall objectives are stated in the abstract and in the intro: to conduct a formal update of the 2005 guideline.

2) The health question(s) covered by the guideline are specifically described.

1 Strongly Disagree	2	3	4	5	6	7x†x‡ Strongly Agree

Comments:
The question is stated as a general question and then three specific clinical questions are spelled out.
Guideline Question
● How should the results of sentinel node biopsy (SNB) be used in clinical practice? What is the role of SNB in special circumstances in clinical practice? What are the potential benefits and harms associated with SNB?
Clinical Question 1
Can ALND be avoided in patients who have tumour-free (ie, negative) findings on SNB?
Clinical Question 2
Is ALND necessary for all patients with metastatic findings on SNB?
Clinical Question 2.1. For women with metastatic sentinel lymph nodes (SLNs) planning to undergo breast-conserving surgery (BCS) with whole-breast radiotherapy?
Clinical Question 2.2. For women with nodal metastases who are planning to undergo mastectomy?
Clinical Question 3
What is the role of SNB in special circumstances in clinical practice (Data Supplement 8)?

3) The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

1 Strongly Disagree	2	3	4	5x‡	6	7x† Strongly Agree

Comments:
populations are defined in the questions, and in the methods section

DOMAIN 2. STAKEHOLDER INVOLVEMENT

C) The guideline development group includes individuals from all relevant professional groups.

1 Strongly Disagree	2	3	4	5	6x†	7x‡ Strongly Agree

Comments:
In one of the supplementary data documents it is stated: Members of the update panel were representing: medical oncology, surgery, community oncology, patient/advocacy representation, and guideline implementation.

D) The views and preferences of the target population (patients, public, etc.) have been sought.

1 Strongly Disagree	2	3	4	5x‡	6x†	7* Strongly Agree

Comments:
The Working Group includes patient representatives. Reported on front page left column.

E) The target users of the guideline are clearly defined.

1 Strongly Disagree	2	3	4	5	6	7x†x‡ Strongly Agree

Comments: reported in the Bottom line box:

Target Audience

Medical oncologists, radiation oncologists, pathologists, surgeons, oncology nurses, patients/caregivers, and guideline implementers.

DOMAIN 3. RIGOUR OF DEVELOPMENT

7. Systematic methods were used to search for evidence.

1 Strongly Disagree	2	3	4	5	6	7 x†x‡ Strongly Agree

Comments: The authors searched PubMed and the Cochrane Library. Search strings for the search are reported in data Supplement 3.

8. The criteria for selecting the evidence are clearly described.

1 Strongly Disagree	2	3	~~4x~~‡	5	6x†	7x† Strongly Agree

Comments:

Inclusion and exclusion criteria are reported in the methods section:

Articles were selected for inclusion in the systematic review of the evidence if they met the following criteria:

- Population: women with early-stage breast cancer.
- For Clinical Questions 1 and 2, fully published or recent meeting presentations of English-language reports of phase III RCTs or rigorously conducted systematic reviews or meta-analyses. Trials with a population of women with early breast cancer that compared SNB with the standard treatment of ALND; this included studies comparing SNB alone with SNB plus ALND, for those patients with negative SLNs.
- For special circumstances, prospective comparative cohort trials were accepted (criteria listed in Data Supplement 8).

Articles were excluded from the systematic review if they were: (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, or narrative reviews; and (3) published in a language other than English.

9) The strengths and limitations of the body of evidence are clearly described.

1 Strongly Disagree	2	3	4	5	6x‡	7 x† Strongly Agree

Comments:

See ***Study Quality and Table 2 in the journal article (2014 publication)***

As summarized in Table 2, study quality was formally assessed for the nine RCTs identified. Design aspects related to individual study quality were assessed by one reviewer, with factors such as blinding, allocation concealment, placebo control, intention to treat, funding sources, and so on, generally indicating a low to intermediate potential risk of bias for most of the identified evidence. Follow-up times varied among studies, lowering the comparability of the results. The Methodology Supplement provides for definitions of ratings for overall potential risk of bias.

10) The methods for formulating the recommendations are clearly described.

1 Strongly Disagree	2	3	4	5	6x‡	7x† Strongly Agree

Comments:

The authors used GLIDES with BridgeWiz

11) The health benefits, side effects, and risks have been considered in formulating the recommendations.

1 Strongly Disagree	2	3	4	5	6x‡	7x† Strongly Agree

Comments:

yes Table 1 in the article lists the health benefits and side effects. For each reccommendation there is a section on literature review and analysis where benefits and side effects are considered.

12. There is an explicit link between the recommendations and the supporting evidence.

1	2	3	4	5	6	7x†x‡

Strongly Disagree						**Strongly Agree**

Comments: Same as above

13. The guideline has been externally reviewed by experts prior to its publication.

1 Strongly Disagree	**2**	**3**	**4**	**5**	**6**	**7 x† x‡ Strongly Agree**

Comments: Sent for external comments before publication and then peer reviewed when published in JCO

14. A procedure for updating the guideline is provided.

1 Strongly Disagree	**2**	**3**	**4x‡**	**5**	**6x‡**	**7x† Strongly Agree**

Comments: Yes described in detail in the supplementary data file

DOMAIN 4. CLARITY OF PRESENTATION

15. The recommendations are specific and unambiguous.

1 Strongly Disagree	**2**	**3**	**4**	**5**	**6**	**7x† x‡ Strongly Agree**

Comments: Presented in text and in the Bottom line box

16. The different options for management of the condition or health issue are clearly presented.

1 Strongly Disagree	**2**	**3**	**4**	**5**	**6**	**7x† x‡ Strongly Agree**

17. Key recommendations are easily identifiable.

1 Strongly Disagree	**2**	**3**	**4**	**5**	**6**	**7x† x‡ Strongly Agree**

DOMAIN 5. APPLICABILITY

18. The guideline describes facilitators and barriers to its application.

1 Strongly Disagree	**2**	**3 x†**	**4x‡**	**5**	**6**	**7 Strongly Agree**

Comments:
Barrier to the application were the inclusion criteria of the studies that formed the basis for the recommendations. Some women were not represented (large tumours, triple negative cancers… so recommendations could not be issued for them. I am not sure this is a barrier to the application of the guideline, it is a limitation of the guideline

19. The guideline provides advice and/or tools on how the recommendations can be put into practice.

1 Strongly Disagree	**2x†**	**3**	**4**	**5x†**	**6x‡**	**7 Strongly Agree**

Comments: I could not see, although the guideline panel included experts in guideline implementation

20. The potential resource implications of applying the recommendations have been considered.

1 Strongly Disagree	**2x†**	**3**	**4**	**5x†**	**6x‡**	**7 Strongly Agree**

21. The guideline presents monitoring and/or auditing criteria.

1 Strongly Disagree	**2x‡ x†**	**3**	**4**	**5**	**6**	**7x† Strongly Agree**

Comments: like all ASCO guidelines it undergoes review every year, and specifics are described in supplementary files.

The Authors do not present thresholds, see AGREE II MANUAL for this question.

DOMAIN 6. EDITORIAL INDEPENDENCE

22. The views of the funding body have not influenced the content of the guideline.

1 Strongly Disagree	2	3	4	5	6x‡	7 x† Strongly Agree

23. Competing interests of guideline development group members have been recorded and addressed.

1 Strongly Disagree	2	3	4	5	6	7x†x‡ Strongly Agree

OVERALL GUIDELINE ASSESSMENT

For each question, please choose the response which best characterizes the guideline assessed:

Overarching Clinical Question

How should the results of SNB be used in clinical practice, and what are the potential benefits and harms associated with SNB?

Rate the overall quality of this guideline.

1 Lowest possible quality	2	3	4	5	6x†x‡	7 Highest possible quality

APPENDIX 5B: Risk of bias of the systematic reviews that met the inclusion criteria assessed with the ROBIS tool [76,280])

Table 1: Phase 1: assessing the relevance

Author, year. Title, Country	Does this review align with the scope of ours?	Does this review align with the methods of ours?	Is this review current (≤2 years)?	Comments	Use as is
Question 1					
Liang, 2017 [7] Omission of axillary staging in elderly patients with early-stage breast cancer impacts regional control but not survival: A systematic review and meta-analysis. **Country:** Canada	**Yes** The scope of this systematic review and meta-analysis is limited to a population of elderly women **Population:** Elderly patients (≥70 years) with early stage (T1/T2, N0) breast cancer **Intervention/Comparison:** Axillary staging with a sentinel node biopsy, axillary sampling or axillary node dissection vs. no axillary surgery **Outcomes**: Local-regional recurrence, disease-free survival, OS. RCTs (two)	**Yes** includes only older women	**No** **Search cut-off date:** August 2014	Can be used for the elderly population and updated. This is a review of direct patient outcomes (i.e. review of treatment interventions).	**Yes** with update; partial match for population
Bromham, 2017 [84-86] Axillary treatment for operable primary breast cancer. **Country:** UK (Also relevant to Q4)	**No** This is a review with a larger scope than ours, and included a different population than ours. **Population:** Women with operable breast cancer T1-3, and T4b with only minor skin involvement; N0-1, and M0 **Intervention/Comparison:** 1. No axillary surgery vs. full axillary surgery surgery 2. Axillary sampling vs. full axillary surgery 3. Sentinel node biopsy vs. full axillary surgery 4. Radiotherapy vs. full axillary surgery 5. Less surgery vs. ALND And in subgroup analyses: 6. Radiotherapy vs. no radiotherapy 7. Further treatment vs. no further treatment **Outcomes:** All cause mortality, Loco-regional recurrence, lymphedema, arm or shoulder movement impairement	**Yes**, however he population included here is more advanced.	**Yes** **Search cut-off date:** 12 March 2015	Can be used as a source of evidence. It's a Cochrane review Because of the difference in the population, we can use only part of the included evidence. Many of the included studies were old, and did not report the stage or size. This is a review of direct patient outcomes (i.e., review of treatment interventions).	**No**
Zhang, 2013 [85] Is axillary dissection necessary for breast cancer in old women? A meta-analysis of randomized clinical trials **Country:** China	**No** It focuses on a subgroup of older pts who mainly have larger tumours that we would not include. The authors conducted a meta-analysis of 4 RCTs. [281] **Population:** women ≥60 years of age. Only one of the studies has pts with tumours<2 cm (Martelli 2005) **Intervention/Comparison:** ALND vs. No ALND **Outcomes:** OS, DFS, QOL	**No** Meta-analysis was performed of RCTs and observational studies together	**No** **Search cut-off date:** 1966 to August 2011	Studies included are old, population is not the same as ours. Can be used a s a source of evidence. This is a review of direct patient outcomes (i.e. review of treatment interventions).	**No**

Author, year. Title, Country	Does this review align with the scope of ours?	Does this review align with the methods of ours?	Is this review current (≤2 years)?	Comments	Use as is
Question 2					
Lyman, 2017, 2014 [3,4] ASCO guideline Sentinel Lymph Node Biopsy for Patients With Early-Stage Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. **Country:** US	**No** The scope of this guideline is limited to SLNB. **Population:** Women with early-stage breast cancer, including women with operable breast cancer and multicentric tumours, with ductal carcinoma in situ (DCIS), who are planning to have mastectomy, who previously underwent breast and/or axillary surgery, or who received preoperative/neoadjuvant systemic therapy. **Intervention/Comparison:** SLNB vs. ALND **Outcomes:** Survival, disease control, and adverse events	**Yes, however it includes populations that we excluded (DCIS)**	**Yes**, the update is current **Search cut-off date:** December 2016	Can be used as a source of evidence. The results of the updated systematic review are in Supplement 2 (http://ascopubs.org/doi/suppl/10.1200/JCO.2016.71.0947/suppl_file/ds_2016.710947.pdf) This is a review of direct patient outcomes (i.e. review of treatment interventions).	**Possibly for the questions regarding SLNB**
Early Breast Cancer Trialists' Collaborative Group IPD [86] Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomized trials. **Country**: multiple	**Yes** **Poulation:** women from 22 trials with 1 to 3 positive lymph nodes. Of these, 1594 women had node-negative disease **Intervention/Comparison:** Surgery + RT of the chest wall, internal mammary chain, and supraclavicular and/or axillary lymph nodes vs. Surgery alone **Outcomes:** Recurrence, breast cancer mortality	**Yes although this is a IPD**	**Yes** the studies included were started much earlier than 2007, but pts were followed up until 2009	Can be used. Has a 20-yrs follow up for OS. Since the data are at the patient level, it is reported among the primary studies. This is a review of direct patient outcomes (i.e. review of treatment interventions).	**yes**
van Wely, 2011 [87,282] Systematic review of the effect of external beam radiation therapy to the breast on axillary recurrence after negative sentinel lymph node biopsy **Country:** The Netherlands	**Yes** Systematic review and meta-analysis **Population:** women with negative SN **Intervention/Comparison:** External beam RT vs. no RT **Outcomes:** axillary recurrence, survival	**No** Includes prospective and retrospective cohort studies together	**No** **Search cut-off date:** *nr;* most recent included trial dates 2010	Can be used as a source of evidence. This is a review of direct patient outcomes (i.e. review of treatment interventions).	No
Verma, 2016 [88] Role of internal mammary node radiation as a part of modern breast cancer radiation therapy: A systematic **Country:** US	**Yes** This paper is a systematic review of radiation to the internal mammary chain; it could fit as a subset of regional nodal radiation. **Population:** patients with favourable or negative SLN at diagnosis or after NAC **Intervention/Comparison:** IMLN RT-RNI vs. no IMLN RT-RNI **Outcomes: OS, AE**	**No** No quality assessment was reported. Only RCTs were included. The authors did not conduct a meta-analysis because	**Yes** **Search cut-off date: May** 2015	Can be used as source of evidence, ref 29 is about pts who received NAC – susbsset of regional node irradiation. This is a review of direct patient outcomes (i.e. review of treatment interventions).	**No**

Author, year. Title, Country	Does this review align with the scope of ours?	Does this review align with the methods of ours?	Is this review current (≤2 years)?	Comments	Use as is
(Also relevant to Q4)		of heterogeneity of interventions.			
Matuschek, 2017 [89] The benefit of adjuvant radiotherapy after breast-conserving surgery in older patients with low risk breast cancer- a meta-analysis of randomized trials **Country:** Germany	**No** **Population:** elderly women with early-stage breast cancer **Intervention/Comparison:** endocrine therapy and RT to the whole breasts vs. endocrine therapy alone **Outcomes:** local recurrence and OS	**No** No quality assessment	**No** **Search cut-off date:** *nr* most recent included article published in 2015	Can be used as a source of evidence. This is a review of direct patient outcomes (i.e., review of treatment interventions).	**No**
Gebruers, 2015 [90] Incidence and Time Path of Lymphedema in Sentinel Node Negative Breast Cancer Patients: A Systematic Review **Country:** Belgium	**Yes** include because we want accurate complications of sentinel node or axillary dissection, which is lymphedema, **Population:** SLNB negative breast cancer patients who underwent SLNE or ALND **Intervention/Comparison:** no comparison **Outcomes**: lymphedema rate (incidence, prevalence) and time path	**No**. It included observational studies because of its question. No comparative studies included	**No** **Search cut-off date:** October 2013	Can be used as a background info for SLNB neg pts for the adverse event lymphedema. This is a review of direct patient outcomes (i.e., review of treatment interventions).	**Background**
van Nijnatten, 2015 [91] The diagnostic performance of sentinel lymph node biopsy in pathologically confirmed node positive breast cancer patients after neoadjuvant systemic therapy: A systematic review and meta-analysis **Country:** The Netherlands	**No**. The population in included studies are stages T0-4 N1-3 **Population:** Female pts with node positive (pathologically proven) receiving NAC and undergoing SLNB followed by ALND **Intervention/Comparison:** SLNB vs. hispathology (gold standard) **Outcomes:** False negative rate, pCR	**Yes**	**Yes** **Search cut-off date:** June 2015	No different population. This is a review of indirect patient outcomes (i.e., review of diagnostic test interventions).	**No**
Shaitelman, 2017 [92] Radiation therapy targets and the risk of breast cancer-related lymphedema: a systematic review and network meta-analysis **Country:** US	**No** This systematic review and network meta-analysis covers only lymphedema from RT in diverse sites **Population:** *nr* **Intervention/Comparison:** RT in various sites **Outcomes:** lymphedema incidence	**No**	**Yes** **Search cut-off date:** December 2015	This manuscript does not specify the patients' condition (whether they were negative at diagnosis, or after NAC) It can be used as a source of evidence for adverse events. This is a review of direct patient outcomes (i.e., review of treatment interventions).	**No**

Author, year. Title, Country	Does this review align with the scope of ours?	Does this review align with the methods of ours?	Is this review current (≤2 years)?	Comments	Use as is
Zhao, 2017 [93] Can axillary radiotherapy replace axillary dissection for patients with positive sentinel nodes? A systematic review and meta-analysis **Country:** China	‡Q4C **Population:** Clinically node negative pts with a positive lymph node **Intervention/Comparison:** axillary RT vs. ALND **Outcomes:** OS, DFS, ARR	**Yes**	**Yes** **Search cut-off date:** 2016	Does not report the month of search, but it is very relevant for this question. This is a review of direct patient outcomes (i.e. review of treatment interventions).	**Yes**
Bromham, 2017 [84] Axillary treatment for operable primary breast cancer **Country:** UK (Also relevant to Q 1)	**No** This is a review with a larger scope than ours. Most studies include more advanced stgees **Population:** Women with operable breast cancer T1-3, and T4b with only minor skin involvement; N0-1, and M0 **Intervention/Comparison:** 1. No axillary surgery vs. full axillary surgery surgery 2. Axillary sampling vs. full axillary surgery 3. Sentinel node biopsy vs. full axillary surgery 4. Radiotherapy vs. full axillary surgery 5. Less surgery vs. ALND And in subgroup analyses: 6. Radiotherapy vs. no radiotherapy 7. Further treatment vs. no further treatment **Outcomes:** All cause mortality, Loco-regional recurrence, lymphedema, arm or shoulder movement impairement	**Yes**, however he population included here is more advanced.	**Yes** **Search cut-off date:** 12 March 2015	Can be used as a source of evidence. It's a Cochrane review Because of the difference in the population, we can use only part of the included evidence. Many of the included studies were old, and did not report the stage or size. This is a review of direct patient outcomes (i.e., review of treatment interventions).	**No**
Zhang 2016b [94] Axillary radiotherapy: an alternative treatment option for adjuvant axillary management of breast cancer **Country:** China	This meta-analysis includes 4 RCTs comparing RT with ALND. **Population:** 85% of participants were clinically node negative; 2 of the trials included pts with node positive at SLNB **Intervention/Comparison:** Axillary RT vs. ALND **Outcomes:** DFS; OS; recurrence rate	**No** because the authors did not report any evaluation of the quality of included studies other than RCT design	**No** **Search cut-off date:** September 2015	It can be used as a source of evidence. This is a review of direct patient outcomes (i.e., review of treatment interventions).	**No** Q4c
Verma, 2016 [88] Role of internal mammary node radiation as a part of modern breast cancer radiation therapy: A systematic review	This is a systematic review of radiation to the internal mammary chain; it could fit as a subset of regional nodal radiation **Yes**	**No** No quality assessment was reported. Only RCTs were included. The authors did not	**Yes** **Search cut-off date:** **May** 2015	Can be used as source of evidence, ref 29 is about pts who received NAC. This is a review of direct patient outcomes (i.e., review of treatment interventions).	**No**

Author, year. Title, Country	Does this review align with the scope of ours?	Does this review align with the methods of ours?	Is this review current (≤2 years)?	Comments	Use as is
Country: US (Also relevant to Q3	**Population:** patients with positive or negative SLN at diagnosis or after NAC **Intervention/Comparison:** IMLN RT-RNI vs. no IMLN RT-RNI **Outcomes: OS, AE**	conduct a meta-analysis because of heterogeneity of interventions.			
Schmidt-Hansen 2016 [31] Axillary surgery in women with sentinel node-positive operable breast cancer: a systematic review with meta-analyses **Country:** UK	**Yes** This systematic review aimed at examining benefits and harms of alternative approaches to axillary surgery including omitting the surgery. **Population:** women with operable breast cancer with positive SLN **Intervention/Comparison:** ALND vs. no axillary surgery; and ALND vs. axillary radiotherapy without ALND **Outcomes:** OS; DFS; disease control in the axilla; breast cancer recurrence; adverse events; longterm complications; and quality-of-life.	**Yes** The authors included only RCTs	**Yes** **Search cut-off date:** March 2015	**Yes** Q4a, Q4c. This is a review of direct patient outcomes (i.e., review of treatment interventions).	Yes
Huang, 2016 [95] Recommendation for axillary lymph node dissection in women with early breast cancer and sentinel node metastasis: A systematic review and meta-analysis of randomized controlled trials using the GRADE system **Country:** Taiwan	**Yes** Q4E **Population:** Woment with SLN micro-, and macro-metastases **Intervention/Comparison:** ALND vs. no ALND **Outcomes:** OS, DFS, recurrence rate, and surgical complications	**Yes**	**Yes** **Search cut-off date:** February 2016	This is a review of direct patient outcomes (i.e., review of treatment interventions).	**Yes**
El Hage Chehade, 2016a [96] Refining the performance of sentinel lymph node biopsy post-NAC in patients with pathologically proven pre-treatment node-positive breast cancer: an update for clinical practice **Country:** UK	**No** does not specify the stage **Population:** Female pts with with node positive (pathologically proven) receiving NAC and undergoing SLNB followed by ALND **Intervention/Comparison:** *nr* **Outcomes:** Identification rate, false negative rate	**No** No quality assessment, no characteristics of included trials	**Yes** **Search cut-off date:** January 2016	Not for use.	No
Verbelen, 2014 [97] Shoulder and arm morbidity in sentinel node-negative breast	**Yes** for Q2, side effects outcomes. **Population:** Sentinel node negative women **Intervention/Comparison:** No comparison	**Yes**	**No** **Search cut-off date:** October 2013	This review dos not provide comparative data, but the information reported is a useful background for adverse events	**No**

Author, year. Title, Country	Does this review align with the scope of ours?	Does this review align with the methods of ours?	Is this review current (≤2 years)?	Comments	Use as is
cancer patients: a systematic review **Country:** Belgium	**Outcomes:** Shoulder and amr imparments after SLNB				
Question 3					
Li, 2015 [98] Axillary lymph node dissection versus sentinel lymph node biopsy alone for early breast cancer with sentinel node metastasis: A meta-analysis **Country:** China	**Yes** Q3A **Population:** women with early breast cancer and axillary metastases **Intervention/Comparison:** SLNB vs. ALND **Outcomes:** OS, DFS, loco-regional recurrence, adverse events	**Yes**, they included observational studies as well as RCTs, and they analysed them separately. They used the Newcastle-Ottawa scale for rating the quality of non-RCTs	**No** **Search cut-off date:** Feb 2014	It can be used. This is a review of direct patient outcomes (i.e., review of treatment interventions).	Yes with update
Joyce, 2015 [99] Meta-analysis to determine the clinical impact of axillary lymph node dissection in the treatment of invasive breast cancer **Country:** Ireland	**Yes** Q3E **Population:** pts with invasive breast cancer **Intervention/Comparison:** ALND vs. no ALND **Outcomes:** OS, recurrence-free survival	**No** Only searched MEDLINE; included only RCTs. It does not report the characteristics of included studies. It does not specify the cancer stage.	**Yes** **Search cut off date:** April 2015	It can be used as a source of evidence. This is a review of direct patient outcomes (i.e., review of treatment interventions)	No
Budach, 2015 [100] Adjuvant radiation therapy of regional lymph nodes in breast cancer – a meta-analysis of randomized trials- an update **Country:** Germany	**Yes** **Population:** pts with early breast cancer; the population in these studies was for the majority node positive **Intervention/Comparison:** RT of internal mammary nodes + whole breast irradiation vs. whole breast irradiation **Outcomes:** OS, DFS, distant metastasis-free survival	**Yes**	**Yes** **Search cut-off date:** September 2015	Includes 3 major studies. This is a review of direct patient outcomes (i.e. review of treatment interventions)	Yes Q4B
Ram, 2014 [101] Sentinel Node Biopsy Alone versus Completion Axillary Node Dissection in Node	**Yes** Q4A **Population:** clinically negative breast cancer patients who had a positive sentinel lymph node. **Intervention/Comparison:** SLNB vs.ALND	**Yes**. This meta-analysis looks at the non-inferiority of SLNB vs. ALND.	**No** Published in 2014 **Search cut-off date:** *nr*	It includes 3 major studies. This is a review of direct patient outcomes (i.e., review of treatment interventions).	Yes with update

