Evidence-Based Series 1-19 IN REVIEW

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

Locoregional Therapy of Locally Advanced Breast Cancer (LABC)

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

Report Date: September 29, 2014

An assessment conducted in February 2021 placed Evidence-based Series (EBS) 1-19 IN REVIEW. This means that it is undergoing a review for currency and relevance. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

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

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

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

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Evidence-Based Series #1-19

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

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LIST OF ABBREVIATIONS

CCO = Cancer Care Ontario
DSG = Disease Site Group
EBS = evidence-based series
PEBC = Program in Evidence-Based Care
RAP = Report Approval Panel
RCT = randomized controlled trial

Disease Characteristics
HER2 = human epidermal growth factor receptor 2
HER2+ = HER2 positive
HER2- = HER2 negative
ER = estrogen receptor
ER+ = ER positive
ER- = ER negative
PR = progesterone receptor
PR+ = PR positive
PR- = PR negative
HR+ = hormone receptor positive
HR- = hormone receptor negative
IM = internal mammary
IMC = internal mammary chain
LABC = locally advanced breast cancer
MS = medial supraclavicular
N0 = node negative, no positive lymph nodes
N+ = node positive
TN = triple negative (PR-, ER-, HER2-)

Diagnosis and Treatment
3D = three-dimensional
ALND = axillary lymph node dissection
BCS = breast-conserving surgery
BCT = breast-conserving therapy (BCS +RT)
BED = biologically equivalent dose
CNB = core needle biopsy
CT = computed tomography
Gy = gray
LN = lymph node
PMRT = postmastectomy radiotherapy
RT = radiotherapy (radiation therapy)
SLN = sentinel lymph node
SLNB = sentinel lymph node biopsy

Systemic Therapy: Chemotherapy or Hormonal Therapy

A = doxorubicin (Adriamycin®)
AC = doxorubicin (Adriamycin®) + cyclophosphamide
C = cyclophosphamide
CAF = cyclophosphamide + fluorouracil + doxorubicin (Adriamycin®)
CMF = cyclophosphamide + methotrexate + fluorouracil
E = epirubicin
EC = epirubicin + cyclophosphamide
F = 5-fluoruracil
FAC = fluorouracil + doxorubicin (Adriamycin®) + cyclophosphamide
FEC = fluorouracil + epirubicin + cyclophosphamide
M = methotrexate
NACT = neoadjuvant chemotherapy
NX = vinorelbine + capecitabine
P = paclitaxel
T = docetaxel (Taxotere®) [less commonly abbreviated as D, with T referring to any taxane; this document generally uses "T" to refer to docetaxel]
TAC = docetaxel (Taxotere®) + doxorubicin (Adriamycin®) + cyclophosphamide
TAM = tamoxifen
X = capecitabine

Outcomes

cCR = clinically complete response
CI = 95% confidence interval
DFS = disease-free survival
DMFS = distant metastasis-free survival
EFS = event-free survival
FN = false negative
HR = hazard ratio
ITT = intention to treat
LRF = locoregional failure
LRFS = locoregional relapse-free survival
LRR = locoregional recurrence
LVI = lymphovascular invasion
NPV = negative predictive value
NS = not significant
OR = odds ratio
OS = overall survival
pCR = pathologically complete response
RFS = recurrence-free survival
RR = relative risk
SLN ID= sentinel lymph node identification

Evidence-Based Series #1-19: Section 1

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

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

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

Report Date: September 29, 2014

QUESTIONS

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

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

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

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

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

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

TARGET POPULATION

This guideline is pertinent to female patients with locally advanced breast cancer (LABC). For purposes of this guideline, LABC includes Stages IIB and IIIABC and inflammatory cancer, as defined in *the AJCC Cancer Staging Manual, 6th edition* (1). Most studies in the

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

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

INTENDED USERS

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

BACKGROUND

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

Historically, LABC has had poor outcomes. Although neoadjuvant (preoperative, induction) therapy was first introduced in an attempt to improve tumour resectability and overall survival (OS) rate with early adjuvant treatment, improved OS was not realized (2-6). However, other clinically important outcomes were observed, including disease downstaging and feasibility of breast conservation in select cases, which form the basis for continued use of this approach. Furthermore, neoadjuvant chemotherapy (NACT)[3] may also allow an in vivo assessment of chemosensitivity, potentially allowing a regimen change that would not otherwise be made with traditional postoperative adjuvant treatment. Finally, NACT provides a platform for important biomarker and correlative studies to enhance our understanding of this disease.

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

NACT has expanded beyond classically unresectable LABC and it is being used more frequently for some smaller tumours, especially certain clinical subtypes (e.g., triple negative, HER2+ [human epidermal growth factor receptor 2 positive]). Although this document does not evaluate effectiveness of NACT, its expanded use means that clinical trials often cover a heterogeneous patient population (see Target Population).