Author, year. Title, Country	Does this review align with the scope of ours?	Does this review align with the methods of ours?	Is this review current (≤2 years)?	Comments	Use as is
Positive Breast Cancer: Systematic Review and Meta-Analysis **Country:** Multiple countries	**Outcomes:** DFS and OS were primary outcomes. Local recurrence rates and surgical morbidity Secondary outcomes were.	It included RCts in the primary analysis and observational studies in a secondary analysis			
Rao, 2013 [102] Axillary node interventions in breast cancer: a systematic review [102,283] **Country:** US (Also Q3? Population is not described enough to say)	**Yes** **Population:** women with breast cancer without palpable lymphnodes or US evidence of axillary lymph node metastases **Intervention/Comparison:** SLNB vs. complete ALND vs. axillary radiation **Outcomes:** isolated recurrence of axillary lymph node metastases, complication rates, and survival	**No** Includes also observational studies. The population is clinically node negative, no description of the SN status	**No** **Search cut-off date:** July 2013	The data collection in the included studies was long time ago (most recent in 2000). I doubt even using it as a source of evidence. This is a review of direct patient outcomes (i.e., review of treatment interventions).	No
Glechner, 2013 [103] Sentinel lymph node dissection only versus complete axillary lymph node dissection in early invasive breast cancer: a systematic review and meta-analysis **Country:** Multiple countries	**Yes** Q3A **Population:** women with early-stage breast cancer **Intervention/Comparison:** SLNB vs. ALND **Outcomes:** 5-year survival, QOL, breast cancer recurrence, and surgery-associated harms	**No**. Same inclusion criteria, includes retrospective trials	**No** **Search cut-off date:** August 2011	It can be usd as a source of evidence. For harms and quality of life outcomes the authors included also studies of node negative women. Although they stated the inclusion criterion was stage T1-T2, the observational studies included had also women with stage T3. This is a review of direct patient outcomes (i.e., review of treatment interventions).	No
Zhang, 2012 [104] **Country:** China (Also for timing, and single or dual tracer)	**Yes** **Population:** pts with breast cancer 98.5% of pts had stage II-III **Intervention/Comparison:** radioisotope + blue dye vs. blue dye; SLNB vs. ALND; SLNB before vs. after NAC **Outcomes:** identification rate, sensitivity, false negative rate, mapping success.	**Yes**	**No** **Search cut off date:** 2011	Included studies are published from 2003 to 2011. This is a review of direct patient outcomes (i.e., review of treatment interventions).	No source of evidence refs 17 and 21
Francissen, 2012 [105] Axillary recurrence after a tumour-positive sentinel lymph node biopsy without axillary treatment: a review of the literature	**No** **Population:** patients with SLNB-positive breast carcinoma confirmed by SLNB **Intervention/Comparison:** SLNB vs. ALND **Outcomes:** Axillary recurrence	**No** . The authors included retrospective and prospective observational studies as well as RCTs	**Search cut-off date:**	Can be used as a source of evidence This is a review of direct patient outcomes (i.e., review of treatment interventions).	No

Author, year. Title, Country	Does this review align with the scope of ours?	Does this review align with the methods of ours?	Is this review current (≤2 years)?	Comments	Use as is
Country: The Netherlands					
Belkacemi, 2011 [106] Radiotherapy for invasive breast cancer: guidelines for clinical practice from the French expert review board of Nice/Saint-Paul de Vence [106] **Country:** France	**No**, this study looks at timing, modalities and indications of RT after surgery for breast cancer **Population:** not desctribed **Intervention/Comparison:** RT various modalities and indications **Outcomes:** survival, local control	Includes RCTs and observational studies. Searched only MEDLINE	**No** **Search cut-off date:** *nr*	It can be used as a sorce of evidence.	No
Question 4					
El Hage Chehade 2016 [107] Is sentinel lymph node biopsy a viable alternative to complete axillary dissection following NAC in women with node-positive breast cancer at diagnosis? An updated meta-analysis involving 3,398 patients Country: UK	**No** This review does not specify breast cancer stage Population: Female pts with node positive (pathologically proven) receiving NAC and undergoing SLNB followed by ALND Intervention/Comparison: SLNB and ALND after NAC Outcomes: Identification rate, false negative rate	**No** No quality assessment, no characteristics of included trials	**Yes** **Search cut-off date:** January 2016	Focus on pts that were node positive at diagnosis. This is a review of indirect patient outcomes (i.e., review of diagnostic test interventions).	yes
Fu, 2014 [108] Feasibility and accuracy of sentinel lymph node biopsy in clinically node-positive breast cancer after NAC: a meta-analysis. **Country:** China	**Yes** Q4C **Population:** clinically node-positive breast cancer after NAC. **Intervention/Comparison:** SLNB vs. ALND (gold standard) **Outcomes:** identification rate, false negative rate	**Yes**	**No** **Search cut off date:** December 2013	It could be used a s a source of evidence. It included observational studies. It is a diagnostic systematic review. This is a review of indirect patient outcomes (i.e., review of diagnostic test interventions).	**No**
Fontein, 2013 [109] Timing of SLNB in breast cancer patients receiving NAC – recommendations for clinical guidance. **Country:** The Netherlands	**Yes** **Population:** clinically node negative pts **Intervention/Comparison:** SLNB before vs. after NAC **Outcomes:** identification rate, false negative rate, accuracy	**No** No quality assessment	**No** **Search cut-off date:** May 2012 (studies were published up to 2011, and patients in the included studies were from 2009)	This is a review of indirect patient outcomes (i.e., review of diagnostic test interventions), and contains a guideine.	**Yes**

Author, year. Title, Country	Does this review align with the scope of ours?	Does this review align with the methods of ours?	Is this review current (≤2 years)?	Comments	Use as is
Zhang, 2012 [104] Is optimal timing of sentinel lymph node biopsy before NAC in patients with breast cancer? A literature review **Country:** China (Also for single or dual tracer)	**Yes** **Population:** pts with breast cancer. 98.5% of patients had stage II-III breast cancer **Intervention/Comparison:** radioisotope + blue dye vs. blue dye; SLNB vs. ALND; SLNB before vs. after NAC **Outcomes:** identification rate, sensitivity, false negative rate, mapping success.	**Yes**	**No** **Search cut-off date:** 2011	Included studies are published from 2003 to 2011. This is a review of indirect patient outcomes (i.e., review of diagnostic test interventions).	**No** (changed women had stage II and III breast cancer)
Question 5					
Peek, 2017 [110] Blue dye for identification of sentinel nodes in breast cancer and malignant melanoma: a systematic review and meta-analysis **Country:** Multiple countries	**No** This systematic review and meta-analysis has a wider scope than ours, focuses on single and dual tracer for SLNB in the breast and melanoma. It does not specifically focus on patients with early breast cancer. **Population:** pts with clnically negative berast cancer or menalnoma **Intervention/Comparison:** *nr* **Outcomes:** survival, identification rate, false negative rate	**Yes**	**No** **Search cut-off date**: June 2015	This can possibly be used as a source of evidence This is a review of indirect patient outcomes (i.e., review of diagnostic test interventions), but conducted as a review of a treatement intervention.	**No**
Geng, 2016 [49] The feasibility and accuracy of sentinel lymph node biopsy in initially clinically node-negative breast cancer after NAC: a systematic review and meta-analysis. **Country:** China	**Yes** **Included patients with clinically negative nodes T1-T4 breast cancer** **Population:** pts with initially clnically node-negative (all stages) breast cancer who had SLNB after NAC **Intervention/Reference index: SLNB / ALND** **Outcomes:** identification rate, false negative rate, accuracy rate	**Yes** **Quality assessed with QUADAS**	**No** **Search cut-off date**: 1993 to November 2015	The evidence is indirect because 2 out of 16 studies included pts with T1-2, while in the others pts had bigger tumours. **Q4: Timing** False negative rate: Estimated FNR: 6% (95% CI, 3% to 8%); FNR ranged from 0% to 33% in the 16 included studies; I^2 = 27.5%. For 6 studies that used H&E staining: FNR 11% (95% CI, 4% to 18%). For 6 studies that used H&E combined with IHC staining: FNR:4% (95% CI,1% to 7%). **Q5: single or dual tracer** Only blue dye (3 studies): identification rate (IR): 96% (95% CI, 91% to 100%) Only radiocolloid (4 studies): 96% (95% CI, 94% to 100%)	**yes**

Author, year. Title, Country	Does this review align with the scope of ours?	Does this review align with the methods of ours?	Is this review current (≤2 years)?	Comments	Use as is
				Blue dye and radiocolloid combined (6 studeis): 97% (95% CI,96% to 98%) No statistically significant differences in IR of SLNB among different mapping methods. Only refs 26 and 27 are studies of T-1/T2 pts, the others included pts with more advanced tumours. This is a review of indirect patient outcomes (i.e., review of diagnostic test interventions).	
Teshome, 2016 [111] Use of a Magnetic Tracer for Sentinel Lymph Node Detection in Early-Stage Breast Cancer Patients: A Meta-analysis **Country:** US	**Yes** This meta-analysis is not a systematic review **Population:** pts with early-stage breast cancer and clinically node negative **Intervention/Comparison:** Sienna+® magnetic tracer **Outcomes:** detection rate	**No**	*nr* **Search cut-off date**: *nr*	Can be used as a source of evidence. It is about a new technique, so out of scope This is a review of indirect patient outcomes (i.e., review of diagnostic test interventions).	**No**
He, 2016 [112] The combination of blue dye and radioisotope versus radioisotope alone during sentinel lymph node biopsy for breast cancer: a systematic review. **Country:** China	**Yes** This meta-analysis includes an analysis of patients who had NAC **Population:** pts with breast cancer undergoing SLNB **Intervention/Comparison:** radioisotope and blue dye vs. radioisotope alone **Outcomes:** identification rate, false negative rate	**Yes** – the authors combined in meta-anbalysis results from post-hoc analyses from RCTs, and 18 non-RCT studies	**No** **Search cut-off date**: June 2015	Can be used as a source of evidence for NAC. This is a review of indirect patient outcomes (i.e., review of diagnostic test interventions), but conducted as a review of a treatement intervention.	**No**
Ahmed, 2014 [113] Novel techniques for sentinel lymph node biopsy in breast cancer: a systematic review **Country:** UK	**No** It includes some interventions (microbubbles) that we are not interested in – novel technique **Population:** *nr* **Intervention/Comparison:** indocyanine green fluorescence, contrast-enhanced US using microbubbles, and superparamagnetic iron oxide nanoparticles vs. blue dye	**No**, it included mostly cohort studies, and included in meta-analysis observational and randomized trials	**No** **Search cut-off date:** November 2013	It can be used as a source of evidence. This is a review of indirect patient outcomes (i.e., review of diagnostic test interventions), but conducted as a review of a treatement intervention.	**No**

Author, year. Title, Country	Does this review align with the scope of ours?	Does this review align with the methods of ours?	Is this review current (≤2 years)?	Comments	Use as is
	Outcomes: identification rate, false negative rate, specificity				
Zhang, 2012 [104] Is optimal timing of sentinel lymph node biopsy before NAC in patients with breast cancer? A literature review **Country:** China (ALSO relevant to timing)	**Yes** **Population:** pts with breast cancer 98.5% of patients had stage II-III breast cancer **Intervention/Comparison:** radioisotope + blue dye vs. blue dye; SLNB vs. ALND; SLNB before vs. after NAC **Outcomes:** identification rate, sensitivity, false negative rate, mapping success.	**Yes**	**No** **Search cut-off date:** 2011	It can be used as a source of evidence Included studies are published from 2003 to 2011. This is a review of indirect patient outcomes (i.e., review of diagnostic test interventions).	**No source of evidence**
Bezu, 2011 [114] Anaphylactic response to blue dye during sentinel lymph node biopsy **Country:** France	**No.** This review has a wider scope (more pt populations) than ours. A secondary question asks whether it is reasonable not to use blue dyes **Population:** Pts with early-stage breast cancer, cancer of the uterus, lymphatic, and pts with melanoma **Intervention/Comparison:** various types of blue dyes vs. no comparison **Outcomes:** incidence of anaphylactic reaction from blue dye	**No**	**No** **Search cut-off date:** January 2009	Focus of this review is on blue dyes for SLNB. This is a review of direct patient outcomes (i.e., review of treatment interventions).	**No**
Zhang, 2016a [115] Diagnostic performance of indocyanine green-guided sentinel lymph node biopsy in breast cancer: a meta-analysis. **Country:** China	**No** **Population:** The majority of pts had stage II-III breast cancer (98.5%). Novel technique **Index test/comparison:** Indocyanine green SLNB/ALND **Reference standard:** histopathology	**No**	**Yes** **Search cut-off date:** September 2015	Novel methods. Do not include because is reporting on a new method of detecting sentinel nodes, using fluorescence dye, which is not considered standard, plus doesn't compare to gold standard dye and radio-isotope. This is a review of indirect patient outcomes (i.e., review of diagnostic test interventions).	**No**
Zhang, 2015 [116] Contrast-enhanced ultrasonography in qualitative diagnosis of sentinel lymph node metastasis in breast cancer: A meta-analysis **Country:** China	**No** This meta-analysis focuses only on accuracy of CEUS. **Population:** women with brest cancer **Index test/Reference standard:** Contrast-enhanced US / histology **Outcomes:** Accuracy of test	**No**	**Yes** for a diagnostic meta-analysis **Search cut-off date:** August 2013	Novel methods. This is a review of indirect patient outcomes (i.e., review of diagnostic test interventions).	**No**

Author, year. Title, Country	Does this review align with the scope of ours?	Does this review align with the methods of ours?	Is this review current (≤2 years)?	Comments	Use as is
van Wely, 2014 [117] Meta-analysis of US-guided biopsy of suspicious axillary lymph nodes in the selection of patients with extensive axillary tumour burden in breast cancer **Country:** The Netherlands	**Yes** This meta-analysis focusses on pts with breast cancer in general. The comparison groups included patients with different prognosis. Also, more interest in pts with >3 nodes involved. The authors included several studies that did not control for baseline confounding. **Population:** Node positive pts (N1 and N2) who: Had ALND after a positive US-guided biopsy of suspicious nodes (US+/biopsy+); Had a negative US-guided biopsy of US suspicious nodes but a positive SLNB (US+/biopsy−/SLNB+); and Had no US suspicious nodes who have a positive SLNB (US−/SLNB+) **Index test/Reference standard:** US-guided biopsy / ALND **Outcomes:** Identification rate	**Yes**	**No** **Search cut-off date:** September 2013	This procedure is performed before any surgery, and preceeds or guides NAC. This is a review of indirect patient outcomes (i.e., review of diagnostic test interventions).	**Yes**
Houssami, 2011, and 2014 [118,193], and Diepstraten, 2013 [192] Clinical utility of ultrasound-needle biopsy for preoperative staging of the axilla in invasive breast cancer [284], and Preoperative ultrasound-guided needle biopsy of axillary nodes in invasive breast cancer: meta-analysis of its accuracy and utility in staging the axilla **Country:** Multiple countries	**No** This meta-analysis looks at the accuracy of the procedure. The 2014 is an update of the 2011 systematic review. The 2013 publication provides additional data It has selection criteria different than ours in that the quality of the studies is not considered for selection, as well as the number of patients included **Population:** Pts with invasive breast cancer **Intervention/Comparison:** FNAB or CNB vs. node histology (gold standard) **Outcomes:** accuracy of pre-operative US guided FNAB or CNB	**Yes**	**No** **Search cut-off date:** April 2010	This intervention is applied pre-operatively. This is a review of indirect patient outcomes (i.e., review of diagnostic test interventions).	**Potentially yes (update)**
Wang, 2012 [119,285] Diagnostic accuracy of ultrasound-guided fine-needle aspiration cytologic in staging of axillary lymph node metastasis in breast cancer patients: a meta-analysis. **Country:** China	**No** This study looks at the diagnostic accuracy of the procedure **Population:** Pts with breast cancer **Test/Comparison**: US-guided fine-needle aspiration cytology vs. SLNB **Reference standard:** histopathologic analysis **Outcomes:** sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic OR	**Yes**	**No** **Search cut-off date:** July 2012	The intervention is fine needle aspiration biopsy, not SLNB. This is a review of indirect patient outcomes (i.e., review of diagnostic test interventions).	**No**
Tan, 2011 [120,286]	**No**	**Yes**	**No**	This study focused on patients who were clinically node	No

Author, year. Title, Country	Does this review align with the scope of ours?	Does this review align with the methods of ours?	Is this review current (≤2 years)?	Comments	Use as is
The feasibility and accuracy of sentinel lymph node biopsy in clinically node-negative patients after NAC for breast cancer–a systematic review and meta-analysis **Country:** Singapore	**Population:** pts with clinically negative axilla who underwent NAC **Intervention/Comparison:** SLNB vs. ALND **Outcomes:** identification rate		**Search cut-off date:** December 2008	negative after NAC. Only 3 of the included studies have a population of patients similar to ours. It can be used as a source of evidence. This is a review of indirect patient outcomes (i.e., review of diagnostic test interventions).	
Gkegkes, 2015 [121] Contrast enhanced ultrasound (CEU) using microbubbles for sentinel lymph node biopsy in breast cancer: a systematic review **Country:** Multiple countries	**No** This systematic review included patients with histologic types that we excluded (e.g., DCIS) **Population:** **Intervention/Comparison:** Intradermal CEUS with microbubbles **Outcomes:** SLN identification rate	**Yes**	**No** **Search cut-off date:** October 2014	The authors included only prospective studies. This is a review of indirect patient outcomes (i.e., review of diagnostic test interventions).	**No**

AE = adverse events; ALND = axillary lymph node dissection; ARR = axillary recurrence rate; CEUS = contrast-enhanced ultrasound; CNB = core needle biopsy; DCIS = ductal carcinoma in situ; DFS = disease-free survival; FNAB = fine needle aspiration biopsy; FNR = false negative rate; H&E = hematoxylin and eosin stain; ICG = indocyanine green; IHC = immunohistochemistry; IMLN RT-RNI = Internal mammary lymph node radiation therapy with regional nodale irradiation; IORT = intra-operative radiation therapy; IPD = individual patient data; IR = identification rate; NAC = neoadjuvant chemotherapy; nr = not reported; OS = overall survival; pCR = pathological complete response; pts = patients; QOL = quality of life; RCT = randomized controlled trial; RT = radiotherapy; SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy; SN = sentinel node; pts = patients; US = ultrasound.

Table 2. Domain 1: Study eligibility criteria

Study, (subquestion)	Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified	1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	1.2 Were the eligibility criteria appropriate for the review question?	1.3 Were eligibility criteria unambiguous?	1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g., date, sample size, study quality, outcomes measured)?	1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g., publication status or format, language, availability of data)?	Concerns regarding specification of study eligibility criteria
Question 1:							
Liang, 2017 [7]	**Inclusion**: Randomized controlled trials of •Adults with invasive breast cancer •Age 70 years + •Clinically node negative •Node negative following image guided node biopsy •T1 or T2 Intervention: surgical axillary staging – including sentinel node biopsy, axillary sampling and primary axillary dissection vs. No surgical axillary intervention **Exclusion**: Quasi experimental designs, observational studies, case control studies, case series, case reports, editorials, commentaries, reviews, opinion pieces •In situ breast cancer •Recurrent disease •T3 or T4 •Clinically node positive •Positive node on preoperative biopsy •NAC •Neoadjuvant radiation	YES	YES	YES	YES	YES	LOW The study was registered in PROSPERO with registration number CRD42014010750; the eligibility criteria were enlarged from age 70+ to at least 50% of pts age 70+.
Question 2:							
No reviews were selected							
Question 3:							
Zhao, 2017 [93]	No registration in PROSPERO is available.	PROBABLY YES	YES	YES	YES	YES	LOW

Study, (subquestion)	Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified	1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	1.2 Were the eligibility criteria appropriate for the review question?	1.3 Were eligibility criteria unambiguous?	1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g., date, sample size, study quality, outcomes measured)?	1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g., publication status or format, language, availability of data)?	Concerns regarding specification of study eligibility criteria
(+ after diagnosis: RT vs. ALND)	Included: studies of women with invasive breast cancer and positive SLN who had BCT or mastectomy; Studies that compared DFS, and OS, and axillary recurrence rates in pts who received SLNB plus ART vs. SLNB plus cALND. Study design RCTs, comparative observational studies, and systematic reviews with meta-analysis						
Schmidt-Hansen 2016 [31] (surgery vs. no treatment; surgery vs. aRT)	Included: RCTs in women with early breast cancer and a positive sentinel lymph node, comparing ALND vs. no axillary surgery; ALND vs. axillary RT without ALND; and reporting the following outcomes: OS, DFS, disease control (axilla); recurrence; AE; longtermcomplications; and QOL. No PORSPERO registration	YES	YES	YES	YES	YES	LOW
Huang, 2016 [95] (surgery vs. no treatment)	RCTs of ALND versus no dissection in women with invasive breast cancer and SLN metastasis. Included: trials that describe (1) the inclusion and exclusion criteria, (2) technique of SLN sampling, (3) definition of SLN metastasis, and (4) evaluation of prognostic outcomes. Excluded: trials that: (1) did not directly evaluate the outcomes of ALND, (2) did not included breast cancer patients with SLN metastasis, including studies that only enrolled SLN-positive patients with no	YES	YES	YES	YES	YES	LOW

Study, (subquestion)	Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified	1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	1.2 Were the eligibility criteria appropriate for the review question?	1.3 Were eligibility criteria unambiguous?	1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g., date, sample size, study quality, outcomes measured)?	1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g., publication status or format, language, availability of data)?	Concerns regarding specification of study eligibility criteria
	ALND, (3) only compared radiotherapy with ALND, (4) did not state clinical outcomes, and (5) involved the duplicate reporting of patient cohorts.						
Li, 2015 [98] (SLNB vs. ALND)	Included: (1) RCTs and observational studies. (2) women with T1 or T2 N0 M0 breast cancer with SLN metastasis. (3) SLNB alone vs. ALND. (5) OS, DFS, loco-regional recurrence and AE. Excluded: <30 pts, abstracts, letters, editorials and expert opinions, reviews without original data, meta-analysis, and case reports. No PROSPERO registration.	PROBABLY YES	YES	YES	YES	YES	LOW
Budach, 2015 [100] (RT of internal mammary nodes + WBI vs. whole breast irradiation)	Assigned treatments needed to be done randomly, risk factors between treatment arm evenly distributed, exclusion of pts from the analysis adequate, and analysis performed on an ITT basis. No PROSPERO registration (previous meta-analysis)	PROBABLY YES	YES	NO	PROBABLY YES	YES	UNCLEAR
Ram, 2014 [101] (SLNB vs.ALND)	PROSPERO registration CRD42013004464. Included: RCTs had a population of breast cancer patients with positive sentinel node, compared SLNB vs. ALND, and reported on DFS, OS, local recurrence and surgical morbidity. A secondary analysis included observational studies	YES	YES	YES	YES	YES	LOW
Question 4:							

Study, (subquestion)	Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified	1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	1.2 Were the eligibility criteria appropriate for the review question?	1.3 Were eligibility criteria unambiguous?	1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g., date, sample size, study quality, outcomes measured)?	1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g., publication status or format, language, availability of data)?	Concerns regarding specification of study eligibility criteria
Geng, 2016 [49] Q4a node negative	Included: Studies of clinically node negative (no suspicious or abnormal-appearing lymph nodes on physical examination or US imaging) breast cancer pts who underwent SLNB after NAC followed by ALND Excluded: Studies where pts received endocrine NAC or preoperative radiotherapy Studies where different mapping methods were used in one study	YES	YES	YES	YES	YES	LOW
El Hage Chehade 2016 [96] Q4b node positive	Included: Female breast cancer pts diagnosed with metastases of the axillary lymph nodes either by physical examination or US scan, with or without needle biopsy. Pts had to be scheduled to receive NAC and undergo SLNB followed by ALND as part of their management. Included studies had to report sentinel lymph node (SLN) identification rate (IR), FNR, and/or pCR. Excluded: *nr*	YES	YES	YES	YES	YES	LOW
Fontein, 2013 [109]	Included: English publications; completion of ALND or SLNB Excluded: Abstract publications	YES	YES	YES	YES	YES	LOW
Question 5:							

Study, (subquestion)	Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified	1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	1.2 Were the eligibility criteria appropriate for the review question?	1.3 Were eligibility criteria unambiguous?	1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g., date, sample size, study quality, outcomes measured)?	1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g., publication status or format, language, availability of data)?	Concerns regarding specification of study eligibility criteria
van Wely, 2014 [117] (US guided SLNB vs. traditional SLNB	Included: English language publications Studies reported on the number of positive nodes found at ALND after positive US-guided biopsy and positive SLNB findings. Excluded: Articles that reported on patients with a high risk of axillary metastasis In the interpretation of the results more interest was given to pts with >3 nodes involved	YES page 160	YES	YES	YES	NO INFORMATION	LOW

AE = adverse events; ALND = axillary lymph node dissection; aRT = axillary radiotherapy; BCT = breast-conserving therapy; cALND = complete axillary node dissection; DFS = disease-free survival; FNR = false negative rate; IR = identification rate; ITT = intention-to-treat; NAC neoadjuvant chemotherapy; *nr* = not reported; OS = overall survival; pts = patients; QOL = quality of life; RCT; randomized control trial; RT = radiotherapy; SLNB = sentinel lymph node biopsy; SLN = sentinel lymph node; US = ultrasound.

Table 3. Domain 2: Identification and selection of studies

Study	Describe methods of study identification and selection (e.g., number of reviewers involved):	2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	2.2 Were methods additional to database searching used to identify relevant reports?	2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	2.4 Were restrictions based on date, publication format, or language appropriate?	2.5 Were efforts made to minimize error in selection of studies?	Concerns regarding methods used to identify and/or select studies
Question 1:							
Liang, 2017 [7]	Eligibility criteria were pilot tested, and 2 independent reviewers selected the articles at the title and abstract and full text level.	YES	YES	YES	YES	YES	LOW
Question 3:							
No reviews were selected							
Question 4:							
Zhao, 2017 [93]	The authors searched PubMed, EMBASE, and the Cochrane library. Two independent reviewers reviewed title and abstract and full text articles	YES	NO	YES	YES	YES	LOW
Schmidt-Hansen 2016 [31]	The authors searched the Specialized Register of the Cochrane Breast Cancer Group, the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, the World Health Organization International Clinical Trials Registry Portal (WHO ICTRP) and ClinicalTrials.gov, the conference proceedings from the American Society of Clinical Oncology (ASCO), and the conference proceedings from the San Antonio Breast Cancer (SABCS). Two authors independently selected the articles.	YES	YES	YES	YES	YES	LOW
Huang, 2016 [95]	No PROSPERO registration. No record of the number of reviewers involved. The searches were very comprehensive. The authors searched PubMed, EMBASE, CINAHL, Scopus, and Cochrane databases, related articles in PubMed; ClinicalTrials.gov registry; the reference lists of included studies and contacted experts and authors	YES	YES	YES	YES	NO INFORMATION	LOW
Li, 2015 [98]	The authors searched PubMed, Embase, Web of Science, and Cochrane Library from 1965 to February 2014, and the related articles function in PubMed. Two reviewers selected the articles.	YES	YES	YES	YES	YES	LOW

Study	Describe methods of study identification and selection (e.g., number of reviewers involved):	2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	2.2 Were methods additional to database searching used to identify relevant reports?	2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	2.4 Were restrictions based on date, publication format, or language appropriate?	2.5 Were efforts made to minimize error in selection of studies?	Concerns regarding methods used to identify and/or select studies
Budach, 2015 [100]	The authors searched PubMed and abstracts of conference proceedings were searched	NO	YES	YES	YES	NO INFORMATION	UNCLEAR
Ram, 2014 [101]	The authors searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and bibliographies of relevant studies. Two reviewers perfomed the search and selected the studies independently	YES	YES	YES	YES	YES	LOW
Geng, 2016 [49]	The authors searched PubMed, EMBASE, and the Cochrane Library; 2 reviewers selected the articles	YES	NO	YES	YES	YES	LOW
El Hage Chehade 2016 [96]	The authors searched PubMed and MEDLINE. Two authors, reviewed the resulting titles and abstracts, and potentially relevant articles were retrieved to review the full text	YES	NO	YES	YES	YES	LOW
Fontein, 2013 [109]	*nr*	NO	NO INFORMATION	NO	YES	NO INFORMATION	HIGH
Question 5:							
van Wely, 2014 [117]	The authors searched PubMed and Embase. Two reviewers independently selected the titles and the abstracts	YES	YES	YES	YES	PROBABLY NOT	LOW

ALND = axillary lymph node dissection; RT = radiotherapy; SLNB = sentinel node excision; WBI = whole breast irradiation; US = ultrasound

Table 4: Domain 3: Data collection and study appraisal

Study, (comparison)	Describe methods of data collection, what data were extracted from studies or collected through other means, how risk of bias was assessed (e.g., number of reviewers involved) and the tool used to assess risk of bias:	3.1 Were efforts made to minimize error in data collection?	3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	3.3 Were all relevant study results collected for use in the synthesis?	3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	3.5 Were efforts made to minimize error in risk of bias assessment?	Concerns regarding methods used to identify and/or select studies
Question 1:							
Liang, 2017 [7] (ALND+SLNB vs. ALND)	YES	YES	YES	YES	YES	YES	LOW
Question 2:							
No reviews were selected							
Question 3:							
Zhao, 2017 [93] (RT vs. ALND)	NO INFORMATION	NO INFORMATION	NO	YES	NO No quality assessment	NO INFORMATION	HIGH It was often impossible to ascertain.
Schmidt-Hansen 2016 [31] (Surgery vs. no treatment)	YES	YES	PROBABLY YES	YES	YES	YES	LOW
Huang, 2016 [95] (surgery vs. no treatment)	YES	YES	YES	YES	YES	YES	LOW
Li, 2015 [98] (SLNB vs. ALND)	YES	YES	YES	YES	YES	NO INFORMATION	LOW
Budach, 2015 [100] (RT of internal mammary nodes + WBI vs. whole breast RT)	NO INFORMATION	NO INFORMATION	PROBABLY YES	NO INFORMATION	PROBABLY YES	NO INFORMATION	HIGH

Study, (comparison)	Describe methods of data collection, what data were extracted from studies or collected through other means, how risk of bias was assessed (e.g., number of reviewers involved) and the tool used to assess risk of bias:	3.1 Were efforts made to minimize error in data collection?	3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	3.3 Were all relevant study results collected for use in the synthesis?	3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	3.5 Were efforts made to minimize error in risk of bias assessment?	Concerns regarding methods used to identify and/or select studies
Ram, 2014 [101] (SLNB vs.ALND)	YES	YES	YES	YES	YES	NO INFORMATION	LOW
Question 4:							
Geng, 2016 [49] (Single vs. dual tracer)	YES	YES	YES	YES	YES	YES	LOW
El Hage Chehade 2016 [96] (SLNB vs. ALND post NAC)	YES	NO	NO	YES	NO	NO	HIGH
Fontein, 2013 [109] (SLNB befopre vs. after NAC)	YES	NO	YES	YES	NO	NO	HIGH
Question 5							
van Wely, 2014 [117] (US guided SLNB vs. traditional SLNB)	YES	YES	YES	YES	YES	NO INFORMATION	UNCLEAR The patients did not have the same prognosis in the groups that were compared

ALND = axillary lymph node dissection; FNR = false negative rate; IR = identification rate; NAC = neo-adjuvant chemotherapy; pt = patient; RCT = randomized control trial; RT = radiotherapy; SLN = sentinel lymph node; SLNB = sentinel node excision; WBI = whole breast irradiation; US = ultrasound; yr = year

Table 5: Domain 4: synthesis and findings

Study	Describe synthesis methods:	4.1 Did the synthesis include all studies that it should?	4.2 Were all pre-defined analyses reported or departures explained?	4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	4.5 Were the findings robust, e.g., as demonstrated through funnel plot or sensitivity analyses?	4.6 Were biases in primary studies minimal or addressed in the synthesis?	Concerns regarding the synthesis and findings
Question 1:								
Liang, 2017 [7]	Meta-analysis	YES[a]	YES	YES	YES	YES	YES	LOW
Question 2:								
No reviews were selected								
Question 3:								
Zhao, 2017 [93]	Meta-analysis	YES[b]	NO INFORMATION	YES	YES[c]	NO[d]	NO	UNCLEAR
Schmidt-Hansen 2016 [31]	Meta-analysis	YES	YES	YES	YES	PROBABLY NOT[e]	YES	LOW
Huang, 2016 [95]	Meta-analysis	YES	PROBABLY YES[f]	YES	NO	NO	YES	LOW
Li, 2015 [98]	Meta-analysis	YES	NO INFORMATION	YES	YES	YES	NO	UNCLEAR
Budach, 2015 [100]	Meta-analysis	PROBABLY NO	NO INFORMATION	PROBABLY YES	NO	PROBABLY NO	NO INFORMATION	HIGH
Ram, 2014 [101]	Meta-analysis	YES	YES	YES	YES	YES	YES	LOW
Question 4:								
Geng, 2016 [49]	Meta-analysis	YES	YES	YES	YES	NO	NO	LOW
El Hage Chehade 2016 [96]	Meta-analysis	YES	YES	YES	YES	YES	NO	UNCLEAR
Fontein, 2013 [109]	Narrative	YES	*nr*	YES	NO	NO	NO	HIGH
Question 5:								
van Wely, 2014 [117]	Meta-analysis	YES	NO INFORMATION	YES[g]	PROBABLY YES[h]	NO INFORMATION	YES[i]	UNCLEAR

[a]only 2 studies
[b]The non-RCTs are not included in the meta-analysis
[c]I^2 was 53.1%, therefore a random-effects model was applied
[d]only 2 studies included, no funnel plot
[e]no funnel plot or sensitivity analyses
[f]no protocol available
[g]pts with different prognosis were compared
[h]I^2 was 22% in one and 89% in the other meta-analyses. Authors talk about qualitative heterogeneity
[i]QUADAS scores are reported
ALND = axillary lymph node dissection; DFS = disease-free survival; OS = overall survival; pts = patients; RCT = randomized control trial; SLN = sentinel lymph node; SLNB = sentinel node excision; US = ultrasound; WBI = whole breast irradiation;

Table 6: Phase 3 of the Risk of bias: Judging the risk of bias – Summary of concerns regarding the risk of bias in relevant reviews

Study	1. Concerns regarding specification of study eligibility criteria - rationale	2. Concerns regarding methods used to identify and/or select studies - rationale	3. Concerns regarding methods used to collect data and appraise studies - rationale	4. Concerns regarding the synthesis and findings - rationale
Question 1:				
Liang, 2017 [7]	LOW	LOW	LOW	LOW
Question 2:				
No reviews were selected				
Question 3:				
Zhao, 2017 [93]	LOW	LOW	HIGH	UNCLEAR
Schmidt-Hansen 2016 [31]	LOW	LOW	LOW	LOW
Huang, 2016 [95]	LOW	LOW	LOW	LOW
Li, 2015 [98]	LOW	LOW	LOW	UNCLEAR
Budach, 2015 [100]	UNCLEAR	UNCLEAR	HIGH	HIGH
Ram, 2014 [101]	LOW	LOW	LOW	LOW
Question 4:				
El Hage Chehade 2016 [96]	LOW	LOW	HIGH	HIGH
Fontein, 2013 [109]	LOW	LOW	LOW	LOW
Question 5:				
Geng, 2016 [49]	LOW	LOW	LOW	LOW
van Wely, 2014 [117]	LOW	LOW	UNCLEAR	LOW

Table 7: Risk of bias in the included systematic reviews

Study	Describe whether conclusions were supported by the evidence:	A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	B. Was the relevance of identified studies to the review's research question appropriately considered?	C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Risk of bias in the review
Question 1					
Liang, 2017 [7]	YES	YES	YES	NO	LOW
Question 2					
No reviews were selected					
Question 3:					
Zhao, 2017 [93]	PROBABLY YES	PROBABLY NO[a]	YES	NO	UNCLEAR
Schmidt-Hansen 2016 [31]	YES Two different groups of studies for two comparisons: SLNB vs. ALND and Surgery vs. RT	YES	YES	YES	LOW
Huang, 2016 [95]	YES	YES	YES	YES	LOW
Li, 2015 [98]	YES	YES	YES	YES	LOW
Budach, 2015 [100]	PROBABLY YES	PROBABLY NO	YES	PROBABLY YES	HIGH
Ram, 2014 [101]	YES	YES	YES	YES	LOW
Question 4					
El Hage Chehade 2016 [96]	PROBABLY NO	NO	NO	YES	HIGH
Fontein, 2013 [109]	PROBABLY NO	NO	PROBABLY NO	NO	HIGH
Question 5					
Geng, 2016 [49]	YES	YES	YES	YES	LOW
van Wely, 2014 [117]	PROBABLY NO	NO	PROBABLY NO	NO	HIGH

[a]The authors stated that they used an early version of one of the included studies (not abs) though. No discussion of the quality of the studies
ALND = axillary lymph node dissection; RT = radiotherapy; SLNB = sentinel lymph node biopsy

Appendix 5B.
Table 1. Appraisal of the meta-analysis of individual patient data (IPD) that met the inclusion criteria [86] for Question 3C, according to Tierney et al. 2015 [80]

General question	Items to check	Comment on the review by EBCTG [86]
Is it part of a systematic review?	A. Does it have a clear research question qualified by explicit eligibility criteria? B. Does it have a systematic and comprehensive search strategy for identifying trials? C. Does it have a consistent approach to data collection? D. Does it assess the "quality" or risk of bias of included trials? E. Are all the methods prespecified in a protocol? F. Has the protocol been registered or otherwise made available?	Yes to all.
Were all eligible trials identified?	A. Were fully published trials identified? B. Were trials published in the grey literature identified? C. Were unpublished trials identified? Look for inappropriate or restrictive eligibility criteria and/or search strategies that do not seek all relevant trials	Yes every trial on early breast cancer was identified
Were IPD obtained from most trials?	A. Were IPD obtained for a large proportion of the eligible trials? B. Was an assessment of the potential impact of missing trials undertaken? C. Were the reasons for not obtaining IPD provided? For risk of missing data: check with data in systematic reviews of aggregate data if anything is missing	All except 4 (out of 26) trials for which data were not available (no reason provided).
Was the integrity of the IPD checked?	A. Were the data checked for missing, invalid, out-of-range, or inconsistent items? B. Were there any discrepancies with the trial report (if available)? C. Were any issues queried and, if possible, resolved?	Yes. This is reported in additional articles and in appendix.
Were the analyses pre-specified in detail?	Methods of analysis should be prespecified in protocol/ analysis plan, and need to be reported (Unplanned analyses need to be justified and labelled as such): • Primary and secondary outcome and their definition • Methods for analysis of efficacy/effectiveness, including those for exploring the impact of tiral or participant characteristics • Methods for quantifying and accounting for heterogeneity • Methods for checking IPD and assessing the risk of bias in trials A. Were the detailed analysis methods included in a protocol or analysis plan? B. Were the outcomes and methods for analysing the effects of interventions, quantifying and accounting for heterogeneity, and assessing risk of bias included?	Yes
Was the Risk of Bias of included trials assessed?	A. Were the randomization, allocation concealment, and blinding assessed? B. Were the IPD checked to ensure all (or most) randomized participants were included? C. Were all relevant outcomes included? D. Was the quality of time-to-event-outcome data checked?	May be. There is a general description of methods for quality assessment at: https://www.ctsu.ox.ac.uk/research/ebctcg/further-information/original-methods-for-ebctcg-meta-analyses/section-3-introduction but it is not specific to this study.
Were the methods of analysis appropriate?	A. Were the Methods of assessing the overall effects of interventions appropriate? • Did the researchers stratify or account for clustering of participants within trials using either a one- or two-stage approach to meta-analysis? • Was the choice of one- or two-stage analysis specified in advance and/or results for both approaches provided? B. Were the methods of assessing whether effects of interventions varied by trial characteristics appropriate? • Did researchers compare treatment effects between subgroups of trials or use meta-regression to assess whether the overall treatment effect varied in relation to trial	Yes

General question	Items to check	Comment on the review by EBCTG [86]
	C. Were the methods of assessing whether effects of interventions vary by participant characteristics appropriate? • Did researchers estimate an interaction separately for each trial and combine these across trials in a two-stage fixed effect or random effects meta-analysis? Or; • Did researchers incorporate one or more a treatment by participant covariate interaction terms in a regression model, whilst also accounting for clustering of participant, separating out this individual participant-level interaction from any trial-level interactions? D. If there was no evidence of a differential effect by trial or participant characteristic, was emphasis placed on the overall result? E Were exploratory analyses highlighted as such?	
Does any report of the results adhere to the Preferred Reporting Items for a Systematic review and Meta-analysis of IPD (The PRISMA-IPD Statement)	Were the Methods of assessing if effects of interventions varied by trial or participant characteristics appropriate? Does any report of the results adhere to the Preferred Reporting Items for a Systematic review and Meta-analysis of IPD (The PRISMA-IPD Statement)	Yes

IPD = individual patient data meta-analysis

Appendix 6: Risk of bias: Nonrandomized Trials (Questions 4 and 5)

Table 1. Study quality of nonrandomized trials of direct patient outcomes that met the inclusion criteria evaluated with the ROBINS-I [78] tool

Study	Bias due to confounding	Bias in selection of Participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcome	Bias in selection of reported results	Overall risk of bias judgement
Question 4 - Initially node positive patients								
Studies of surgery (SLNB vs. ALND)								
Kim, 2015 [44]	MODERATE	MODERATE	SERIOUS[a]	MODERATE	LOW	SERIOUS[b]	SERIOUS[c]	SERIOUS (OS)/VERY SERIOUS (DFS and recurrence)
Studies of radiotherapy								
Kantor, 2017 [180]	SERIOUS[d]	MODERATE	MODERATE	LOW	SERIOUS[e]	MODERATE	LOW	SERIOUS
Rusthoven, 2016 [45]	SERIOUS[d]	MODERATE	LOW	LOW	LOW	MODERATE	LOW	MODERATE
Liu, 2016 [181]	SERIOUS[d]	MODERATE	LOW	LOW	MODERATE	MODERATE	LOW	MODERATE
Krug, 2019 [43]	MODERATE	MODERATE	LOW	LOW	MODERATE	MODERATE	MODERATE	MODERATE
Studies of SLNB Timing before vs. after NAC								
Fernandez-Gonzalez, 2018 [168]	SERIOUS[g]	MODERATE	LOW	LOW	MODERATE	SERIOU[Sg]	LOW	MODERATE[h]
Hunt, 2009 [53]	SERIOUS[j]	LOW	MODERATE	LOW	LOW	MODERATE	LOW	MODERATE
Papa, 2008 [173]	SERIOUS[k]	LOW	MODERATE	NO INFORMATION	LOW	SERIOUS[l]	MODERATE	SERIOUS
Question 5								
US-guided SLNB vs. traditional SLNB								
Verheuvel, 2017 [55]	SERIOUS[m]	CRITICAL[n]	SERIOUS[o]	LOW	SERIOUS[p]	LOW	LOW	CRITICAL

[a]The information used to define intervention groups may have been recorded after the start of interventions as this is a retrospective trial.
[b]For DFS and axillary recurrence the outcome measure might have been influenced by knowledge of the intervention received.
[c]The reported results might have been selected on the basis of multiple analyses of intervention-outcome relationship or different subgroups.
[d]Paticipants did not have a pathological classification at diagnosis, only a clinical staging.
[e]Participants with missing data were excluded
[f]Inherent with the retrospective design of this trial
[g]This study was affected by time varying bias because the follow-up time in intervention and control groups were very different, with the intervention group having a much shorter follow-up. This would impact the detection of patient-relevant outcomes such as recurrence and progression-free survival in favour of the intervention (i.e., SLNB after NAC), but not so much ALND rate.
[h]The risk of bias is lower for ALND rate and higher for recurrence rate and PFS
[j]Time varying confounding: intervention and control groups have different length of follow-up
[k]The Authors did not measure and control for tumour stage (only size), and patient characteristics other than age
[l]Outcome measures could have been influenced by knowledge of the intervention received; outcome assessors were not blinded to assignment of interventions
[m]TheAuthors did nott do an interaction test with age and method of axillary staging for OS
[n]Only patients that were US-neg had an SLNB;
[o]This was a retrospective trial; the Authors assumed that patients who had an ALND – but did not have a SLNB, had a positive US-guided procedure
[p]The authors stated that there were missing data, but they did not report how they were handled. In the presence of missing data, a sensitivity analysis showed that data were not robust.

ALND axillary lymph node dissection; DFS = disease-free survival; NAC = neo-adjuvant chemotherapy; OS = overall survival; PFS = progression-free survival; SLNB = sentinel lymph node biopsy; US = ultrasound

Table 2 . Risk of Bias of trials of diagnostic outcomes that met the inclusion criteria evaluated with the QUADAS-2 [79] tool

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
QUESTION 4							
Surgical studies of initially node-positive pts							
Classe, 2019 [169]	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Kim, 2015 [44]	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Studies of timing of axillary staging							
Zetterlund, 2017 [170]; Zetterlund, 2017 [171]	LOW	LOW	LOW	LOW	LOW	LOW	LOW
van der Heiden-van der Loo [172]	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	LOW
Kuehn, 2013 [46] **SENTINA**	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Tausch, 2011 [48]	LOW	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW
Papa, 2008 [173]	LOW	HIGH	HIGH	HIGH	LOW	LOW	LOW
Gimbergues, 2008 [54]	LOW	HIGH	HIGH	LOW	LOW	LOW	LOW
Fernandez-Gonzalez, 2018 [168]	LOW	LOW	HIGH	HIGH	HIGH	LOW	HIGH
Hunt, 2009 [53]	LOW	LOW	HIGH	HIGH	HIGH	LOW	LOW
QUESTION 5							
Single versus dual tracer							
O'Reilly, 2015 [47]	LOW	UNCLEAR	HIGH	LOW	UNCLEAR	LOW	HIGH
Boileau, 2015 [52]	LOW	HIGH	HIGH	LOW	LOW	LOW	LOW
Kuehn, 2013 [46]	LOW*	LOW	UNCLEAR	LOW	LOW	LOW	LOW
Boughey, 2013 [51]	LOW	HIGH	UNCLEAR	LOW	LOW	LOW	LOW
Kang, 2010 [60]	LOW	UNCLEAR	HIGH	LOW	HIGH	LOW	HIGH
Nathanson, 2007 [50]	LOW	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW
US-guided SLNB vs. traditional SLNB							
Caudle, 2016 [61]	LOW	UNCLEAR	LOW	UNCLEAR	HIGH	LOW	LOW
Kramer, 2016 [56]	LOW	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW
Kim, 2016 [57]	LOW	LOW	UNCLEAR	LOW	LOW	LOW	LOW
Cools-Lartigue, 2013 [58]	HIGH	LOW	UNCLEAR	UNCLEAR	LOW	LOW	LOW
US vs. SLNB							
Stachs, 2013 [59]	LOW	LOW	UNCLEAR	LOW	LOW	LOW	LOW

*The patients in this study are the subgroup treated with NAC, and the results appy to them

NAC = neoadjuvant chemotherapy; Pts = patients; SLNB = sentinel ymph node biopsy; US = ultrasound;

Appendix 7: Characteristics of included studies

Table 1A. Characteristics and summary results of included studies: Question 1

Characteristics	Agresti, 2014 [8]	Martelli 2012 [6]	Avril, 2011 [122]	Rudenstam, 2006 [5]
N	565, 517 in analysis	238, 219 in analysis	625	473
Study design	RCT single centre noninferiority trial	RCT	Multicentre RCT phase 3 equivalence, pragmatic trial	Multicentre RCT
Comparison	245 QU vs. 272 QUAD	109 ALND vs. 110 no ALND	297 no ALND vs. 310 ALND	234 surgery + ALND vs. 239 surgery
Follow-up (median)	127.5 mos (IQR 112.5 - 141.1)	150 mos (125–175) in the axillary dissection arm 149 mos (124–174) in the no axillary dissection arm	5 yrs The study was terminated early, at first interim analysis, because of lack of equivalence and low accrual.	6.6 yrs
Other treatment	• RT to the operated breast • Adjuvant treatment planned according to lymph node status and biological factors (good or poor factors) • Anthracycline-based adjuvant chemotherapy (epirubicin, cyclophosphamide, methotrexate, and 5-fluorouracile. • All pts had hormonal treatment with tamoxifen	• Breast conserving surgery • RT to the residual breast • Tamoxifen 20mg/d for 5 yrs	Either Radical Modified Mastectomy or lumpectomy. RT was given to all lumpectomy pts and most mastectomy pts. Tamoxifen 20 mg/d for pts with estrogen- or progesterone-positive or unknown status (for 3 or 5 yrs, depending on the randomization date). For negative receptor pts adjuvant chemotherapy	All pts received tamoxifen 20 mg/d for 5 yrs
Included pts	• Age: 18 yrs to 65 yrs • Stage: T1, N0 • Pts with unexpected pathologic findings of bifocal BC (a smaller lesion close to the reference cancer) • Pts with T1 disease with tumours of diameter >2 cm at final histology	• Age: 65 yrs to 80 yrs • Stage: primary T1, N0 of ≤2 cm in diameter; • No palpable aillary lymph nodes	• post-menopausal women • aged ≥50 • with early invasive breast cancer • tumour size ≤ 10 mm	• postmenopausal patients • ≥60 years • with clinically node-negative operable breast cancer
Patients excluded	• Pts with bilateral or pluricentric BC • Pts with histologic evidence of noninfiltrating carcinoma only • Pts with distant metastases • Pts with a history of previous malignancy	• Pts with bilateral BC • Pts with distant metastases at diagnosis • Pts with history of other cancer except basal cell carcinoma of the skin	• inflammation • palpable axillary nodes (N+) • metastasis • prior contralateral invasive cancer • another carcinoma • limited survival prognosis (<10 years)	*nr*
Age, median (range)	Age (mean ± SD): 52.6 ± 7.7 yrs	70 yrs (65-80)	No-ALND: 62.6 yrs (range 50-81 yrs) ALND: 61.6 yrs (range 50-87 yrs)	median, range: 74 yrs, 60–91 yrs
Stage	T1N0	T1N0	*nr*	T1a, T1b, T2a, T2b, T3, N0, or M0. 80% estrogen receptor-positive
Grade	I, II, III	ALND vs. no ALND • G1: 22 (20.2%) vs. 27 (24.5%)	*nr*	*nr*

Characteristics	Agresti, 2014 [8]	Martelli 2012 [6]	Avril, 2011 [122]	Rudenstam, 2006 [5]
		• G2: 73 (67%) vs. 72 (65.5%) • G3: 12 (11%) vs.8 (7.3%		
Tumour size, median, range, cm	QUAD 1.5 vs. QU 1.4 (clinical tumour size)	• ≤2 cm diameter	tumours ≤10 mm	≤2 cm: 56% >2cm: 42% Unknown: 2%
Tumour type	DCIS 48.4%	AD vs. no AD • Ductal carcinoma: 60 (55%) vs. 61 (55.4%) • Lobular carcinoma: 20 (18.3%) vs. 19 (17.3%) • Other infiltrating carcinoma: 29 (26.7%) vs. 30 (27.3%)	Invasive ductal carcinoma: No ALND: 78% ALND: 76% Invasive lobular carcinoma: No-ALND: 8% ALND:9%	*nr*
Receptor status	QUAD vs. QU ER1/PgR1+: 66.9% vs. 72.2% ER1/PgR-: 14.0% vs. 9.4% ER-/PgR-: 13.2% vs. 13.5% ER-/PgR1+: 5.9% vs. 4.9% P=0.384	AD vs. no AD ER+ PgR+: 68 (62.4%) vs. 81 (73.6%) ER+ PgR−: 25 (23%) vs. 17 (15.5%) ER− PgR+: 1 (0.9%) vs. 1 (0.9%) ER− PgR−: 15 (13.7%) vs. 10 (9.1%)	ER/PR status: Both negative No-ALND: 6%; ALND: 7% At least one positive: No-ALND: 79%; ALND: 85% Unknown: No-ALND: 15%; ALND: 8%	ER status: Positive: 80% Negative: 16% Unknown: 3%
Lymph node metastases	25/78 pts with lymph node-positive disease	*nr*	*nr*	0: 36% 1-3: 10% ≥4: 4%
Surgeon experience	nr	*nr*	*nr*	*nr*
Method for SLNB	Cytology of the tumour: Formalin-fixed paraffin-embedded surgical specimens were sectioned and stained with hematoxylin and eosin at room temperature	*nr*	*nr*	*nr*
Study shortcomings	*nr*	Didn't recruit the required number of pts (makes it underpowered to demonstrate noninferiority between the 2 arms)	This was a pragmatic trial, and we considered the risk of bias higher than others.	The trial was originally designed to assess equivalence between the axillary clearance and no axillary clearance treatment groups in terms of DFS and OS, but the accrual was slower than anticipated
Summary results	OS: ALND = 93.3% (95% CI, 89.4%-95.8%) vs. Obs = 91.5% (95% CI, 87.0%-94.4%) Adjusted HR for Obs. vs. ALND: 1.09 (95% CI, 0.59-2.00; p=0.783)	OS: NS BC mortality: 15-yr crude cumulative incidence of BC death: 7.6% (95% CI, 2.5 to 12.7) vs.9.2% (95% CI, 3.7 to 14.6). Crude cumulative incidence curves for BC mortality and distant	OS at 5 yrs: 98% vs. 94%; HR 2.91 (95% CI, 1.33 to 6.36) (ITT analysis) Equivalence is not demonstrated due to a higher than expected OS in the no ALND group (expected 95%), and lack of statistical power.	OS: 75% vs. 73%, HR 1. 05; 95% CI, 0.76 to 1.49; p=0.77 DFS: 67% vs. 66%, HR 1. 06; 95% CI, 0.79 to 1.42; p=0.69 Total breast cancer events:

Characteristics	Agresti, 2014 [8]	Martelli 2012 [6]	Avril, 2011 [122]	Rudenstam, 2006 [5]
	The 90% CI of the HR was (90% CI, 0.65-1.81), the right boundary being below the noninferiority margin (degree of difference, 1.9) noninferiority p = 0.037 DFS: ALND = 92.4% (95% CI, 88.5%-95.1%) vs. Obs. = 91.3% (95% CI, 86.7%-94.3%), Adjusted HR for Obs. vs. ALND: 1.04 (95% CI, 0.56-1.94; p=0.898) The 90% CI of the HR was 0.62 to 1.76; noninferiority p=0.029	metastases p=0.64 and p=0.95 respectively. HR of death: 1.18 (95% CI, 0.73 to 1.92) Axillary disease: 15-yr crude cumulative incidence: 0% vs. 6% (95% CI, 0 to 12.6). Ipsilateral breast disease: 15-yr cumulative incidence: 4% (95% CI, 0.1 to 7.8) vs. 8.3% (95% CI, 2.1 to 14.5). Distant metastases: 15-yr crude cumulative incidence: 8.6% (95% CI, 3.2 to 13.9) vs. 9.6% (95% CI, 3.3 to 15.9)	EFS at 5 yrs: 96% vs. 90%; HR 2.26 (95% CI, 1.32 to 3.86) (per protocol analysis, ITT analysis nr) At 5 yrs: Axillary metastases: 0 vs. 1.3% (p value nr) Breast/chest wall metastases: 1.3% vs. 1.7% Metastatic event: 0.3% vs. 1.3% Contralateral breast cancer: 0.3% vs. 0.7% Breast cancer death: 0. 3% vs. 1.7% (All of the above per protocol analysis) Functional outcomes (on 543 of 625 pts): Null vs. moderate and/or major: Arm fatigue: 254/4 vs. 249/24, p=0.0002 Shoulder mobility: 252/5 vs. 250/21, p=0.0005 Parestesia: 252/6 vs. 233/41, p<0.0001 Lymphedema: 255/3 vs. 246/29, p<0.0001 Other functional impairments: 251/12 vs. 260/16, p=0.252 N. of pts with functional impairment: 242/8 vs. 200/15, p=0.0005	18% vs. 16%: p=NS including: Deaths because or recurrence: 31% vs. 30% p=*nr* Local recurrence: 4% vs. 2% Contralateral recurrence: 1% vs. 2% Axillary recurrence: 1% vs. 3% Distant recurrence: 12% vs. 10%

AD = axillary dissection; ALND = axillary lymph node dissection; BC = breast cancer; BCT = breast-conserving therapy; CI = confidence interval; DFS = disease-free survival; ER = estrogen receptor; HR = hazard ratio; mos = months; IQR = interquartile range; NA = not applicable; nr = not reported; obs. = observational study; OS = overall survival; PgR = progesterone receptor; QU = quandrantectomy without axillary lymph node dissection; QUAD = quandrantectomy with axillary lymph node dissection; RCT = randomized controlled trial; RT = radiotherapy; SD = standard deviation; SLN = sentinel lymph nodes; SLND = sentinel lymp node dissection; SLNB = sentinel lymph node biopsy; yrs = years

Table 2A. Characteristics and summary results of included studies. Question 2, Radiotherapy trials for patients with early breast cancer who did not receive NAC and are sentinel lymph node negative at diagnosis

Characteristics	Poortmans, 2015 [23]	Early Breast Cancer Trialists' Collaborative Group, 2014 [86]	Wang, 2011 [25]	Zurrida, 2013 [132]
N	4006	8135	681	285 (66% of the 435 pts in the original study)
Study design	RCT	RCT	RCT	RCT
Comparison	Regional + whole breast or thoracic RT vs. whole breast or thoracic RT alone	Surgery + RT of the chest wall, internal mammary chain, and supraclavicular and/or aLN vs. surgery alone	Chemotherapy + RT vs. Chemotherapy	145 Axillary RT vs. 140 no axillary RT
Follow-up (median)	10.9 yrs	9.4 yrs (IQR 3.7- 17.3)	86.5 mos (62.2-119.0)	63 mos
Other treatment	• Adjuvant systemic therapy (chemo, hormonal therapy, both) • Breast surgery (mastectomy, BCS and ALND)	• Mastectomy • AD • Chemo- and hormonal therapy	• Total mastectomy • Chemotherapy	• BCT • Chemo- or endocrine therapy
Included pts	• Unilateral histologically confirmed breast carcinoma of stage I, II, or II • Centrally or medially located primary tumour, irrespective of axillary involvement or an externally located tumour with axillary involvement • Had undergone mastectomy or BCS and AD • Median age: 54 yrs During the last years of the trial: • Had undergone SNB followed by an AD in the case of a positive node	• Pts from 22 trials • pN0 • pN1	• Triple-negative stage I–II breast carcinoma	• Age: ≥45 yrs • Axilla negative on palpation • Tumour size ≤1.4 cm • 55.4% luminal A,'34% luminal B • 1.8% HER2- positive • 8.8% triple negative
Patients excluded	• Concurrent disease • Tumour that was not stage I, II, or III • Not treated according to protocol	*nr*	*nr*	[Data from main study [14]] • Pts with non-invasive carcinoma • Pts with history of previous malignancy
Age, median (range)	54 yrs (22-75) vs. 54 yrs (19-75)	*nr*	*nr*	57 yrs (IQR 51-63)
Stage	T1: 60.1%, T2: 35.7%, or T3[a]:3.5%; pN0: 44.4% pN1a: 43.1% pN2a:9.9% pN3a: 2.6%	Stage: I, II and III Has separate results for stage pN0	Chemo vs. Chemo + RT Stage I: 233 (74.0%) vs. 259 (70.8%) Stage II: 82 (26.0%) vs. 107 (29.2%) P>0.05	pT1a: 14.7% pT1b: 54.4; pT1c: 30.9% ER+: 89.5% low (<14%) Ki67: 60.7%
Grade	*nr*	*nr*	*nr*	aRT vs. no aRT I: 62 (42.8%) vs. 54 (38.6%) II:59 (40.7%) vs. 63 (45.0%) III: 24 (16.6%) vs. 22 (15.7%)
Tumour size,	pT1: ≤2 cm: 60.2% vs. 60.1% pT2: 2-5 cm: 35.8% vs. 35.7%	*nr*	Chemo vs. Chemo + RT	≤1.4 cm

Characteristics	Poortmans, 2015 [23]	Early Breast Cancer Trialists' Collaborative Group, 2014 [86]	Wang, 2011 [25]	Zurrida, 2013 [132]
median, range, cm	pT3: >5 cm: 3.5% vs. 3.5%		≤2 cm: 119 (37.8%) vs. 132 (36.1%) 2.1-5.0 cm: 196 (62.2%) vs. 234 (63.9%) p>0.05	
Tumour type	*nr*	*nr*	*nr*	aRT vs. no aRT • Ductal : 105 (72.4%) vs. 96 (68.6%) • Lobular: 23 (15.9%) vs. 26 (18.6%) • Other: 17 (11.7%) vs. 18 (12.9%)
Receptor status	*nr*	*nr*	*nr*	ER/PgR • Both <1%: 13 (9.0%) vs. 17 (12.1%) • ER or PgR 1–49% : 84 (57.9%) vs. 81 (57.9%) • ER and PgR ≥50% 48 (33.1%) vs. 42 (30.0%)
Study shortcomings	Unable to determine whether internal mammary irradiation or medial supraclavicular irradiation contributed more to the outcome. Recorded little about adjuvant therapy because it was less variable in the early 1990s when the study began	*nr*	*nr*	Performed on a small, selected subgroup (ER, PgR, HER2 and Ki67 available) of those recruited to the GRISO trial which may have resulted in selection bias Use of multiple statistical tests increased the likelihood of false positive results
Summary results	(RNI vs. CG) OS: 82.3% vs. 80.7% HR 0.87; 95% (95% CI, 0.76-1.00), p = 0.06 DFS: 72.1% vs. 69.1% HR 0.89 (95% CI, 0.80-1.00), p=0.04 DDFS: 78.0% vs. 75.0% HR 0.86 (95% CI, 0.76-0.98), p =0.02 BC mortality: 12.5% vs. 14.4% HR 0.82 (95% CI, 0.70-0.97), p=0.02	ALND pts: Loco-regional recurrence rate: 22.4% vs. 21.1%, RR 1.81 (95% CI, 0.63 to 5.17, 2 sided) p>0.1 Overall recurrence: RR 1.06 (95% CI, 0.76 to 1.48) Axillary sampling pts: Loco-regional recurrence rate: 3.7% vs. 17.8% RR 0.25 (95% CI, 0.16 to 0.38, 2 sided p<0.00001) Overall recurrence rate: 22.1% vs. 34.2%, RR 0.61 (95% CI, 0.47 to 0.80, 2 sided p=0.0003)	Neutropenia and nausea/emesis: 38% and 14.8%, vs. 37.1% and 13.0%, p>0.05 for both. RFS at 5 yrs: 88.3% vs. 74.6%, HR 0.77 (95% CI, 0.72 to 0.98) Distant metastases: 1-2 metastases: 24.2% vs. 38.5%, p<0.05	OS at 10 yrs follow-up: 96% (95% CI, 90% to 98%) vs. 90% (95% CI, 84% to 94%), p=0.078 HR 0.39 (95% CI, 0.14 to 1.05), p=0.062 **DFS At 10 yrs follow-up:** 94% (95% CI, 88% to 97%) vs. 89% (95% CI, 82–93%), p=0.077 HR 0.50 (95% CI, 0.24 to 1.04), p=0.065 Subgroups: Ki67 ≤14%: 93% (95% CI, 88% to 99%) vs. 95% (95% CI, 90% to 100%), HR 1.26 (95% CI, 0.43 to 3.64), p=0.91 Ki67 ≥14%: 95% (95% CI, 89% to 100%) vs. 79% (95% CI, 69% to 92%), HR 0.23 (95% CI, 0.08 to 0.67), p=0.005

AD = axillary dissection; ALND = axillary lymph node dissection; aLNs = axillary lymph nodes; aRT = axillary radiotherapy; BC = breast cancer; BCS = breast-conserving surgery; BCT = breast conserving therapy; chemo = chemotherapy; CG = control group; CI = confidence interval; DDFS = distance disease-free interval; DFS = disease-free survival; ER = estrogen receptor; Gy = gray (unit); HER2 = Human epidermal growth factor receptor 2; HR = hazard ratio; mos = months; IQR = interquartile range; Ki67 = tumour proliferation index; NA = not applicable; NAC = neo-adjuvant chemotherapy; nr = not reported; obs. = observational study; OS = overall survival; PgR = progesterone receptor; pts = patients; QU = quandrantectomy without axillary lymph node dissection; QUAD = quandrantectomy with axillary lymph node dissection; RCT = randomized controlled trial; RFS = relapse-free survival; RNI = regional nodal irradiation; RR = relative risk; RT = radiotherapy; SLN = sentinel lymph nodes; SLND = sentinel lymp node dissection; SLNB = sentinel lymph node biopsy; SNB = sentinel node biopsy; yrs = years

Table 2B. Characteristics and summary results of included studies. Question 2, Surgical trials for patients with early breast cancer who did not receive NAC and are sentinel lymph node negative at diagnosis

Characteristics	Veronesi, 2010 [22]	Krag, 2010 [15]	Gill, 2009 [20]	Canavese, 2009 [19]	Zavagno, 2008 [18]
N	532 pts with tumour of the breast ≤2 cm, 516 pts in the per protocol analysis	5611 (3986 in analysis)	1088 women with unifocal, clinically node-negative early BC ≤3 cm	248 women with early BC ≤3 cm, clinically negative axilla (225 in analysis)	697 pts with BC ≤3 cm, and a clinically negative axilla
Study design	RCT	RCT	RCT	Noninferiority RCT trial	RCT
Comparison	SLNB + ALND vs. SLNB alone (+ ALND only if positive at SLNB)	2807 SLNB (2011 SN-) + ALND vs. 2804 (1978 SN-) SLNB alone (and subsequent ALND if SN positive)	544 SLNB (+ ALND if node + or not detected) vs. 544 ALND	ALND vs. SLNB	SLNB + routine ALND vs. SLNB + ALND only if node+
Follow-up (median, range)	102 mos (1-20)	95.6 mos (mean) (70.1-126.7)	12 mos	5.5±1.4 yrs	56 mos (IQR 42.4 to 63.1) mos
Other treatment	• BCS	• Surgery • Systemic adjuvant treatment • RT	Postoperative adjuvant therapies	Mastectomy of quadranctectomy +RT of the breast, and adjuvant or hormone therapy according to prognostic factors	All pts who underwent breast-conserving surgery received RT ot the breast. Pts with unfavourable prognostic features received adjuvant chemo-and/or hormonal therapy
Included pts	Adult (age ≥18 yrs) women with primary breast cancer ≤2 cm with clinically negative axillary lymph nodes	• Female >18 years • Invasive breast cancer • Clinically node-negative	Clinically node negative women with primary unifocal breast cancer ≤3 cm in diameter, if their World Health Organization (WHO) performance status was 0 or 1, and if they were able to maintain regular follow-up	Women of 18–75 yrs of age, with primary invasive breast carcinoma as revealed by mammography and cytohistology, clinically negative axillary lymph nodes and unifocal tumour sized ≤3 cm as estimated by ecography.	Patients with invasive breast cancer ≤3 cm and clinically negative axilla.
Patients excluded	• History of other cancer, except nonmelanoma skin cancer • Multicentric breast cancer • Previous excisional biopsy	*nr*	• Surgery for a prior ipsilateral breast cancer or prior ipsilateral axillary surgery; • Age ≤18 years, were pregnant, • Allergy to blue dye or radioisotope, • Evidence of metastatic disease	• Pts with tumours ≥3 cm in diameter (would undergo ALND) • Pts who had prior surgery to same breast or on ipsilateral axilla • Pts suffering suffering from chronic life-threatening disease possibly preventing adjuvant therapy	• Nonpalpable tumours • Multiple tumours • DCIS • Tumours >3 cm • Clinically positive axilla • Distant metastases • Previous neoadjuvant therapy • Pregnancy • Age >80 yrs
Age, median (range)	ALND arm: 56 yrs (40 to 75) SLNB arm: 55 yra (40 to 75)	≤49 yrs: 979 (24.5%) ≥50 yrs 3010 (75.5%)	Age: SLNB vs. ALND: 30-49 yrs: 118.(21%) vs. 117 (22%) 50-69 yrs: 354 (65%) vs. 358 (66%) ≥70 years: 71 (13%) vs. 66 (12%)	59 yrs (28 to 75)	Age (mean [SD]): ALND: 58.2 [10.6] yrs SLNB: 57.6 [10.4] yrs
Stage	*nr*	*nr*	*nr*	pTis: 2 (0.9%)	*nr*

Characteristics	Veronesi, 2010 [22]	Krag, 2010 [15]	Gill, 2009 [20]	Canavese, 2009 [19]	Zavagno, 2008 [18]
				pT1mic: 2 (0.9%) pT1a: 21 (9.3%) pT1b: 42 (18.7%) pT1c: 116 (51.5%) pT2: 42 (18.7%)	
Grade	AD vs. SLNB I: 81 (32%) vs. 82 (32%) II: 119 (46%) vs. 128 (49%) III: 54 (21%) vs. 47 (18%)	*nr*	SNBM vs. RAC 1: 174 (32%) vs. 165 (31%) 2: 234 (44%) vs. 237 (44%) 3: 131 (24%) vs. 132 (25%)	ALND vs. SLNB 1: 7 (6.1%) vs. 5 (4.6%) 2: 46 (40.0%) vs. 44 (40.0%) 3: 60 (52.2%) vs. 59 (53.6%)	AD vs. SLNB 1: 69 (19.6%) vs. 54 (15.6%) 2: 180(51.1%) vs. 181 (52.6%) 3: 94 (26.7%) vs. 105 (30.4%)
Tumour size, median, range, cm	<2 cm	Tumour size: ≤2 cm: 3344 (83.8%) 2.1-4.0 cm: 585 (14.7%) ≥ 4.1 cm: 60 (1.5%)	Tumour size: SLNB vs. ALND ≤1 cm: 149 (27%) vs.146 (27%) 1-2 cm: 243 (45%) vs. 244 (46%) 2-3 cm: 101 (19%) vs. 103 (19%) >3 cm: 48 (9%) vs. 42 (8%)	*nr*	AD vs. SLNB T1a: 7 (2.0%) vs. 12 (3.5%) T1b: 72 (20.4%) vs. 67 (19.5%) T1c: 208 (59.1%) vs. 198 (57.6%) T2 ≤3 cm: 63 (17.9%) vs. 63 (17.9%) T4: *nr* vs. 3 (0.9%) NA: 2 (0.6%) vs. 2 (0.6%)
Tumour type	AD vs. SN • Ductal : 212 (83%) vs. 209 (81%) • Lobular: 20 (8%) vs. 18 (7%) • Other: 25 (10%) vs. 32 (12%)	*nr*	*nr*	ALND vs. SLNB • Ductal : 110 (95.7%) vs. 107 (97.3%) • Lobular:2 (1.7%) vs. 1 (0.9%) • Other: 2 (1.7%) vs. 1 (0.9%)	*nr*
Receptor status	AD vs. SN • ER +: 236 (92%) vs. 237 (92%) • ER-: 21 (8%) vs. 21 (8%)	*nr*	*nr*	ALND vs. SLNB • ER+ /PgR+: 65 (56.6%) vs. 70 (63.7%) • ER- /PgR+: 0 (0%) vs. 2 (1.8%) • ER+ /PgR-: 29 (25.2%) vs. 2 (20.0%) • ER- /PgR-: 16 (13.9%) vs. 13 (11.8%)	AD vs. SLNB • ER+ /PgR+: 257 (73.0%) vs. 231 (67.0%) • ER- /PgR+: 12 (3.4%) vs. 9 (2.6%) • ER+ /PgR-: 36 (10.2%) vs. 48 (13.9%) • ER- /PgR-: 42 (11.9) vs. 52 (15.1%) • NA: 5 (1.5%) vs. 5 (1.4%)
Micrometastases	NS	*nr*	*nr*	ALND: 6 pts with micrometastatic SLN SLNB: 3 pts with micrometastatic SLN	Positive SLNs found in 73 patients (17 micrometastases)
Macrometastases	*nr*	*nr*	*nr*	ALND: 18 pts with macrometastatic SLN SLNB: 22 pts with macrometastatic SLN	Positive SLNs found in 73 patients (56 macrometastases)

Characteristics	Veronesi, 2010 [22]	Krag, 2010 [15]	Gill, 2009 [20]	Canavese, 2009 [19]	Zavagno, 2008 [18]
Surgeon experience	*nr*	Of the 224 surgeons audited, protocol compliance was excellent.	*nr*	*nr*	This was a multicentric study enrolling both academic centers and small community hospitals with limited experience in breast cancer surgery.
Method for SLNB	Radiocolloid. A gamma ray-detecting probe in a sterile glove was used to identify the "hot" SN and assist its removal during surgery	Radiocolloid and blue dye. Lymph nodes that were radioactive, blue, or clinically positive were judged to be sentinel nodes. SLNs from were assessed postoperatively with routine stains at about 2 mm intervals through the node. Immuno histochemistry was not permitted, except for confirmation of suspicious findings on routine haematoxylin and eosin stains. SLNs from group 2 were assessed intraoperatively with cytology.	Blue dye and radiocolloid in combination or blue dye alone. Lymph nodes that were clinically suspect were also removed at the same time, irrespective of radioactivity or blue-dye staining, were included in the sentinel-node-biopsy procedure for defining diagnostic accuracy and the subsequent surgical management.	Radiocolloid and blue dye. Through a small axillary incision, the radioactive SLN was localized with a c-ray detecting probe and removed for immediate intraoperative search for metastases. The SLN was bisected along its major axis and five pairs of frozen sections, each 4-lm thick, were cut every 10 lm in each half of the node. The first, third and fifth sections were stained with hematoxylin–eosin. If this histological evaluation resulted negative or ambiguous, the second and the fourth sections were tested by immunehisto-chemistry for the presence of cytokeratins. The remaining tissue was paraffin embedded for definitive postoperative evaluation.	RAdiocolloid only and examination of a frozen section examination
Summary results	OS at 10 yrs: 89.7% (95% CI, 85.5 to 93.8) vs. 93.5% (95% CI, 90.3% to 96.8%) Death rate: 8.9% vs. 5.8%, p=0.15 BC-related event rates: 88.8% vs. 89.9%	**OS at 5 yrs:** HR 1.19 (95% CI, 0.95 to 1.49), p=0.13 Adjusted DFS: HR 1.07 (95% CI, 0.90–1.22), p=0.57	[a]**Changes in pt self-ratings in the SSSS (between-group difference):** Overall summary score: 4.4 vs. 7.0, difference 2.6% (95% CI, 1.3 to 3.9), p<0.001; Arm symptoms: 5.5 vs. 9.7 difference: 4.2% (95% CI, 2.8 to 5.7), p<0.001; Arm swelling: 3.4 vs. 7.3 difference: 4.0% (95% CI, 2.3 to 5.5), p<0.001; Arm dysfuntion: 3.6 vs. 5.5, difference: 1.9% (95% CI, 0.3 to 3.5), p=0.02 Arm disabilities: 2.9 vs. 3.4, difference 0.5% (95% CI, -0.1 to 2.1), p=0.5	OS rate: 97.2% vs. 97.2%, p=0.697 **EFS at 5 yrs:** 89.8% vs. 94.5% , p=0.715 Recurrence of any type: RR 0.87 (95% CI, 0.38 to 2.01), p=0.741	OS estimate rate at 5 yrs: 95.5% (95% CI, 92.2 to 97.5) vs. 94.8% (95% CI, 91.6 to 96.8) Death rate due to BC: 2.3% vs. 2.9% p value nr DFS rate at 5 yrs: 89.9% (95% CI, 85.3 to 93.1) vs. 87.6% (95% CI, 83.3 to 90.9); difference 2.3% (95% CI, -3.1% to 7.6%), p=0.77. The upper bound is more than the set boundary for noninferiority of 6%, therefore the possibility that DFS is worse with SLNB could not be excluded.

Characteristics	Veronesi, 2010 [22]	Krag, 2010 [15]	Gill, 2009 [20]	Canavese, 2009 [19]	Zavagno, 2008 [18]
			Percentage changes in clincian's ratings from baseline to the average between 6 and 12 months: Increase in arm volume: 2.8% vs. 4.2%, difference: 1.4 (95% CI, 0.6 to 2.3), p=0.002 Decrease in lateral abduction: 2.5% vs. 4.4%, difference 1.9 (95% CI, 0.3 to 3.5), p=0.02 **Arm volume and function:** **Increase in arm volume**: (per protocol 519 vs. 509): 2.8% vs. 4.2%; difference 1.4% (95% CI, 0.6 to 2.3%), p=0.002 Number with an increase in arm volume ≥15%: 4.2% vs. 6.9%; difference: 2.7% (95% CI,-0.1 to 5.5), p=0.06. Decrease in lateral abduction: 2.5% vs. 4.4%; difference 1.9% (95% CI, 0.3 to 3.5), p=0.02		

[a]As measured with the SNAC Study Specific Scales (SSSS), average of 6 and 12 months scorees

AD = axillary dissection; ALND = axillary lymph node dissection; BC = breast cancer; BCS = breast-conserving surgery; CG = control group; chemo = chemotherapy; CI = confidence interval; DCIS = ductal carcinoma in situ; DFS = disease-free survival; EFS = event-free survival; ER = estrogen receptor; HR = hazard ratio; IQR = interquartile range; mos = months; NA = not applicable; *nr* = not reported; NS = not significant; OS = overall survival; PgR = progesterone receptor; pts = patients; RAC = routine axillary clearance; RT = radiotherapy; SLN = sentinel lymph nodes; SN = sentinel node; SNBM = sentinel lymph node-based management; SLNB = sentinel lymph node biopsy; yrs = years

Table 3A. Question 3, patients with positive lymph nodes who did not receive NAC. Trials included for comparison A) ALND + SLNB vs. SLNB alone.

Characteristics	ACOSOG Z0011 [26,27] [13]	IBCSG 23-01 [29,30,150]	ATTRM-048-13-2000 [32]
N	891: 445 vs. 446 856 (420 vs. 436) in analysis	934: 469 vs. 465 931 (467 vs. 464) in analysis	247: 123 vs. 124 233 (112 vs 121) in analysis
Study design	Non-inferiority RCT	Non-inferiority RCT	Parallel group RCT
Comparison	SLNB vs. SLNB+ALND	No-ALND vs. ALND	SLNB + ALND vs. SLNB + observation
Follow-up (median)	6.3 yrs (IQR 5.2 to 7.7 yrs)	9.7 yrs (IQR 7.8-12.7)	5 yrs (2-8.92)
Other treatment	• Adjuvant systemic therapy (chemo-, and/or endocrine therapy) • Whole breast irradiation: 45 to 50 Gy in fractions of 1.8 to 2.0 Gy/d, 5 ds/wk delivered via tangential fields with a coplanar border. • Pts with a medial hemisphere lesion had preoperative lymphoscintigraphy to confirm axillary drainange.	Mastectomy or BCT with RT and chemo or hormonal systemic therapy.	Breast-conserving surgery (92.3%), or mastectomy + whole breast RT (89.7%), and post-operative adjuvant chemotherapy
Included pts	• Macroscopic but limited axillary involvement, • Clinically negative axilla, • 1-2 involved nodes The criteria for eligibility were broadened in June, 2006, to include patients with one or more positive sentinel nodes (formerly only one); multicentric or multifocal tumours (formerly only unicentric); and largest lesion size of 5 cm or smaller (formerly ≤3 cm).	• Early BC, • tumours ≤5 cm, • clinically negative axilla, • ≥1 micro-metastases (≤2 mm) or isolated tumour cells	• Early BC • micrometastases in the axillary lymph nodes
Patients excluded	• Withdrew consent. • No positive SLN. • First histologic diagnosis of invasive breast cancer was 60 or more ds before SLNB. • Breastfeeding. • History of another malignancy in the previous 5 yrs • Bilateral BC • Multicentric disease • ≥3 positive SLNs; until 2006 • Gross extracapsular invasion or matted nodes at SLNB • Medical contraindications to ALND** or other risk factors precluding treatment.	• Pregnant or breastfeeding • Ineligible for follow-up • Previous or concomitant malignancy • Pure DCIS • Previous systemic therapy for BC • Chemoprevention in the preceding yr • Distant metastases or macrometastatic disease • Palpable axillary nodes • Paget's disease without invasive cancer	• Pregnant or breastfeeding • Age >75 yrs • Metastatic cell clusters smaller than 0.2 mm (from 2002 onward excluded; from 2001 to 2002 included)
Age, median (range)	56 yrs (24-92) vs. 54 yrs (25-90)	54 (26-81) yrs	55.3 yrs (29-75) vs. 53.2 yrs (33-75)
Stage	T1: 284 (67.9%) vs. 303 (70.6%) T2: 134 (32.1%) vs. 126 (29.4%) N0, M0 (1 or 2 positive SLN)*	Early breast cancer	T<3.5 cm, clinical N0, M0
Grade	*nr*	Grade I: 118 (25%) vs. 90 (19%) Grade II: 214 (46%) vs. 241 (52%) Grade III: 129 (28%) vs. 135 (29%) Unknown: 3 (<1%) vs. 1 (<1%)	Grade II and III: 73 (68.2 %) vs. 87 (79.8%)
Tumour size, median, range, cm	1.7 (0.4 to 7.0) vs. 1.6 (0.0-5.0)	<2 cm: 316 (68%) vs. 322 (69%) 2-2.9 cm: 106 (23%) vs. 112 (24%) ≥3 cm: : 35 (8%) vs. 28 (6%)	Mean (range): 1.57 cm (0.15-3.50) vs. 1.78 cm (0.10-3.50)

Characteristics	ACOSOG Z0011 [26,27] [13]	IBCSG 23-01 [29,30,150]	ATTRM-048-13-2000 [32]
		Unknown: 7 (2%) vs. 5 (1%)	
Tumour type	Infiltrating ductal: 82.7% vs. 84% Infiltrating lobular: 6.5% vs. 8.5% Other: 10.8% vs. 7.5%	*nr*	Ductal: 103 (92.8%) vs. 105 (89.0%) Lobular: 4 (3.6%) vs. 6 (5.1%) Other: 4 (3.6%) vs. 7 (5.9%)
Receptor status	ER+/PR+: 256 (66.8%) vs. 270 (68.9%) ER+/PR-: 61 (15.9%) vs. 54 (13.8%) ER-/PR+: 3 (0.8%) vs. 4 (1%) ER-/PR-: 63 (16.5%) vs. 64 (16.3%)	ER+: 409 (88%) vs. 425 (91%) ER-: 51 (11%) vs. 40 (9%) PR+: 352 (76%) vs. 350 (75%) PR-: 108 (23%) vs. 115 (25%)	ER expression: 86 (85.1%) vs. 88 (83.0%) PR expression: 74 (73.3%) vs. 82 (78.8%)
Isolated tumour cells	*nr*	≤1 mm: 323 (70%) vs. 320 (69%)	*nr*
Micrometastases	*nr*	1.1 to 2 mm: 131 (28%) vs. 135 (29%)	*All pts had miocrometastases*
Macrometastases	*nr*	>2 mm: 10 (2%) vs. 11 (2%)	*nr*
Lymph node metastases	0: 4 (1.2%) vs. 29 (7%) 1: 199 (58%) vs. 295 (71.1%) 2: 68 (19.8%) vs. 76 (18.3%) 3: 25 (7.3%) vs. 11(2.7%) ≥4: 47 (13.7%) vs. 4 (1%)	Number of metastatic lymph nodes: 1: 440 (95%) vs. 450 (96%) 2: 23 (5%) vs. 17 (4%) 3: 1 (<1%) vs. 0	*nr*
Surgeon experience	≥20 SLNB	*nr*	*nr*
Method for SLNB	Isosulphan blue, a radiopharmaceutical, or both (based on the surgeon's experience)	*nr*	*nr*
Study shortcomings	Ended early for low event rate – low power Randomized pts after results of SLNB were known	Open label Randomized pts after results of SLNB were known	Underpowered Randomized pts after results of SLNB were known
Summary results	**OS at 5 yrs:** 92.5% (95% CI, 90.0% to 95.1%) vs. 91.8% (95% CI, 89.1% to 94.5%) HR 0.87 (90% CI, 0.62 to 1.23), p=0.008 for noninferiority **DFS at 5 yrs:** 83.9% (95% CI, 80.2% to 87.9%) vs. 82.2% (95% CI, 78.3% to 86.3%) p=0.14	10-year DFS 75% (95% confidence interval [CI]: 72%–81%) in the no-AD group and 75% (95% CI, 71%–79%) in the AD group (HR [no-AD vs. AD]=0.85; 95% CI, 0.65–1.11; log-rank p=0.23; non-inferiority p=0.002) 10-year OS: 91% (95% CI, 88%–94%) in the no-AD group and 88% (95% CI, 85%–92%) in the AD group (HR [no-AD vs. AD]=0.77; 95% CI, 0.56–1.07; log-rank p=0.19). Conclusion: Findings after a median follow-up of 9.8 years fully support the findings at 5 years in that no-AD is not inferior to AD with respect to DFS, and there is no significant difference between the arms for DFS and OS.	**Recurrence**: 2.5% vs**.** 1% p=0.348 **DFS:** NS

*SLN were positive if analysis of frozen section, touch preparations, or hematoxylin –stained permanent sections – but not immunohistochemistry identified any metastases
**ALND was defined as the removal of all anatomic level I and II nodes on the affected side with ≥10 identified nodes per axillary specimen.

AD = axillary dissection; ALND = axillary lymph node dissection; BC = breast cancer; BCT = breast conserving therapy; chemo = chemotherapy; CI = confidence interval; DCIS = ductal carcinoma in situ; ds = days; DFS = disease-free survival; ER = estrogen receptor; Gy = gray (unit); HR = hazard ratio; IQR = interquaritile range; mos = months; NAC = neo-adjuvant chemotherapy; *nr* = not reported; OS = overall survival; PR = progesterone receptor; pts = patients; RCT = randomized control trial; SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy; wks = weeks; yrs = years

Table 3B. Question 3, patients with positive lymph nodes who did not receive NAC. Trials included for comparison B) Radiotherapy and surgery (ALND or SLNB) versus no treatment.

Characteristics	MA-20 Trial [24]
N	1832
Study design	RCT prarallel group
Comparison	Surgery (BCT or mastectomy + ALND or SLNB) vs. Surgery + aRT
Follow-up (median)	9.5 yrs
Other treatment	Breast-conserving surgery, ALND (96%) or SLNB, and adjuvant systemic therapy (with chemo- or hormonal therapy)
Included pts	(N1) of the breast with positive axillary nodes or negative axillary nodes and high-risk features (i.e., primary tumour measuring ≥5 cm, or ≥2 cm with fewer than 10 axillary nodes removed and at least one of the following: grade 3 histologic categorization, estrogen-receptor negativivty, or lymphovascular invasion)
Pts excluded	T4 tumours, (clinical evidence of direct extension to chest wall or skin) or N2–3 nodes (involvement of axillary nodes that are fixed or of internal mammary nodes), distant metastasis, or serious non-malignant disease (e.g., cardiovascular or pulmonary) that would preclude definitive radiation therapy.
Age, median (range)	CG: 53 (26–84) yrs; IG: 54 (29–84) yrs
Stage	N1
Grade	*nr*
Tumour size, median, range, cm	WBI (N [%]) / RI (N [%]) ≤2 cm: 501 (54.7) / 459 (50.1) 2.1 to 5 cm: 409 (44.7) / 443 (48.4) >5 cm: 6 (0.7) / 13 (1.4)
Tumour type	
Receptor status	Estrogen-receptor status — no. (%) / WBI (N [%]) / RI (N [%]) Positive: 682 (74.5) / 685 (74.8) Negative: 234 (25.5) / 231 (25.2) Progesterone-receptor status Positive: 549 (59.9) / 553 (60.4) Negative: 365 (39.8) / 360 (39.3) Estrogen-receptor status — no. (%) / WBI (N [%]) / RI (N [%]) Positive: 682 (74.5) / 685 (74.8) Negative: 234 (25.5) / 231 (25.2)
Isolated tumour cells	*nr*
Micrometastases	*nr*
Macrometastases	*nr*
Lymph node metastases/ N. of positive axillary nodes	WBI (N [%]) / RI (N [%]) 0: 89 (9.7) / 88 (9.6) 1: 447 (48.8) / 460 (50.2)

Characteristics	MA-20 Trial [24]
	2: 233 (25.4) / 209 (22.8) 3: 100 (10.9) / 109 (11.9) >3: 47 (5.1) / 50 (5.5)
Surgeon experience	*nr*
Method for SLNB	*nr*
Study shortcomings	The the MA-20 Trial [24] was a parallel group RCT that enrolled almost 2000 women with early breast cancer. We considered this study at moderate risk of bias. The sequence was generated in a random manner, allocation was concealed, and the authors conducted an intention-to-treat analysis. The authors, however, did not state whether patients, clinicians or outcome assessors were blinded. Results for some of the outcomes mentioned in the protocol (NCT00005957) and methods section, such as quality of life and cosmetic and arm function outcomes, were not reported, potentially exposing a selective reporting bias. Finally, we believe that a follow-up at 9.5 years for may be too short to detect some of the long-term adverse effects of radiotherapy. Although subgroup analyses were prespecified, they were not adequately powered to assess the benefit of treatment in different subgroups. Furthermore, the p values of the subgroup analyses were not adjusted for multiple testing. Small number of node-negative pts so the application of results to node-negative pts is unclear. At the time of the study the size of nodal metastasis was not routinely measured, so it is difficult to generalize the findings to pts with micrometastases.
Summary results	**OS:** 82.8% vs. 81.8%, p=NS HR for death 0.91 (95% CI, 0.72 to 1.13, p=0.38) Mortality at 9.5-yr: 10.3% vs. 12.3%, HR 0.80 (95% CI, 0.61 to 1.5, p=0.11) ER-negative pts: 81.3% vs. 73.9%, HR 0.69 (95% CI, 0.47 to 1.00, p=0.05) DFS rates: 82% vs. 77%, HR 0.76 (95% CI, 0.61 to 0.94, p=0.01) Isolated loco-regional DFS rates: 95.2% vs. 92.2%, HR 0.59 (95% CI, 0.39 to 0.88, p=0.009) DDFS rates: 86.3% 82.4%, HR 0.76 (95% CI, 0.60 to 0.97, p=0.03) Isolated loco-regional recurrence: 6.8% vs. 4.3%, HR 0.62 (95% CI 0.42 to 0.92, p=NS) Regional recurrence only: 2.5% vs. 0.5% Distant recurrence: 16.5% vs. 12.9% (HR 0.76 (95% CI 0.60 to 0.96, p=NS)

*SLN were positive if analysis of frozen section, touch preparations, or hematoxylin –stained permanent sections – but not immunohistochemistry identified any metastases
**ALND was defined as the removal of all anatomic level I and II nodes on the affected side with ≥10 identified nodes per axillary specimen.

ALND = axillary lymph node dissection; aRT = axillary radiotherapy; BCT = breast conserving therapy; CG = control group; chemo = chemotherapy; CI = confidence interval; DDFS = distant disease-free survival; DFS = disease-free survival; ER = estrogen receptor; HR = hazard ratio; IG = intervention group; *nr* = not reported; NS = not significant; OS = overall survival; pts = patients; RCT = randomized control trial; RI = regional irradiation; SLN = sentinel lymph node; WBI = whole breast irradiation; yrs = years

Table 3C. Question 3, patients with positive lymph nodes who did not receive NAC. Trials included for comparison C) Radiotherapy of the axilla versus surgery.

Characteristics	EORTC 10981-22023 -AMAROS trial [34-36]	OTOASOR trial [33]	Early Breast Cancer Trialists' Collaborative Group, 2014 [86]
N	1425	474 (planned 2116 vs. 1054)	8135
Study design	Noninferiority, multicentre RCT: randomization before SLNB	Single centre superiority RCT: randomization before SLNB	IPD meta-analysis
Follow-up (median)	6.1 yrs (IQR 4.1-8.0 yrs)	*nr*	9.4 yrs median; 10 yrs for recurrence, 20 yrs for mortality
Other treatment	Systemic treatment; BCS: 88% and 89%, mastectomy 12% and 11%	BCS or mastectomy	Mastectomy and ALND followed by chemo- and hormonal therapy
Comparison	surgery (ALND) vs. Axillary RT	surgery (ALND) vs. Axillary RT	ALND or axillary sampling + RT of the chest wall, internal mammary chain, and supraclavicular and/or axillary LN vs. Surgery alone (i.e., 353 ALND pts and 445 axillary sampling pts) 24 pts had unknown extent of axillary surgery
Outcomes	5-years axillary recurrence AE DFS OS Shoulder mobility, Lymphedema, QOL EORTC quality-of-life questionnaire (EORTC-QLQ-C30; version 3) and breast cancer module (QLQ-BR23)	OS, DFS QOL	Recurrence BC mortality
Included pts	T1-2, unifocal, multifocal invasive breast cancer, no palpable lymphadenopathy	Clinically negative primary invasive breast tumours, clinically <3 cm in diameter no axillary lymphadenopathy	Women with node positive invasive early BC from 22 trials
Patients excluded	metastatic disease, previous treatment of the axilla by surgery or radiotherapy, previous treatment of cancer (except basal cell carcinoma of the skin and in situ carcinoma of the cervix), pregnancy	>75 yrs old or life expectancy <5 yrs, noninfiltrating carcinoma, previous excision biopsy of the breast, primary chemotherapy or endocrine treatment, pregnancy, breast tumour >3 cm, or clinically evident metastatic involvement of the axilla.	*nr*
Age, median (range)	ALND: 56 yrs (48-64), RT: 55 yrs (48-63)	54.7 yrs (26-74) vs. 55.2 yrs (27-74)	*nr*
Stage	T1-2	T1-2	pN0 to pN4+; Has separate results for stage pN0.
Grade	Grade I: 22% and 24%; Grade II: 47% and 45% Grade III 28% and 29%	Grade I: 16% and 22%; Grade II: 51% and 48% Grade III 33% and 30%	I, II and III
Tumour size, median, range, cm	ALND: 17 mm (13-22); RT: 18 mm (13-23)	<3 cm	*nr*
Tumour type	Ductal 563 (762%) and 515 (764%), lobular 100 (13%) and 99 (152%), other 81 (115%) and 66 (104%)	Ductal 193 (79%) and 188 (82%), lobular 40 (16%) and 28 (12%), other 11 (5%) and 14 (6%)	*nr*
Receptor status	Not collected	ER+: 203 (83%) vs. 194 (84%) ER-: 41 (17%) vs. 36 (16%)	*nr*

Characteristics	EORTC 10981-22023 -AMAROS trial [34-36]	OTOASOR trial [33]	Early Breast Cancer Trialists' Collaborative Group, 2014 [86]
		PR+: 178 (73%) vs. 168 (73%) PR-: 66 (27%) va. 62 (27%)	
Micrometastases	*nr*	25% vs. NA	*nr*
Lymph node metastases	Macrometastases in the SLN: 61% and 66%	*nr*	*nr*
Surgeon experience	NA	*nr*	*nr*
Method for SLNB	Radioactive isotope + blue dye	*nr*	*nr*
Study shortcomings	Open label, and did not report long term complications, other than lymphedema and shoulder mobility for which a progressively larger or unclear number of data were missing	At risk for reporting bias for morbidity outcomes, and, for all outcomes, at risk for selection and detection bias, because very little information was reported about patient selection, allocation, and blinding.	This study did not have important shortcomings. The included trials were conducted several years ago, and modern RT planning has improved since, resulting in better results for patients.
Summary results	The sentinel node was identified in 96% of pts with a multifocal tumour and in 98% of those with unifocal disease. In the multifocal group, 51% had a metastasis in the SN compared to 28% in the unifocal group; and further nodal involvement after a positive SN was found in 40% (38/95) and 39% (39/101) respectively.	Between August 2002 and June 2009, 2106 pts were randomized for cALND (arm A-standard treatment, 1054 pts) or ANI (arm B-investigational treatment, 1052 pts). SLN was identified in 2073 pts (98.4%) and was positive in 526 pts (25.4%). 52 SLN-positive pts were excluded from the study (protocol violation, pt's preference). Clinical and tumour characteristics were similar between 244 of 474 pts randomized to cALND and 230 randomized to SLNB plus ANI. Primary endpoint of the study was axillary recurrence and secondary endpoints were OS, BC specific survival, DFS, distant DFS. Mean follow-up was 97 mos (Q-Q3 80-120, range 54-134). Axillary recurrence (primary end point) was 2.0% vs 1.7% (p=NS). OS at 8 yrs was 77.9% vs 84.8%; DFS was 72.1% with cALND and 77.4% with SLNB plus ANI.	**BC mortality rates:** 42.3% vs. 50.2%, 20-yr gain 7.9% (SE 3.1), RR 0.80 (95% CI, 0.67 to 0.95), log-rank 2-sided p=0.01 **Subgroups:** In 1133 women who had pN1-3 in trials treated with mastectomy plus ALND, and chemotherapy, RT reduced breast cancer mortality by slightly more than a fifth: RR 0.78 (95% CI, 0.64 to 0.94), 2-sided p=0.01 **Loco-regional recurrence rate at 10 yrs:** 3.8% vs. 20.3%, log-rank 2-sided p<0.0001 **Overall recurrence rate at 10 yrs:** 34.2% vs. 45.7%; 10-yr gain 11.5% (SE 2.9), RR 0.68 (95% CI, 0. 57 to 0.82, p=0.00006) *2541 pN+ women treated with mastectomy and axillary sampling:* **Loco-regional first recurrence rates:** 6.3% vs. 37.2% RR 0.21 (95% CI, 0.17 to 0.26), log-rank 2-sided p<0.00001 **Overall recurrence rate:** 48.3% vs. 67%, RR 0.59 (95% CI, 0.53 to 0.66), log-rank 2-sided p<0.00001 Overall recurrence rate was larger in pts treated with axillary sampling than with ALND. Difference between RR, 0.003. **Subgroups**: In 1133 women who had pN1-3 in trials treated with mastectomy and ALND, plus chemotherapy, RT reduced overall recurrence rates by a third: RR 0.67 (95% CI, 0.55 to 0.82, 2-sided p=0.00009 Of 318 women with only one positive node: Loco-regional recurrence rate: 2.3% vs. 17.8%, 2-sided p<0.00001 At 9 yrs overall recurrence rate: 36.4% vs. 24.1%, RR 0.60 (95% CI, 0.39 to 0.92, 2-sided p=0.02

ALND = axillary lymph node dissection; ANI = axillary node irradiation; BC = breast cancer; BCS = breast-conserving surgery; cALND = completion ALND; CI = confidence interval; DFS = disease-free survival; ER = estrogen receptor; Gy = gray (unit); IPD = individual patient data; IQR = interquartile range; mos = months; NA = not applicable; NS = not significant; nr = not reported; OS = overall survival; pts = patients; PgR = progesterone receptor; RCT = randomized controlled trial; RT = radiotherapy; SLN = sentinel lymph node; SN = sentinel node; yrs = years

Table 3D. Question 3, patients with positive lymph nodes who did not receive NAC. Trials included for comparison D) Radiotherapy versus no treatment.

Characteristics	Killander, 2009 [41]	Killander, 2007 [40]
N	395, 367 fully evaluable	724, 668 fully evaluable
Study design	RCT phase 3	RCT phase 3
Follow-up (median)	24 yrs	23 yrs
Other treatment	Chemotherapy with cyclophosphamide (C)	Hormonal therapy with tamoxifen
Comparison	Pre-menopausal women: 1) (n=134) RT 2) (n=125) RT+ cyclophosphamide 3) (n=136) C alone RT = doses were 38 Gy to the chest wall, 48 Gy to the axilla and parasternal lymph nodes and 45 Gy to the supra and infraclavicular fossae. All fields were treated in 20 fractions. Chemotherapy: 12 courses of oral cyclophosphamide 130 mg/m^2 days 1–14 in 28 day cycles.	1) (n=221) RT 50 Gy/25 fractions to chest wall and regional lymph nodes 2) (n=214) RT + tam 30 mg/day for one yr 3) (n=233) tam alone Tam: given 10 mg tamoxifen orally three times daily for one year.
Outcomes	Time to recurrence, type of recurrence and OS, mortality. No distinction was made between primary and secondary outcome	Time to recurrence Type of recurrence OS, mortality
Included pts	Premenopausal women with stage II invasive mammary adenocarcinoma treated with modified radical mastectomy.	Postmenopausal women with stage II invasive mammary adenocarcinoma treated with modified radical mastectomy
Patients excluded	(1) Not radical surgery, (2) Other malignant disease other than squamous cell cancer of the skin or cervical cancer in situ (3) Bilateral breast cancer.	6% of all randomized patients were excluded because in one institution >80% of the charts were destroyed, except for the analysis of OS. Pts who violated the entry criteria
Age, median (range)	47 yrs	63 yrs
Stage	Stage II, mostly pN1	Stage II
Grade	*nr*	*nr*
Tumour size, median, range, cm	Median 25 mm (RT and RT+C arms) or 26 mm (C arm)	Median 25 mm
Tumour type	Invasive adenocarcinoma	Invasive adenocarcinoma
Receptor status	Hormone receptor status (number of patients with) RT(n=124) RT+C (n=118) C (n=125) ER+ and/or PgR+ 45 (36%) 41 (35%) 50 (40%) ER- and PgR- 28 (23%) 22 (19%) 33 (26%) Rec unknown 51 (41%) 55 (47%) 42 (34%)	Receptor positive: n=313 Recepor negative: n=131
Isolated tumour cells	*nr*	*nr*
Micrometastases	*nr*	*nr*
Macrometastases	*nr*	*nr*
Lymph node metastases	Number of positive nodes RT RT+C C pN0 41 (33%) 38 (43%) 43 (34%) pN1-3 57 (46%) 54 (46%) 50 (40%) p≥4 23 (19%) 24 (20%) 26 (21%)	Number of positive nodes: R T+Tamoxifen Tamoxfen pN0 90 (41%) 85 (40%) 96 (41%) pN1-3 91 (41%) 79 (37%) 94 (40%) pN≥4 36 (16%) 44 (21%) 40 (17%)
Surgeon experience	*nr*	*nr*
Method for SLNB	NA	NA

Characteristics	Killander, 2009 [41]	Killander, 2007 [40]
Study shortcomings	The RT interventions were done from 1978 to 1985 and may be different from nowadays techniques	The RT interventions were done from 1978 to 1985 and may be different from nowadays techniques
Summary results	Overall mortality at 20 yrs: NS **RT** **RT+C** **C** 44% 42% 44% Cumulative incidence of loco-regional recurrence: RT vs. C: 3.5% vs. 13.9%, p=0.0071	**Overall mortality** at 20 yrs: RT: 71% (95% CI 65% to 77%) RT + tam: 68% (95% CI 62% to 74%) Tam: 62% (95% CI 56% to 68%) RT + tam vs. tam p=NS **Subgroup**: Receptor + tam vs. tam: p=0.047 **Loco-regional recurrence reduction:** RT + tam vs. Tam: 5.3% vs. 18.5%, p<0.001 **Recurrence of systemic disease at 20 yrs**: RT+tam vs. tam: 40% vs. 50%, p=0.047

BC = breast cancer; C = cyclophosphamide; ER = estrogen receptor; Gy = gray (unit); NA= not applicable; *nr* = not reported; NS = not significant; OS = overall survival; pts = patients; PgR = progesterone receptor; pN0 = no regional lymph node metastasis; RCT = randomized controlled trial; RNI = regional nodal irradiation; RT = radiotherapy; Tam = tamoxifen; yrs = years

Table 4A. Question 4, patients with positive lymph nodes at diagnosis who received NAC. Trials included for comparison a) SLNB vs. ALND.

Characteristics	Kim, 2015 [44]
N	386
Study design	Retrospective multicentre
Follow-up (median)	19.5 mos (range, 2–65 mos)
Other treatment	*nr*
Comparison(s)	Group 1: yp SLNB- n= 31 (no ALND) Group 2: ypN- n=20 (ALND) Group 3: ypN+ n=69 (ALND) Group 4: ypN- n=79 (ALND) Group 5: ypN+ n=187 (ALND)
Outcomes	OS DFS Recurrence FNR IR
Included pts	Pts with a diagnosis of invasive BC and metastatic axillary nodes documented by US-guided FNA treated with NAC followed by surgery
Excluded pts	Pts with bilateral BC, previous ipsilateral axillary surgery, inflammatory breast cancer or distant metastasis
Age, mean (range)	45.6 ±9.3 yrs
Stage	Stage (Groups 1-4): ypT0-is 84 (42.2%) ypT1-2: 96 (48.2%) ypT3: 19 (9.5%)
Grade	I/II: 94 (47.2%) III: 36 (18.1%)
Tumour size, median, range, cm	*nr*
Tumour type	Ductal: 195 (98.0%); Lobular and others: 4 (2.0%)
Receptor status	Positive: 96 (48.2%); Negative: 103 (51.7%)
Method for SLNB	Both radiocolloid and blue dye
Study shortcomings	Retrospective, high risk of bias
Summary results	OS (Groups 1 vs. 2 vs.3 vs.4): NS DFS (Groups 1 vs. 2): p=NS DFS (Groups 1 vs. 4): 77.1% vs 85.4%, p=0.031 Axillary recurrence rate: (3.3%, 5.0%, and 1.3% for groups 1, 2, and 4, respectively, p>0.05). FNR was calculated for group 2: 2/20 (10%)

ALND = axillary lymph node dissection; BC = breast cancer; DFS = disease-free survival; FNA = fine needle aspiration; FNR = false negative rate; IR = identification rate; mos = months; *nr* = not reported; NAC = neoadjuvant chemotherapy; NS = not significant; OS = overall survival; pts = patients; US = ultrasound; ypN+ = patients with positive or undetected SLNs undergoing further ALND; ypN- = patients with negative SLN status undergoing further ALND

Table 4B. Question 4, patients with positive lymph nodes at diagnosis who received NAC. Trials included for comparison b) Radiotherapy and surgery vs. no treatment.

Characteristics	Kantor, 2017 [180]	Rusthoven, 2016 [45]	Liu, 2016 [181]	Krug, 2019 [43]	
N	8321	15315	1580 (1560 in final analysis) initially clinically node posistive and node negative after NAC (ypN0)	817	
Study design	Retrospective population study analysis of the 2013 NCDB	Retrospective population study analysis of the NCDB	Retrospective population study analysis of the NCDB	Pooled analysis of 3 RCTs testing different regimens of NAC	
Accrual period	2004-2008	2003-2011	1998-2009	2002-2010	
Comparison	PMRT vs. no PMRT	Mast group: PMRT vs. No PMRT BCS group: Bsreast and RNI vs. Breast irradiation only	PMRT vs. no PMRT	PMRT including chest wall irradiation with (76.7%) or without (98.7%) supraclavicular nodes vs. no PMRT	
Follow-up (median)	69 mo	median 39 mos (range 1–132 mos)	56 moss (range, 6.14-185.4 mos).	51.5 months	
Other treatment	Surgery: Mast (71.3%)	Surgery: Mast or BCS	Surgery: Mast	Surgery: Mast	
Included pts	Women with clinically node positive disease (cN1 and cN2) that underwent NAC followed by mastectomy	Pts with ypN+ or ngative ypN0	Women ≥18 yrs, clinically node-positive and stage II-III (AJCC) breast cancer, treated with NAC and mastectomy with pathologically confirmed complete nodal response (ypN0)	Pts with clinical tumour stage T1 to T4a-c BC who received mastectomy	
Pts excluded	Women with metastatic disease, history of cancer, no lymph nodes examined on pathology, no surgery recorded, missing treatment information, or those treated outside of the reporting facility were excluded	Pts treated without radiation, or treated with <15 fractions	Pts with positive or unknown surgical margin, pathological tumour size > 5 cm after NAC, distant metastatic disease, or prior malignancy were excluded. Unknown clinical or pathological tumour/node stage, preoperative or intraoperative radiotherapy, or radiotherapy not for chest wall and draining lymphatics	Pts with progression or death before surgery, with missing surgery data, without further randomization after two initial cycles of NAC (docetaxel, doxorubicin, and cyclophosphamide; pts with inflammatory BC, and those who did not receive RT.	
Age, median (range)	Median *nr* < 50 yrs: 46.1% 50-70 yrs: 46.6% ≥70 yrs: 7.3%	Median *nr* <50 yrs: 7670 (50.1%) >50 yrs: 7645 (49.9%)	Median (range): No PMRT: 50 yrs (20-86 yrs) PMRT: 50 (22-88) ≤40 yrs: 346 (22.2%) 41-60:931 (59.7%) >60: 283 (18.1%)	49 yrs (21-78yrs)	
Stage	cT1: 7% cT2: 27.9% cT3: 29.4% cT4: 33.2% Pathological stage after NAC: ypT0:8.4% ypT+:91.6% ypN+: 76.6%	cT1: 2169 (14.2%) cT2: 8056 (52.6%) cT3: 5090 (33.2%)	cT1: 134 (8.6%) cT2: 530 (34.0%) cT3: 449 (28.8%) cT4: 447 (28.7%) Pathologic T stage (after NAC) T0/Tis: 676 (43.3%) T1: 536 (34.4%) T2: 348 (22.3%)	Clinical tumour stage: cT1 4.7% cT2 49.3% cT3 31.0% cT4a-c 14.6%	Pathological tumour stage after NAC: ypT0 9.5% ypT1 25.3% ypT2 21.2% ypT3 14.1% ypT4a-c 3.1% ypT4d 0.6%

Characteristics	Kantor, 2017 [180]	Rusthoven, 2016 [45]	Liu, 2016 [181]	Krug, 2019 [43]	
				missing 0.5% Clinical nodal stage: cN0 37.8% cN+ 61.3% missing 0.9%	ypTis 4.5% Missing 0.6% Pathological nodal stage: ypN0 41.0% ypN+ 56.8% Missing 2.2%
Grade	Grade I: 3.9% Grade II: 30% Grade III:56%	Grade I: 826 (5.4%) Grade II: 5091 (33.2%) Grade III:8378 (54.7)	*nr*	G1 3.8% G2 59.1% G3 33.2% Missing 3.9%	
Tumour type	Ductal: 78.3% Lobular:7% Mixed:6.9% Inflammatory: 7.8%	*nr*	No PMRT vs. PMRT Ductal: 82.2% vs. 79.6% Lobular:7.6% vs. 6.7% Other: 10.2% vs. 13.7%	Ductal 76.3% Lobular 17.7% Other 6.0%	
Receptor status	ER/PR+: 56.4% ER/PR-:39.1%	**Mast-ypN0 (No PMRT vs. PMRT)** ER+/HT+: 35% vs. 43% ER+/HT-: 8% vs. 5% ER-: 52% vs. 48% p <0.001 **Mast ypN+(No PMRT vs. PMRT)** ER+/HT+: 47% vs. 65% ER+/HT-: 11% vs. 4% ER-: 34% vs. 25% p <0.001 **BCS-ypN0 (No PMRT vs. PMRT)** ER+/HT+: 38% vs. 39% ER+/HT-: 4% vs. 4% ER-: 51% vs. 53% p = 0.332 **BCS-ypN+ (No PMRT vs. PMRT)** ER+/HT+: 56% vs. 58% ER+/HT-: 5% vs. 4% ER-: 33% vs. 32% p = 0.279	No PMRT vs. PMRT ER-: 50.2% vs. 55.7% ER+: 31.7 vs. 36.7% PR-: 57.7% vs. 62.3% PR+: 24.2% vs. 29.9%	ER status: ER+ 68.1% ER- 31.6% Missing 0.4% PR status: PR+ 56.8% PR- 42.7% Missing 0.5% HER2 status: HER2+ 25.3% HER2- 69.0% Missing 5.6%	
Isolated tumour cells	*nr*	*nr*	*nr*	4.5%	
Study shortcomings	These three studies used the same data source with overlapping years, and possibly counting in the same patients			Risk of bias due to retrospective design; the population included mostly pts with high-risk features; the NAC treatments were heterogeneous, and the RT recommendations differed among the included trials. Irradiation of the intermal mammary nodes were infrequently used.	

Characteristics	Kantor, 2017 [180]	Rusthoven, 2016 [45]	Liu, 2016 [181]	Krug, 2019 [43]
Design and risk of bias	Retrospective moderate risk of bias	Retrospective moderate risk of bias	Retrospective moderate risk of bias	Retrospective design Operator experience is not reported
Summary results	Adjusted survival analysis: PMRT vs. no PMRT: 5 yr OS rate: Pts with cN1: 75.8% vs. 71.9%, p<0.01) Pts with cN2: 69.2% vs. 58.6%, p<0.01). Subgroups of pts that were ypN0 after NAC compared with those who were not ypN0, OS: p>0.11 except for pts with hormone-receptor negative tumours, who had improved OS with PMRT (HR 0.65, p<0.01).	OS On multivariate analysis: **Mast cohorts:** Mast-ypN0: HR 0.729 (95% CI, 0.566–0.939), p=0.015; Mast-ypN+: HR 0.772, (95% CI, 0.689–0.866), p<0.001. **BCS cohorts:** BCS-ypN0: HR 0.969 (95% CI, 0.699–1.344), p=0.851; BCS-ypN+: HR 1.037 (95% CI 0.862–1.248), p=0.700). *On propensity score-matched analysis:* **Mast cohorts:** Mast-ypN0: (n=1039 PMRT vs. n=1039 no-RT): HR 0.695 (95% CI, 0.518–0.929), p=0.014 Mast-ypN+: (1787 PMRT vs. 1787 no-RT: HR 0.845 (95% CI, 0.738–0.968), p=0.015 **BCS cohorts:** BCS-ypN0: (n=860 RNI vs. n=860 no-RNI): HR 1.028 (95% CI, 0.716–1.477), p=0.880 BCS-ypN+ (n=1244 RNI vs.n=1244 no-RN): HR 0.962 (95% CI, 0.785–1.175), p=0.704 *Subgroups* Mast pts who received PMRT and RNI, vs. PMRT p=NS All cohorts: No significant interactions between the survival impact of PMRT or RNI based on age, axillary surgery, ypN stage, or in-breast pathologic response. Mast/ypN+: PMRT vs. no RT cT1-2: 559 vs. 238 events, p=0.03 (multivariate analysis) cT3: 545 vs. 202 events, p<0.001	OS: no between-groups statistical difference by univariate and multivariate analyses (p=0.120; HR 1.571, [95% CI 0.839-2.943]). Subgroup analyses, PMRT significantly improved OS in pts with clinical stage IIIB/IIIC disease, T3/T4 tumour, or residual invasive breast cancer after NAC (p<0.05). This improvement in OS remained significant after sensitivity analyses for the propensity score-matched pts.	In multivariate analysis: **LRR** PMRT vs. no PMRT = p=0.23 ER-: HR 4.5 (95% CI, 2.42-8.37), p<0.01 PR-: HR 0.52 (95% CI, 0.29-0.96), p=0.04 cT2: HR 1.59 (95% CI, 0.39-6.57), p=0.52 cN+: HR 2.14 (95% CI, 1.19–3.87, p=0.01) cN0: NS ypN0: HR 0.2 (95% CI, 0.06–0.62), p=0.01 **DFS** PMRT vs. no PMRT: HR 1.14 (95% CI, 0.75–1.73), p=0.55 ER-: HR 1.93 (95% CI, 1.33-2.80), p<0.01 PR-: HR 1.45 (95% CI, 1.01-2.08), p=0.05 cT2: HR 3.07 (95% CI, 0.96-9.84), p=0.06 cN0: HR 3.4 (95% CI 1.46–7.91), p=0.01 (worse for PMRT than no RT).

AJCC = American Joint Committee on Cancer; BC = breast cancer; BCS = breast-conserving surgery; DFS = disease-free survival; ER = estrogen receptor; HT = hormone therapy; LRR = loco-regional recurrence; mast = mastectomy; mos = months; N = number; NAC = neoadjuvant chemotherapy; NCDB = National Cancer Database; *nr* = not reported; NS = not significant; OS = overall survival; PMRT = postmastectomy radiotherapy; PR = progesterone receptor; pts= patients; RT = radiotherapy; ypN0 = post-treatment negative axillary nodes; ypN+ = post NAC lymph node stage positive; ypN- = patients with negative RNI = regional nodal irradiation; SLN status undergoing further ALND; ypN0 = post NAC lymph node stage negative; yrs = years

Table 4-C Studies of Timing of SLNB – Studies of direct patient outcomes

Characteristics	Fernandez-Gonzalez, 2018 [168]	Hunt, 2009 [53]	Papa, 2008 [173]
N	172	3746 clinically negative pts	117 clinically node negative pts treated with NAC
Study design	Retrospective cohort study of prospectively collected data at one institution (historical control)	Retrospective cohort study	Prospective cohort study
Accrual period	Pre-NAC: Dec 2006 to Apr 2014 Post-NAC: May 2014 to Jul 2016	Mar 1994 to 2007	Jan 2002 to Mar 2005
Comparison	SLNB pre-NAC vs. SLNB post-NAC	SLNB after NAC **n**=575 (15.3%) vs. SLNB before NAC **n**=3171 (84.7%)	Group 1: NAC followed by SLNB +ALND+ lumpectomy/mastectomy n= 31 vs. Group 2: SLNB followed by NAC then surgery and ALND n=58 vs. Group 3: SLNB followed by NAC then surgery and, only for pts with positive SLN, ALND n=28 (21 ALND, and 7 only surgery)
Follow-up (median)	Pre-NAC group: 5.2 yrs, (0.75-10.1 yrs) Post-NAC: 1.3 yrs, (0.42-4.75 yrs)	SLNB after NAC: 47 mos (range 0-169 mos)	*nr*
Other treatment	NAC = Endocrine NAC: letrozole (2.5 mg/d for 6 to 12 mos), or Chemotherapy NAC: a regimen that included anthracyclines + taxanes for 6 mos; trastuzumab in HER2-positive Surgery: conservative or radical depended on response to NAC. Pts with negative SLNs or micrometastases did not undergo further axillary treatment	*nr*	NAC was an anthracycline based chemotherapy
Included pts	T1c to T3 and N0 (clinically and according to ultrasound) candidates for NAT	*nr*	Pts with locally advanced cancer with clinically negative nodes clinical stage IIAT2NOMO and IIB T3NOMO treated with primary chemotherapy
Pts excluded	Axillary LN +ve pts, identified using fine needle aspiration if suspected on pre-NAC US; pts >80 yrs old; pts with tumours <10 mm; stage T4 tumours; a personal history of ipsilateral BC; and thos who refused to participate	*nr*	*nr*
Age, median (range)	Age (mean±SD): Pre-NAC: 52.1±13.4 yrs Post-NAC: 54.9±14.1 yrs	SLNB before NAC: 57 yrs (range: 22-92) SLNB after NAC: 51 yrs (range: 25-84),	45.4 yrs
Stage	Stage / Pre-NAC / Post-NAC cT1c / 1.6% / 6% cT2 / 84.4% / 84% cT3 / 13.9% / 10%	SLNB before NAC: T1: 81.2% T2: 17.7% T3: 1.1% SLNB after NAC: T1: 12.7% T2: 75% T3: 12.3%	IIA T2N0M0 and IIB T3N0M0
Grade	GRADE / Pre-NAC / Post-NAC	*nr*	*nr*

	1 | 5.7% | 6% 2 | 38.5% | 40% 3 | 55.7% | 54%		
Tumour size, median, range, cm	*nr*	*nr*	mean±SD: 3.97±1.17 cm; range: 2.3-8 cm
Tumour type	See Table 1 in [168]	*nr*	*nr*
Receptor status	*nr*	*nr*	*nr*
Isolated tumour cells	*nr*	*nr*	*nr*
Micrometastases Macrometastases	| Pre-NAC | Post-NAC Micrometastases | 34% | 16.7% Macrometastases | 66% | 83.3%	*nr*	*nr*
Lymph node metastases	*nr*	*nr*	*nr*
Surgeon experience	*nr*	*nr*	*nr*
Method for SLNB	radiocolloid	Single dye: 33% Dual dye: 67%	Pts underwent prior lymphatic mapping with radiocolloid in the nuclear medicine suite. Subsequently, in the operating room, they underwent periareolar injection of blue dye. The axilla was then approached using a small incision, and an intraoperative gamma probe was used, in conjunction with blue dye identification to identify the sentinel node.
Study shortcomings	The information used to define intervention groups may have been recorded after the start of interventions as this is a retrospective trial.	Single institution trial	The authors did not measure and control for tumour stage (only size), and patient characteristics other than age
Design and risk of bias	This study was affected by time varying bias because the follow-up time in intervention and control groups were very different, with the intervention group having a much shorter follow-up. This would impact the detection of patient-relevant outcomes such as recurrence and progression-free survival in favour of the intervention (i.e., SLNB after NAC), but not so much ALND rate.	Time varying confounding: intervention and control groups have different length of follow-up	Outcome measures could have been influenced by knowledge of the intervention received; outcome assessors were not blinded to assignment of interventions
Summary results	Pre-NAC vs. post-NAC: ALND rate: 28.3% vs. 8%, OR 3.48 (95% CI, 1.3 to 9.3), p=0.004. Recurrence rate: 11.5% vs. 0 at 16 mos follow-up, p=0.85 Probability of PFS at 60 mos: Pre-NAC vs. Post NAC: 8.4% vs. 1% p=0.85 IR >98% in both groups, p=0.118	*Overall technical success (ability to map) rate: 98.5% Mapping success: With 1 agent: 1209 of 1240 pts: 97.5% vs. Combination of two agents: 2481 of 2506 pts: 99%, p<0.0001 In multivariate analysis: False negative rate: SLNB before NAC group: 4.1% (22 events over 542), SLNB after NAC group: 5.9% (5 events over 84 pts), p=0.39	Response rate: Group 1: 12.9% Group 2: 13.8% Group 3: 14% p=NS

		False negative rate by mapping techniques: Mapping with blue dye vs. mapping with blue dye plus radiocolloid: OR 2.61 (95% CI, 0.78 to 8.76), p<0.0001 Number of ALND performed: p=NS Recurrence at 47 months follow-up SLNB before NAC group vs. SLNB after NAC group: Local recurrence rate: 1.2% vs. 2.1% Regional recurrence rate: 0.9% vs.1.2% Distant recurrence rate: 2.7% vs. 7.5% After adjusting for clinical stage p=NS	

ALND = axillary lymph node dissection; CI = confidence interval; HER2 = human epidermal growth factor receptor 2; NAC = neodadjuvant chemotherapy; nr = not reported; NS = not significant; OR = odds ratio; PFS = progression-free survival; pts = patients; SLN = sentinal lymph node; SLNB = sentinal lymph node biopsy

Table. 4-D Question 4, studies of diagnostic outcomes

Study / Design	Intervention/methods	Comparison	Clinically node positive at diagnosis	Clinically node negative at diagnosis	Pathologically positive	Pathologically negative	Population and tumour characteristics	Summary results
Zetterlund, 2017 [170] Prospective cohort	SLNB before NAC Methods of SLNB: Blue dye, radiocolloid, or both	ALND (reference standard) after NAC	No	Yes (N=224)	No	*nr*	Age (median): 47 yrs (range 22-78 yrs) Stage: T1 8% T2 66.5% T3 25.4%	IR rate = 100% FN rate after NAC =7.4% (95% CI, 4 to 13.5)
Zetterlund, 2017 [171] Prospective cohort	SLNB after NAC Methods of SLNB: Blue dye (3.6%), radiocolloid (5.2%) or both (87.5%) or magnetic tracer alone or incombination with blue dye (3.6%)	ALND (reference standard) after NAC	Yes	No	Yes (n=195)	No	Age (median) 50 yrs, range 27–84 Stage at presentation: T1:12.8% T2:48.2% T3:31.3%	IR All mapping methods IR=77.9% (152 or 195 pts) Dual mapping: IR=80.7% FNR Overall: 14.1% (13 over 92 pts)
van der Heiden-van der Loo et al. [172] Retrospective cohort	SLNB after NAC Methods of SLNB: *nr*	SLNB before NAC	No	Yes (n=1183)	No	No	**Age (median, range)** 49 yrs, 23 to 77 yrs **Stage: SLNB before vs. after NAC**: cT1-(≤20mm) 11% vs. 17% cT2 (21-50mm) 70% vs. 51% cT3 (>50mm) 17% vs 22%	SLNB before vs. SLNB after NAC: IR: 98% vs. 95%, p=0.032

Study / Design	Intervention/methods	Comparison	Clinically node positive at diagnosis	Clinically node negative at diagnosis	Pathologically positive	Pathologically negative	Population and tumour characteristics	Summary results
Kuehn, 2013 [46] SENTinel NeoAdjuvant (SENTINA) trial Prospective cohort - multicentre	**Arm A:** cN0 who had SLNB before NAC and received no further axillary surgery if they were pN0sn.	ALND (reference standard)	No	Yes (N=662)	No	Yes	**Age: median (range) yrs** **Arm A:** 48 (20–75) **Arm B:** 48 (26–78) **Arm C:** 49 (22–98) **Arm D:** 50 (29–87) **Stage**: cN0, cN1, and cN2 Tumour size >20mm to ≤50mm: **Arm A:** 75% **Arm B:** 71% **Arm C:** 80% **Arm D**: 76%	*Results for question 4: nr*
	Arm B: cN0 pts with a pathologically positive SN ($pN1_{sn}$) before NAC who received SLNB before and a second SLNB after NAC followed by ALND	ALND (reference standard)	No	Yes (N=360)	Yes (n=64)	No		**FNR Arms B and C:** B: 51.6% [33 of 64 pts]; (95% CI 38.7 to 64.2) C: 14·2% [32 of 226]; (95% CI, 9.9 to 19.4)
	Arm C: Initially cN1 or cN2 pts who had NAC and then had SLNB and ALND if they converted to a clinically negative axillary status (ycN0).	ALND (reference standard)	Yes (N=592) converted to cN0 after NAC	No	Yes (n=226)	Yes		
	Arm D: Pts with suspicious nodes before and after NAC (ycN1) and who received ALND Methods of SLNB: radiocolloid alone: **A&B before NAC:** 57% **B, after NAC:** 66% **C, after NAC:** 66% blue dye alone: **A&B before NAC:** 1% **B, after NAC:** 1% **C, after NAC:** 1% Combined: **A&B before NAC:** 39% **B, after NAC:** 29% **C, after NAC:** 28%	(N=N=123) No comparison, only received ALND	NA	NA	NA	NA		*Results for question 4: nr*
Tausch et al. [48] Prospective (subprotocol of a drug RCT)	SLNB Methods of SLNB: Only blue dye was used in 28 (25%) cases, radionuclide was used as a single method in 13 (12%), and the	ALND	No (N=111)	No	Yes (N=47)	No	**Age (mean):** 48.4 yrs (range 28 to 79) **Stage**: All M0 tumour sizes and stages, except for T4d (inflammatory BC)	IR: 90% (≥1 LN removed in 100 pts) FNR: 12.8% (6 of 47)

Study / Design	Intervention/methods	Comparison	Clinically node positive at diagnosis	Clinically node negative at diagnosis	Pathologically positive	Pathologically negative	Population and tumour characteristics	Summary results
	combination of both methods was applied in 70 (63%) cases Injection site and methods were at the discretion of the surgeon							
Papa, 2008 [173] Prospective cohort	**Group 1:** NAC followed by SLNB +ALND+ lumpectomy/mastectomy **n**= 31 Methods of SLNB: Pts underwent prior lymphatic mapping with radiocolloid in the nuclear medicine suite. Subsequently, in the operating room, they underwent periareolar injection of blue dye. The axilla was then approached using a small incision, and an intraoperative gamma probe was used, in conjunction with blue dye identification to identify the sentinel node.	**Group 2:** SLNB followed by NAC then surgery and ALND **n**=58 vs. **Group 3:** SLNB followed by NAC then surgery and, only for pts with positive SNL, ALND **n**=28 (21 ALND, and 7 only surgery)	No	Yes (N=117)	No	No	**Age (mean):** 45.4 **Stage**: IIA T2N0M0 and IIB T3N0M0	IR: group 1 (SLNB after NAC): 87% group 2 (SLNB before NAC): 97%% and group 3: 100%, Group 1 vs groups 2 &3, p<0.05 FNR: group 1: 15.8% (3 of 19) group: 2: 0% Group 1 vs. group 2 p=0.04, group 3 NA because pts did not receive the reference standard
Gimbergues, 2008 [54] Prospective cohort	SLNB Methods of SLNB: radioisotope	ALND (reference standard)	*nr*	*nr*	Yes (N=129)	No	**Age (median range):** 53 yrs, 25 to 84 yrs **Stage**: T1: 1.6% T2: 71.3% T3: 27.1%	IR: 93.8% FNR: 14.3% (all pts)

ALND = axillary lymph node dissection; BC = breast cancer; CI = confidence interval; FN = false negative; FNR = false negative rate; IR = identification rate; NA = not applicable; NAC = neoadjuvant chemotherapy; nr = not reported; pts = patients; RCT = randomized controlled trial; SLN = sentinel lymph node; yrs = years

Table 5A. Question 5, patients treated with NAC. Trials of direct patient outcomes included for comparison a) single vs. dual dye.

Characteristics	Hunt, 2009 [53]
N	3746
Study design	Retrospective observational
Follow-up (median)	47 mos
Other treatment	*nr*
Comparison(s)	One agent vs. combination of two agents
Outcomes	Mapping success
Included pts	Pts with initially clnically negative axilla with T1-T3 BC, and had surgery from March 1994 to 2007 A clinically node-negative axilla was defined as the absence of palpable disease in the nodal basin and the absence of suspicious or abnormal appearing lymph nodes based on imaging studies (ultrasound and computed tomography scanning) when performed
Excluded pts	*nr*
Age, mean (range)	SLNB before NAC: 57.4 yrs SLNB after NAC: 51.7 yrs, p<0.0001
Stage	SLNB before NAC: T1: 81.2% ;T2: 17.7%; T3: 1.1% SLNB after NAC: T1: 12.7%; T2: 75%; T3: 12.3%
Grade	*nr*
Tumour size, median, range, cm	T1 (≤2.0): 70.69% T2 (2.1–5.0): 26.48% T3 (>5.0): 2.82%
Tumour type	IDC: 81.12% ILC: 7.58%
Method for SLNB	SLN surgery was performed using 1% isosulfan blue dye (Lymphazurin, US Surgical Corporation, Norwalk, CT), 99mTc-labeled sulfur colloid, or a combination of the 2 agents. Mapping agents were injected in the subdermal plexus, the subareolar region or in the peritumoural location at the discretion of the operating surgeon.
Study shortcomings	This was mainly designed as a study of diagnostic outcomes
Summary results	With 1 agent: 1209 of 1240 pts: 97.5% vs. Combination of two agents: 2481 of 2506 pts: 99%, p<0.0001

BC = breast cancer; IDC = invasive ductal carcinoma; Mos = months; NAC = neoadjuvant chemotherapy; pts = patients; SLNB = sentinel lymph node biopsy; yrs = years

Table 5B. Question 5B. Trials of direct patient outcomes included for comparison b) US-guided vs. traditional SLNB.

Characteristics	Verheuvel, 2017 [55]
N	11820
Study design	Retrospective population study (data prospectively collected from the Netherlands Cancer Registry)
Follow-up (median)	5 yrs
Other treatment	*nr*
Comparison(s)	US-guided biopsy vs. SLNB
Outcomes	OS
Included pts	Pts with T1 or T2 node-positive invasive BC between 2008 and 2014 in the Netherlands; pts without clinically palpable lymphadenopathy (cN0) who had node-positive disease after an ALND were included
Excluded pts	Pts with stage IV BC, with clinical stage T3-T4 breast tumour, those receiving neoadjuvant systemic treatment, those with palpable axillary nodes (cN C 1), and those who did not undergo an ALND
Age, mean (range)	59 yrs (range 21 to 97 yrs) US-guided: 63 yrs (range 23to 97 yrs) SLNB: 58 yrs (range 21 to 95 yrs)
Stage	Stage (pathological): US-G SLNB pT1a 1.9% 1.0% pT1b 9.2% 8.8% pT1c 40.5% 46.1% pT2 48.3% 44.1%
Grade	US-G SLNB Grade 1 18.6% 21.3% Grade 2 46.2% 48.2% Grade 3 31.4% 27.5% Unknown 3.78% 2.94%
Tumour size, median, range, cm	*nr*
Tumour type	US-G SLNB Ductal 73.8% 77.8% Lobular 13.1% 12.0%
Receptor status	US-G SLNB ER- 11.3% 6.3% ER+ 84.4% 88.3% Unknown 4.3% 5.35% PR- 21.6% 14.5% PR+ 68.3% 71.8% Unknown 29.46% 13.67%
Study shortcomings	See quality assessment
Summary results	OS rate at 5 yrs: 81.6% vs. 89.6%, p<0.001 In multivariate analysis, adjusting for age at diagnosis, year of diagnosis, type of surgery, hormone receptor status, tumour morphology, tumour size, tumour grade, multifocality, number of positive LN, radiation therapy, and adjuvant systemic therapy, US-guided SLNB had a worse OS than traditional SLNB: HR=1.38; (95% CI, 1.23 to 1.56), p<0.001 Sensitivity analysis:When excluding pts >70 yrs of age, in multivariate analysis, the method of staging was no longer significant: HR=1.13, (95% CI, 0.94 to 1.35), p=NS

ALND = axillary lymph node dissection; BC = breast cancer; CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; LN = lymph node(s); *nr* = not reported; NS = not significant; OS = overall survival; PR = progesterone receptor; pts = patients; SLNB = sentinel lymph node biopsy; US = ultrasound; US-G = ultrasound-guided; yrs = years

Table 5C. Question 5. Trials that reported on diagnostsic outcomes

Study / Design	Intervention /methods	Comparison	Clinically node positive at diagnosis	Clinically node negative at diagnosis	Pathologically positive	Pathologically negative	Population and tumour characteristics	Summary results
A) Single vs. dual dye								
Pts treated with NAC								
Boileau, 2015 [52] SN FNAC trial Prospective multicentre cohort	SLNB **Method of SLNB:** At surgeon's discretion, isotope only (n=35, 28%) or dual tracer (n=92, 72%). All pts received ALND.	SLNB vs. ALND **Reference standard**; central review of pathology after ALND	*nr*	*nr*	Yes T0-3, N1-2	No	Pts with stage II to IIIa biopsy-proven node positive BC treated with NAC; **Age (median):** 50 yrs (range 26 to 75) **Stage**: T-stage T0: 4%; T1: 6%; T2: 50%; T3: 39%; N0: 11%; N1: 83%; N2: 5%; Size: >5 cm: 40% Receptor status: Triple negative: 15% HER2-+: 28% **Excluded pts:** clinical T4 or N3 BC, prior axillary surgery (including SLNB before NAC), and neoadjuvant radiotherapy to the breast or axilla	FNR with dual tracer: 5.2% (3 of 58 pts) FNR with isotope only: 16.0% (4 of 25 pts), p=0.190
Tausch, 2011 [48] ABCSG-Trial 14 Prospective cohort – subprotocol of an RCT	SLNB **Method of SLNB:** Only BD was used in 28 (25%) cases, radionuclide was used as a single method in 13 (12%), and the combination of both methods was applied in 70 (63%) cases. Injection site and methods were at the discretion of the surgeon.	SLNB vs. ALND **Reference standard:** ALND	no	yes	yes	no	Age (mean): 48.4 yrs (range 28 to 70 yrs) Stage: All M0 tumour sizes and stages, except for T4d (inflammatory BC)	BD alone: 82% (23 of 28) Radiosisotope alone: 85% (11 of 13) Radioisotope + BD combined: 94% (66 of 70), p=nr

Study / Design	Intervention /methods	Comparison	Clinically node positive at diagnosis	Clinically node negative at diagnosis	Pathologically positive	Pathologically negative	Population and tumour characteristics	Summary results
Kuehn, 2013 [46] SENTINA trial Four arm prospective multicentre cohort	SLNB Method of SLNB: radiocolloid alone: **A&B before NAC:** 57% **B, after NAC:** 66% **C, after NAC:** 66% blue dye alone: **A&B before NAC:** 1% **B, after NAC:** 1% **C, after NAC:** 1% Combined: **A&B before NAC:** 39% **B, after NAC:** 29% **C, after NAC:** 28%	SLNB before vs. after NAC; Reference standard ALND	Did not receive SLNB before NAC: Arm C: converted to node negative after NAC Arm D: Remained node positive after NAC	Underwent SLNB before NAC: Arm A: Arm B:	Arm B: Received a second SLNB and ALND after NAC	Arm A: did not receive ALND or SLNB after NAC	**Age: median (range)** Arm A: 48 (20–75) Arm B: 48 (26–78) Arm C: 49 (22–98) Arm D: 50 (29–87) **Stage:** cN0, cN1, and cN2 Tumour size >20mm to ≤50mm: Arm A: 75% Arm B: 71% Arm C: 80% Arm D: 76%	**Detection rate between radiocolloid and BD combined vs. radiocolloid alone:** **Arms A&B, SLNB before NAC:** 99.5% (399 of 401 pts; [95% CI, 98.2–99.9]), p=NS **Arm B:** 76.2% (80 of 105 pts vs. 52.9% (126 of 238 pts) **Arm C:** 87.8% (144 of 164 pts) vs. 77.4% (301 of 389 pts) **Arm C**: In multivariate regression analysis: Factors having an impact on detection rate: BD and radiocolloid combination: OR 2.13 (95% CI, 1.01 to 4.46), p=0.046 Factors having an impact on FNR: FNR was consistently <10% for pts who had ≥3 SLN removed Number of SLNs (per 1 SN): OR 0.487 (95% CI, 0.287 to 0.825), p=0.008 FNR for radiocolloid and BD vs. radiocolloid alone in Arm C: 8.6% (6 of 70 pts) vs. 16% (23 of 144 pts); in multivariate analysis: OR 0.353 (95% CI, 0.087 to 1.43), p=0.145 **FNR Arms B and C:** B: 51.6% [33 of 64 pts]; (95% CI, 38.7 to 64.2) C: 14·2% [32 of 226]; (95% CI, 9.9 to 19.4) FNR according to technique: Radiocolloid alone: Arm B: 46.2% (14 of 25 pts) vs. Arm C 16% (23 of 144 pts) Radiocolloid and BD: Arm B 60.9% (15 of 25 pts) vs. Arm C 8.6% (6 of 70 pts) p=NS

Study / Design	Intervention /methods	Comparison	Clinically node positive at diagnosis	Clinically node negative at diagnosis	Pathologically positive	Pathologically negative	Population and tumour characteristics	Summary results
								FNR according to number of SNs removed (arms B and C) 1 node removed: B: 66.7% (16 / 24), C: 24.3% (17 / 70) 2 nodes removed: B: 53.8% (7 / 13), C: 18.5% (10 / 54) 3 nodes removed: B: 50% (5 / 10), C: 7.3% (3 / 41) 4 nodes removed: B: 50% (3 / 6), C 0% (0 / 28) 5 nodes removed: B:18.2% (2 / 11), C: 6.1% (2 / 33)
Boughey, 2013 [51] ACOSOG Z1071 Prospective multicentre cohort	SLNB Method of SLNB: BD only (4.1%); radiocolloid only (16.8%); BD + radiocolloid (79.1%); ≥2 SLN resected	SLNB vs. ALND or histopathology Reference standard: ALND or histopathology	Yes	Yes	yes	yes	Adult women with cN1, cN2 biopsy proven node-positive BC who had been treated with NAC and were T0-T4, N1-N2, M0 Pts excluded: Inflammatory BC, cN3 disease, No evidence of axillary lymph node biopsy before chemotherapy, neoadjuvant treatment other than chemotherapy, only isolated tumour cells in lymph nodes before chemotherapy, stage IV disease, registered after surgery was completed	**IR:** ≥1 SLN detected in 639 of 689 pts: 92.7% (95% CI, 90.5% to 94.6%) **Subgroups:** cN1: 605 of 663 pts: 92.9% (95% CI, 90.7% to 94.8%) cN2: 34 of 38 pts: 89.5% (95% CI, 75.2% to 97.1%) **FNR:** **Pts with ≥2 SLNs and cN1**: **FNR:** cN1 pts: 7.1% cN2 pts: 12.6% (90% Bayesian credible interval 9.85%-16.05%) On multivariable analysis: FNR: BD 10.8%, and single tracer: 20.3%, p=0.05 By examination of number of SLN detected: ≥3 vs. 2: FNR, 9.1% for ≥3 SLNs vs. 21.1% for 2, p=0.007; no other factors made a significant contribution in explaining the variability in likelihood of a false-negative SLN finding.

Study / Design	Intervention /methods	Comparison	Clinically node positive at diagnosis	Clinically node negative at diagnosis	Pathologically positive	Pathologically negative	Population and tumour characteristics	Summary results
								Pts with ≥2 SLNs and cN2 (26 SLNB + ALND): 12 pts no residual nodal disease **pCR:** 46.1% (95% CI, 26.6% to 66.6%) Residual disease detected by SLNB only 6 pts Residual disease detected by both ALND and SLNB: 8 pts **FNR:** 0% (95% CI, 0% to 23.2%)
Hunt, 2009 [53] Retrospecti ve single institution cohort	SLNB Methods of SLNB: Blue dye with or without radiocolloid	SLNB after vs. before NAC Reference standard ALND	No	Yes	*nr*	*nr*	**Age (median):** SLNB before NAC: 57.4 yrs SLNB after NAC: 51.7 yrs, p<0.0001 **Stage**: SLNB before NAC: T1: 81.2% T2: 17.7% T3: 1.1% SLNB after NAC: T1: 12.7% T2: 75% T3: 12.3%	In multivariate analysis: **False negative rate by mapping techniques**: Mapping with blue dye vs. mapping with BD plus radiocolloid: OR 2.61 (95% CI, 0.78 to 8.76), p<0.0001 *A false-negative event was defined as a case where the SLN(s) was negative but an axillary (non-SLN) node was positive on pathologic examination.*
Gimbergue s, 2008 [54] Prospectiv e cohort	SLNB after NAC Methods of SLNB: radioisotope	SLNB vs. ALND Reference standard ALND	Yes	Yes	yes	no	**Age (median range):** 53 yrs, 25 to 84 yrs **Stage:** T1: 1.6% T2: 71.3% T3: 27.1% Pts excluded: inflammatory BC	IR: 93.8% Factors impacting IR: Age ≥60 yrs vs. aged <60 yrs: 82.1% vs. 97.9%, p=0.0063 FNR: 14.3% (all pts) Factors impacting FNR: Larger tumour size before NAC: 5.7% for T1-T2 vs. 28.5% for T3 cases, p=0.045 Positive clinical lymph node status before NAC: 0% for N0 vs. 29.6% for N1-N2 cases; p=0.003.
Patients who did not receive NAC								

Study / Design	Intervention /methods	Comparison	Clinically node positive at diagnosis	Clinically node negative at diagnosis	Pathologically positive	Pathologically negative	Population and tumour characteristics	Summary results
O'Reilly, 2015 [47] Single centre RCT	Dual tracer Methods of SLNB: Radioisotope injection was given on the day of surgery. Three hours after isotope injection surgery was performed. Pts randomized to the BD arm received an intradermal injection of isosulfan BD (1 mL) over the tumour after induction of anesthesia. All hot and blue nodes were removed during surgery.	Dual tracer vs. radiocolloid alone	no	Yes	No	yes	**Age**: Mean 48 yrs, (range 19 – 83 yrs) (48.3 vs. 47.7 yrs; p=0.47) **Stage:** Tumour size: mean 24.2 mm (24.3 mm vs. 24.1 mm; p=0.7). Histologically positive pts were excluded; as well as pts with >3 positive nodes	Dual tracer group vs. Radioisotope only: IR: 100% vs. 100%, p=0.86 Number of nodes retrieved (mean): 1.5 (range 1-9, median: 1) vs. 1.4 (range: 1-8, median: 1), p=0.86 IR: The addition of BD increased the IR by 1.5%. Identification of metastatic disease: p=0.64 AE with BD: Anaphylaxis rate: 0.3% Skin tattooing rate: 0.6%
Kang, 2010 [60] Retrospect ive cohort	Dual tracer Methods of SLNB: Lymphatic mapping was performed with technetium Tc99 m-labeled sulfur colloid, at dose of 2.5 mCi for pts scheduled for operation the following day and 0.5 mCi for pts having same-day surgery. Intraoperative lymphatic mapping was performed with radiocolloid, with or without 1% isosulfan blue dye at the	Dual tracer vs. radiocolloid	no	yes	No	no	Clinically node negative pts who underwent lymphatic mapping with radiocolloid Dual tracer vs. radiocolloid: **Age (median, range):** 56 (23–91) yrs vs. 54 (22–99) yrs **Stage**: **Tis:** 13.1% vs. 19.9% **T1:** 59.5% vs. 58.7% **T2:** 23.9% vs. 19.3% **T3:** 2.5% vs. 1.8% **T4:** 1% vs. 0.3%	Dual tracer vs. radiocolloid only: IR: 98% vs. 98%, p=0.8 Mean number of lymph nodes removed: 2.7 vs. 2.9, p=0.03

Study / Design	Intervention /methods	Comparison	Clinically node positive at diagnosis	Clinically node negative at diagnosis	Pathologically positive	Pathologically negative	Population and tumour characteristics	Summary results
	discretion of the operating surgeon.							
Nathanson, 2007 [50] Prospective cohort	High volume surgeons Methods of SLNB:	High volume vs. low volume surgeons	no	yes	*nr*	*nr*	Details of the population not reported	The odds of finding SLNs was 2.6 times greater among surgeon group 1 compared with surgeon group 2 (95% CI, 1.7 to 4.1; p<0.0001). IR (300 cases): 90% FNR: 2.6%
B) US guided vs. traditional SLNB								
Caudle, 2016 [61] Prospective registry study	Clipped node SLNB **Methods of SLNB:** An iodine-125 seed was placed in the clipped node under US guidance 1 to 5 ds before surgery. Mapping agents, including radiocolloid and/or BD, were injected before or at the time of surgery. During surgery, a gamma probe was used to identify SLNs. All nodes containing BD radioactivity, or which were palpable were removed and labeled as SLNs	Clipped node SLNB vs. ALND	*nr*	*nr*	yes	no	**Age (median):** 49 yrs, (range 23-84 yrs) **Stage:** T0: 0.5% T1: 9% T2: 65% T3: 23% T4: 2%	1) Clipped node to predict nodal status after NAC (191 pts who underwent ALND): FNR in the clipped nodes (in 5 of 120 pts pathologically + the clipped node did not show metastases): 4.2% (95% CI, 1.4 to 9.5) 2a) SLNB alone to predict nodal status: 7 false negative events in 118 pts: FNR for SLNB alone (dual tracer: 55%): 10.1% (95% CI, 4.2 to 19.8) 2b) SLNB + evaluation of the clipped node: FNR: 1.4% (95% CI, 0.03 to 7.3) Companing 2a) and 2b), p=0.03 3) TAD to predict nodal response after NAC (85 pts underwent both TAD and ALND): FNR for TAD (i.e., SLNB + clipped nodes removal) 2.0% (95% CI, 0.2 to 10.7) SLNB alone: FNR 10.6% (95% CI, 3.6 to 23.1), TAD vs. SLNB alone: p=0.13
Kramer, 2016 [56] Retrospective cohort	US-guided FNAC **Methods:** FNAC was performed on most suspicious nodes: when a lymph node with a minimum cortex thickness of 2.3 mm, focal cortical	Histological outcome of SLNB or ALND (reference standard)	Yes	Yes	*nr*	*nr*	**N**=2123 pts with invasive breast cancer not treated with NAC **Age:** Mean: 60 yrs (range 26 to 91 yrs) **Stage**:	FNR on 137 of 2130 pts: 6.4%

Study / Design	Intervention /methods	Comparison	Clinically node positive at diagnosis	Clinically node negative at diagnosis	Pathologically positive	Pathologically negative	Population and tumour characteristics	Summary results
	thickening or a replaced or anomalous hilum were found.						**T1**: 66.2% **T2**: 31.2% **T3**: 2.3%	
Kim, 2016 [57] Retrospective cohort	US followed by US-guided FNA **Methods:** Pts with axillary LN metastases confirmed by US-FNA proceeded directly to ALND. Other pts (e.g., pts with no suspicious LN at US or negative cytology at US-FNA) underwent SLNB. If metastasis was confirmed at SLNB, ALND was performed.	Surgery (reference standard)	Yes	Yes	No	No	N=142 pts: 7 clinically positive, and 135 clinically negative Age Mean ± SD: 50.7±8.9 yrs Stage (pathological): T1: 65.5% T2: 32.4% T3: 2.1% N0: 69.0% N1: 21.1% N2: 6.3% N3: 3.5%	FNR: on 8 of 23 pts 34.8%
Cools-Lartigue, 2013 [58] Retrospective cohort	aUS followed by FNAB **Methods:** aUS was performed by a dedicated axillarysonographer. LNs were identified as abnormal according to sonographic criteria including absence of a fatty nodal hilum, eccentric cortical thickening, and a round hypoechoic node. Axillae with multiple enlarged (>1 cm) nodes were also considered abnormal. US-guided FNAB was performed on pts at the discretion of the ultrasonographer: while the pt was under	Histopathology after SLNB or ALND (reference standard)	No	Yes	Yes	Yes	**Age (mean ± SD, range):** 57.8±13.1 yrs, 22-97 yrs **Stage:** T1: 51.1% T2: 48.9%	FNR for all US: 17.4% (41/235) FNR with FNAB: 40.8% (20/49)

Study / Design	Intervention /methods	Comparison	Clinically node positive at diagnosis	Clinically node negative at diagnosis	Pathologically positive	Pathologically negative	Population and tumour characteristics	Summary results
	local anesthesia, a 22-gauge needle attached to a 10-mL syringe was used to obtain specimens for cytologic examination. Two samples were routinely obtained from the selected LN hypoechoic node.							
C) US vs. SND								
Stachs, 2013 [59] Retrospective cohort	US confirmed by FNB vs. SLNB **Methods:** LNs were identified as abnormal according to sonographic criteria including absence of a fatty nodal hilum or a round hypoechoic node. Pts with sonographically negative nodes were subjected to SLNB. Pts with sonographically positive LNs or contraindications to SLNB underwent ALND. Secondary, completion ALND was carried out in pts with positive SLN.	histology after SLNB or ALND (reference standard)	Yes	Yes	Yes	Yes	**Age:** ≤50 yrs of age: 15.7% >50 yrs of age: 84.3% Mean age of pts who underwent SLNB (N=360): 63 yrs, (range 29-90 yrs) **Stage**: **pT1:** 59.1% **pT2:** 34.9% **pT3&T4:** 0.06%	FNR: 87 of 378 pts: 23% **NOTE**: in multivariate logistic regression analysis pathological size of nodal metastases was the only significant parameter associated with false negative US findings: size of nodal metastases ≤10 mm vs. >10 mm OR: 2.66 (95% CI, 1.81 to 3.91), p=0.001

ALND = axillary lymph node dissection; aUS = axillary ultrasound; BC = breast cancer; BD = blue dye; CI = confidence interval; FNAB = fine needle aspiration biopsy; FNAC = fine needle aspiration cytology; FNR = false negative rate; IR = identification rate; HER2 = human epidermal growth factor receptor 2; LN(s) = lymph nodes; NAC = neoadjuvant chemotherapy; *nr* = not reported; OR = odds ratio; Pts = patients; SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy; TAD = targeted axillary dissection; US = ultrasound; yr(s) = year(s)

Appendix 8: Ongoing trials

Table 1. May 2, 2019 clinicaltrials.gov search search term: "breast cancer AND axilla" in clinicaltrials.gov: studies that met our inclusion criteria out of 614 hits

Study number	Study design, target sample	Study title	Primary outcome	Start / Completion date	Intervention(s)/ comparison(s) or reference standard	Status	Location
QUESTION 1							
NCT02167490 IEO S637/311	RCT N=1560	A randomized trial comparing sentinel lymph node biopsy vs. no axillary surgical staging in patients with small breast cancer and a negative preoperative axillary assessment (IEO S637/311)	Distant-disease-free survival [Time Frame:6 months]	Jan 2012 / Dec 2017	SLNB vs. no axillary staging	Recruiting	Chile, Italy
NCT02271828 BOOG 2013-08	RCT N=1644	Clinically node negative breast cancer patients undergoing breast conserving therapy, sentinel lymph node procedure versus follow-up: a Dutch randomized controlled multicentre trial	Regional recurrence rate [Time Frame: Up to 10 years]	Apr 2015 / Apr 2027	SLNB vs. no staging	Recruiting	The Netherlands Principal investigators : Marjolein L Smidt, Hans JW de Wilt https://www.ncbi.nlm.nih.gov/pubmed/28668073?dopt=Abstract
QUESTION 2							
NCT01351974	Prospective observational N=3369	Cohort Study of Axillary Recurrences and Survival After Negative Sentinel Node Biopsy Without Completion Axillary Clearance	Axillary recurrence after negative sentinel node biopsy [Time Frame: 5 years]	Sept 2000 / Jan 2004	SLNB vs. ALND	Completed	Sweden
NCT02992574 PMRT-NNBC 1602 trial CTRI/2016/12/007532	RCT N=1022	Post-Mastectomy Radiation Therapy in High Risk, Node Negative Women With Early Breast Cancer (PMRT-NNBC)	Disease-free survival [Time Frame: 5 years]	Mar 2016 / Dec 2028	PMRT to the chest wall and ipsilateral supra-clavicular fossa to a dose of 40 Gy in 15 fractions over 3 weeks vs. No treatment	Recruiting	India Tabassum Wadasadawala

Study number	Study design, target sample	Study title	Primary outcome	Start / Completion date	Intervention(s)/ comparison(s) or reference standard	Status	Location
NCT02651142	RCT N=200	Sentinel lymph node biopsy with or without para-sentinel lymph node dissection in breast cancer	Disease-free survival [Time Frame: Up to 10 years]	Jan 2015 / Jan 2025	SLNB without para-SLN dissection vs. SLNB with para-SLN dissection	Recruiting	China
NCT03488693 TAILOR RT trial	RCT N=2140	TAILOR RT: A Randomized Trial of Regional Radiotherapy in Biomarker Low Risk Node Positive Breast Cancer	To compare the breast cancer recurrence-free interval (BCRFI) between patients that received regional RT or not [Time Frame: 9.5 years]	May 2018 / Dec 2027	Regional radiotherapy vs. No regional radiotherapy	Recruiting	US
QUESTION 3							
NCT03102307	Prospective cohort N=300	A Prospective, Multicenter, Registry Trial to Evaluate Utilization Frequency and Feasibility of Targeted Axillary Dissection (TAD) After Needle Biopsy and Clip Placement in Early Breast Cancer With Clinically Affected Lymph Nodes	Surgical detection rate of the clip labeled target lymph node [Time Frame: 6 month for patients undergoing NACT after initial needle biopsy/clip placement and subsequent surgical resection of the clipped node] Successful intraoperative detection and targeted resection of clip labeled target lymph node as confirmed by specimen radiography and/or surgeon	Mar 2017 /Feb 2019	Targeted Axillary dissection (TAD) vs. ALND	Recruiting	Germany
NCT02466737 INSEMA	RCT N=5505	Comparison of axillary sentinel lymph node biopsy versus no axillary surgery in patients with early-stage invasive breast cancer and breast-conserving surgery: a randomized prospective surgical trial. intergroup-sentinel-mamma (INSEMA)-Trial	Invasive disease-free survival (IDFS) after breast-conserving surgery [Time Frame: 5 years] non-inferiority question	Sept 2015 / Sept 2024	No axillary surgery vs. SLNB SLNB vs. completion ALND	Active, not recruiting	Germany

Study number	Study design, target sample	Study title	Primary outcome	Start / Completion date	Intervention(s)/ comparison(s) or reference standard	Status	Location
NCT01717131 SERC TRIAL has a prelim publication fist 1000 pts that will be caught by updated search https://www.ncbi.nlm.nih.gov/pubmed/30463611?dopt=Abstract	RCT non-inferiority N=3000	A Non Inferiority Randomized Multicenter Phase III Trial of Axillary Node Dissection Versus no Axillary Node Dissection in Case of Positive Sentinel Lymph Node in Invasive Breast Cancer	Disease Free survival [Time Frame: Time to relapse or progression up to 10 years]	Oct 2012 / Jul 2028	Surgery for standard ALND vs. No ALND	Recruiting	France
NCT02401685 POSNOC	RCT N=1900	POSNOC - POsitive Sentinel NOde: Adjuvant Therapy Alone Versus Adjuvant Therapy Plus Clearance or Axillary Radiotherapy. A Randomised Controlled Trial of Axillary Treatment in Women With Early-stage breast cancer Who Have Metastases in One or Two Sentinel Nodes	Axillary recurrence [Time Frame: 5 years] Axillary recurrence is defined as pathologically (cytology or biopsy) confirmed recurrence in lymph nodes draining the primary tumour site.	Jan 2014 / Mar 2023	Adjuvant chemotherapy vs. Axillary treatment	Recruiting	UK, Australia, New Zealand
NCT03669705	Observational N=1584	Prospective Cohort Study With no Axillary Surgery for Breast Cancer T</= 10 mm	Axillary recurrence [Time Frame: at 15 years]	Sept 1997 / Dec 2017	ALND vs no further surgery	Completed	Sweden
NCT02240472 SENOMAC Trial has a preliminary publication that will be caputred by the update search https://www.ncbi.nlm.nih.gov/pubmed/28549453?dopt=abstract	RCT N=3500	Survival and Axillary Recurrence Following Sentinel Node-positive Breast Cancer Without Completion Axillary Lymph Node Dissection - a Randomized Study of Patients With Macrometastases in the Sentinel Node	Breast cancer-specific survival [Time Frame: up to 15 years]	Sept 2014 / Dec 2022	Omission of axillary clearance vs. ALND	Recruiting	Sweden

Study number	Study design, target sample	Study title	Primary outcome	Start / Completion date	Intervention(s)/ comparison(s) or reference standard	Status	Location
NCT03083314	RCT N=158	Selective Axillary Lymph Node Dissection vs. Complete Axillary Dissection: A Randomised Clinical Trial to Assess the Prevention of Lymphedema in Breast Cancer Treatment	To compare the occurrence of breast-cancer-related lymphoedema (BCRL) after selective axillary dissection (SAD) and after axillary lymph node dissection (ALND) [Time Frame: 36 months]	Jun 2014 / Jun 2017	Selective axillary lymph node dissection (SAD) Procedure: complete axillary dissection (ALND)	Unknown	Italy
NCT01468883	RCT N=256	The Treatment of Stage I and II Carcinoma of the Breast With Mastectomy and Axillary Dissection vs. Excisional Biopsy, Axillary Dissection, and Definitive Irradiation	Results of excisional biopsy followed by radiation therapy versus modified radical mastectomy [Time Frame: survival rate completion of study]	Sept 1979 / Nov 2016	Total mastectomy and axillary dissection; vs. excisional biopsy, axillary dissection, and definitive irradiation.	Completed	US Author: Camphausen
NCT01279304 RAPCHEM Trial	Prospective Observational N=710	Radiotherapy After Primary CHEMotherapy for cT1-2cN1M0 Breast Cancer: a Multicentre Prospective Registration Study.	loco-regional recurrence rate [Time Frame: 5 Yr]	Jan 2011 / Dec 2017	ALND vs. WBI	Completed	Netherlands Investigators : L.J Boersma A Voogd R Houben Maastricht University Medical Centre
NCT02335957 OPTIMAL trial	RCT N=1422	OPTimizing Irradiation Through Molecular Assessment of Lymph Node (OPTIMAL)	Disease Free Survival up to 5 years	Apr 2015 / Dec 2021	WBI vs. RNI	Recruiting	US
NCT03127995 HypoG01 Trial	RCT N=1012	Multicenter Randomized Phase III Trial Comparing Hypofractionated Vs. Standard Radiotherapy in Breast Cancer With an Indication for Regional Lymph Node	Arm Lymphedema [Time Frame: Before treatment, week 3 or week 7 of treatment according the treatment arm and boost	Setpt 2016 / Oct 2029	Hypofractionated (40 Gy / 15 fractions, 2.67 Gy per fraction, 5 fractions per week) vs.	Recruiting	France Sofia RIVERA

Study number	Study design, target sample	Study title	Primary outcome	Start / Completion date	Intervention(s)/ comparison(s) or reference standard	Status	Location
		Irradiation in Terms of Lymphedema Occurrence	realization, 6 months after the last fraction received, every year during 5 years, 10 years]		Normofractionated (50 Gy / 25 fractions, 2.0 Gy per fraction, 5 fractions per week) radiotherapy to the breast and lymph nodes		
QUESTION 4							
NCT01872975 NSABP-B-51 trial	RCT N=1636	A randomized phase III clinical trial evaluating post-mastectomy chestwall and regional nodal xrt and post-lumpectomy regional nodal xrt in patients with positive axillary nodes before neoadjuvant chemotherapy who convert to pathologically negative axillary nodes after neoadjuvant chemotherapy	Invasive **breast cancer** recurrence free interval (IBC-RFI) [Time Frame: Time from randomization until invasive local, regional, or distant recurrence, or death from breast cancer, assessed up to 10 years]	Jun 2013 /Jul 2028	Regional nodal XRT vs. chestwall XRT vs. WBI	Recruiting	US
NCT03381092 BCP21	Prospective cohort N=348	Sentinel lymph node biopsy in clinically node-negative early breast cancer patients after neoadjuvant chemotherapy	Positive Rate of Axillary Sentinel Lymph Nodes. [Time Frame: Within 6 weeks after obtaining the post-surgery pathological results.]	Dec 2017 / Decc 2020	SLNB before vs. after NAC	Recruiting	China
NCT03719833 SLNB-ACP trial	Prospective Observational N=100	Sentinel lymph node biopsy after neoadjuvant oncological treatment in luminal B, HER-2 positive and triple negative breast cancer patients in stage T1-3 N0-2 m0 at the time of diagnose Population of node positive that turned negative	Impact of sentinel lymph node biopsy procedure on loco-regional recurrence for group 3 sentinel node negative patients [Time Frame: 5 postoperative years] Correlation of sentinel node negative patients from group 3 patients and overall survival [Time Frame: 5 postoperative years]	Sept 2018 / May 2027	SLNB in different combinations with surgery, clip placement	Enrolling by invitation	Croatia Ana Car Peterko

Study number	Study design, target sample	Study title	Primary outcome	Start / Completion date	Intervention(s)/ comparison(s) or reference standard	Status	Location
			Correlation of sentinel node negative patients from group 3 and disease progression free survival [Time Frame: 5 postoperative years]				
NCT02031042	Prospective observational N=224	Sentinel node biopsy before and/or after neoadjuvant chemotherapy in breast cancer	False negative rate [Time Frame: Up to two years]	Oct 2010 / Dec 2015	SLNB before or after NAC	Completed	Sweden
NCT01901094 MAC.19 trial	RCT N=2918	A randomized phase III trial comparing axillary lymph node dissection to axillary radiation in breast cancer patients (cT1-3 N1) who have positive sentinel lymph node disease after neoadjuvant chemotherapy	Invasive breast cancer recurrence-free interval (IBC-RFI) [Time Frame: Up to 5 years after completion of radiation therapy]	Feb 2014 / Feb 2024	ALND (surgery) and RT to the cancer area vs. RT to the axillary lymph nodes and the cancer area	Recruiting	Canada
QUESTION 5							
NCT03280134 CK19B	Prospective observational N=388	CK19 combined with contrast-enhanced ultrasound for predicting non-sentinel lymph node status in early breast cancer: a prospectively validation cohort study of the predictive model	disease-free survival (DFS) [Time Frame: 3-year(mid-term) 5-year]	Sept 2017 / Dec 2018	ALND SLNB	Not yet recruiting	China
NCT03791840	Prospective observational N=135	The accuracy of high-resolution ultrasound in the detection of lymph node metastasis from breast cancer and the proposal of node imaging reporting and data system	Sensitivity of US [Time Frame: Through study completion, an average of 1 year]	Dec 2017 / Jan 2019	US vs. ALND (gold standard)	Recruiting	China Shu Wang

ALND = axillary lymph node dissection; Gy = gray (unit); HER2 = human epidermal growth factor receptor 2; NAC = neoadjuvant chemotherapy; NACT = neoadjuvant chemotherapy treatment; RCT = randomized controlled trial; RNI = regional nodal irradiation; RT = radiotherapy; SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy; US = ultrasound; WBI = whole breast irradiation

Appendix 9: Guideline Document History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original April 2021	2007 to March 26, 2020	Full Report	Peer review publication Web publication	N.A.

Appendix 10: Glossary

Acronym	Definition
α	Alpha
µCi	Microcuries
ABS	Abstract
ACOSOG	American College of Surgeons Oncology Group
AD	Axillary dissection
AE	Adverse event
AGREE	Appraisal of Guidelines for Research and Evaluation
ALMANAC	Axillary Lymphatic Mapping Against Nodal Axillary Clearance
ALN	Axillary lymph node
ALND	Axillary lymph node dissection
AMAROS	After Mapping Of The Axilla: Radiotherapy Or Surgery
ANI	Axillary nodal irradiation
AR	Absolute reduction
ARR	Absolute risk reduction
aRT	Axillary radiotherapy
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Radiation Oncology
Aus	Australia
aUS	Axillary ultrasound
BC	Breast cancer
BCRL	Breast-cancer-related lymphoedema
BCT	Breast conserving therapy
BD	Blue dye
BOOG	Borstkanker Onderzoek Groep
BPI	Brachial plexus injury
C	Cyclophosphamide

Acronym	Definition
cALND	Completion ALND
CCO	Cancer Care Ontario
CEUS	Contrast-enhanced ultrasonography
Chemo	Chemotherapy
CI	Confidence interval
CMF	Cyclophosphamide, methotrexate, and 5-fluorouracil
cN0	Clinically node-negative
cN1	Disease in movable axillary nodes
cN2	Disease in fixed or matted axillary lymph nodes
CNB	Core needle biopsy
CT	Computed tomography
D(s)	Day(s)
DASH	Disability of Arm, Shoulder, and Hand
DCIS	Ductal carcinoma in situ
DDFS	Distant disease-free survival
Dec	December
DFS	Disease free survival
DM	Distant metastases
DRFI	Distant recurrence-free interval
DSS	Disease-specific survival
Dx	Diagnosis
EBCTCG	Early Breast Cancer Trialists' Group
EFS	Event-free survival
EMBASE	Excerpta Medica dataBASE
EORTC	European Organization for Research and Treatment of Cancer
ER	Estrogen receptor
ESMO	European Society for Medical Oncology

Acronym	Definition
ESTRO	European SocieTy for Radiotherapy and Oncology
FN	False negative
FNA	Fine needle aspiration
FNAB	Fine needle aspiration biopsy
FNAC	Fine needle aspiration cytology
FNR	False negative rate
GCSF	Granulocyte-colony stimulating factor
GDG	Guideline development group
GIVOM	Gruppo Interdisciplinare Veneto di Oncologia Mammaria
GLIDES	GuideLines Into Decision Support
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GRISO 053	Italian Oncological Senology Group 053 trial
Gy	Gray (unit)
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
hs	Hours
HT	Hormone therapy
IBC-RFI	Invasive breast cancer recurrence-free interval
IBCSG	International Breast Cancer Study Group
ICG	Indocyanine green
IDFS	Invasive disease-free survival
IHC	Immunohistochemical
IMLN	Internal mammary node radiation
INSEMA	Intergroup-Sentinel-Mamma
IORT	Intraoperative radiation therapy
IPD	Individual patient data
IQR	Interquartile range

Acronym	Definition
IR	Identification rate
ITT	Intention to treat
Ki67	Antigen KI-67
LABC	Locally advanced breast cancer
LN	Lymph node
LRR	Loco-regional recurrence rate
LRRFI	Loco-regional recurrence-free interval
LRRFS	Loco-regional recurrence-free survival
LSG	Lymphoscintigraphy
MAEBCGDG	Management of the Axilla in Early Breast Cancer Guideline Developing Group
Mast	Mastectomy
MEDLINE	Medical Literature Analysis and Retrieval System Online
mos	months
NA	Not applicable
NAC	Neoadjuvant chemotherapy
NCCN	National Comprehensive Cancer Network
NCDB	National Cancer Database
NCI	National Cancer Institute
NCIC	Canadian Cancer Trials Group
NICE	National Institute for Health and Care Excellence
nr	Not reported
NS	Not significant
NSABP	National Surgical Adjuvant Breast and Bowel Project
obs	Observational studies
OH	Ontario Health
OM	Occult metastasis
OMHLTC	Ontario Ministry of Health and Long-Term Care

Acronym	Definition
OPTIMAL	OPTimizing Irradiation Through Molecular Assessment of Lymph Node
OR	Odds ratio
OS	Overall survival
OTOASOR	Optimal Treatment Of the Axilla - Surgery Or Radiotherapy
pCR	Pathological complete response
PEBC	Program in Evidence-Based Care
PFS	Progression-free survival
PgR	Progesterone receptor
PICO	Population, Intervention, Control, Outcome
PMRT	Post mastectomy radiation therapy
PMRT-NNBC	Post Mastectomy Radiotherapy in Women With Node Negative Early Breast Cancer
pN0	No regional lymph node metastasis at pathological analysis
pT	Pathological T stage
pt(s)	Patient(s)
QOL	Quality of life
QU	Quandrantectomy without axillary lymph node dissection
QUAD	Quandrantectomy with axillary lymph node dissection
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RAC	Routine axillary clearance
RACS	Royal Australasian College of Surgeons
RAP	Report Approval Panel
RCT	Randomized control trial
RevMan	Review Manager
RFS	Recurrence-free survival
RFS	Relapse-free survival
RI	Regional irradiation
RNI	Regional nodal irradiation

Acronym	Definition
ROBINS-I	Risk Of Bias In Non-randomised Studies - of Interventions
ROBIS	Risk of bias in systematic reviews
RR	Relative risk
RT	Radiotherapy
SAD	Selective axillary lymph node dissection
SAGE	Standards and Guidelines Evidence
SD	Standard deviation
SE	Standard error
SENOMAC	Sentinel node macrometastases
SENTINA	SENTinel NeoAdjuvant
SERC	Sentinelle Envahi et Randomisation du Curage
SIGN	Scottish Intercollegiate Guidelines Network
SLN	Sentinel lymph node
SLNB	Sentinel lymph node biopsy
SN	Sentinel node
SNAC	Sentinel Node Versus Axillary Clearance
SNB	Sentinel node biopsy
SNBM	Sentinel node based management
SLNB	Sentinel lymph node biopsy
SOUND	Sentinel Node Vs Observation After Axillary Ultra-souND
SPC	Second primary cancer
SSO	Society of Surgical Oncology
SSSS	SNAC study specific scale
SUPREMO	Selective Use of Postoperative Radiotherapy aftEr MastectOmy
TAD	Targeted axillary dissection
Tam	Tamoxifen
TN	Triple negative

Acronym	Definition
UK	United Kingdom
US	Ultrasound
USA	United States of America
WBI	Whole breast irradiation
WHO	World Health Organization
wk(s)	Week(s)
ypN0	Post- neoadjuvant treatment negative axillary nodes
ypN-	Patients with pathological negative SLN status after neoadjuvant chemotherapy
ypN+	Patients with pathological positive or undetected SLN status after neoadjuvant chemotherapy
ypSLNB-	Patients for whom SLNB revealed no residual axillary metastasis and no further dissection was performed
yr(s)	Year(s)