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

RECOMMENDATIONS

Preamble

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

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

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

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

Recommendation 1

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

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

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

- No randomized controlled trials (RCTs) that directly compared BCS with mastectomy in patients with LABC were found in the literature review (see Section 2).
- Evidence in early breast cancer is that BCS plus radiation is equivalent to mastectomy alone (8,9). There is a continuum in breast cancer stage, as opposed to a sharp cut-off between early and locally advanced (see Target Population). The Cancer Care Ontario/Program in Evidence-Based Care (CCO/PEBC) guideline (9) included all of Stage I and II, although the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) defined *early* as "breast cancer in which all clinically apparent disease can be removed surgically" (10). Therefore, at least some cancers defined as LABC in the current guideline (e.g., Stage IIB) are covered in the recommendations of these other guidelines.

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

Qualifying Statements

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

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

Recommendation 2a

Radiotherapy following mastectomy is recommended for patients with LABC.

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

- The EBCTCG meta-analyses (15,16) (see Section 2 Table 1) found postmastectomy radiotherapy (PMRT) significantly reduced 5-year and 10-year recurrence risk in patients with positive nodes (including subgroups with 1-3 positive nodes or with ≥4 positive nodes) or who received systemic therapy (primarily cyclophosphamide + methotrexate +

fluorouracil [CMF] and/or tamoxifen; >85% of patients with positive nodes received systemic therapy). This recurrence risk reduction applied to patients who had mastectomy plus ALND, mastectomy plus axillary sampling, or mastectomy only.

- In the EBCTCG meta-analyses PMRT significantly improved 20-year breast cancer mortality (including all subgroups). PMRT also significantly improved 20-year overall mortality for node positive patients with ALND (overall or with ≥4 positive nodes) or with axillary sampling.
- The benefit of RT in reducing breast cancer recurrence and mortality rates appears to be offset by adverse effects in older trials (primarily cardiovascular and lung adverse effects) especially in female patients with lower risk of recurrence. The ratio of breast cancer mortality rate to other mortality rates was strongly affected by nodal status, age, and decade of follow-up. The absolute benefit still favoured RT overall, but not necessarily in subgroups with particularly low risk of recurrence. More recent reviews found that the effectiveness of RT is increased and cardiopulmonary adverse effects are greatly reduced with modern RT planning and technique; therefore, the non-cancer mortality rate data in the EBCTCG meta-analyses may not be relevant to current practice.

Qualifying Statements

- The use of three-dimensional (3D) treatment planning is important to minimize the dose to the lung and heart to ensure improvements in breast-cancer-specific survival rates are not offset by non-breast cancer mortality rates. Treatments provided should conform to accepted standards with respect to tissue coverage and dose. Techniques such as gated RT or active breath-hold are used in some centres to reduce cardiotoxicity, although these were not evaluated in this guideline series.
- Radiotherapy after BCS was not part of this review, however guidelines for early breast cancer recommend radiation following BCS (8,9) and this is the current standard of care. In the absence of RCTs to the contrary, it is logical that radiation be used following BCS for LABC as well. Radiotherapy following BCS for LABC is the current standard of care.
- The EBCTCG meta-analyses found RT improved recurrence and survival rates in the subgroup of patients with systemic treatment. Several of the studies used older regimens such as CMF. Whelan et al (17) also found RT reduced mortality in patients with node-positive breast cancer who received systemic treatment. Figure 1 of Section 2 indicates RT significantly improved the local recurrence rate in patients receiving anthracycline-based chemotherapy but there was no effect on survival rate. No studies were included in the systematic review (Section 2) using taxane-based chemotherapy. Newer chemotherapies and targeted therapies may reduce the absolute benefit of RT for some patients, although in the absence of RCTs, RT is still recommended.
- Patients should be informed that improvements in recurrence and disease-specific survival rates have not necessarily translated into advantages in OS, possibly related to radiation-induced adverse effects in older studies. This applies especially in patients at lower risk of recurrence; however, most LABC patients who receive NACT would not be considered at low risk. Of patients with LABC, those with T3N0 confirmed by SLNB as N0 prior to chemotherapy are of lower risk than N+ patients. RT reduced the recurrence rates in all groups reported, but the absolute benefit in patients with very low risk of recurrence due to disease characteristics and systemic therapy may be small, and some may consider the incremental benefit of RT, although statistically significant, to be clinically unimportant.
- Lymphedema is more likely when surgical procedures include ALND or/and when RT includes the nodal areas (see Section 2). Decreased shoulder mobility, decreased strength, arm weakness, and paresthesia/hypesthesia have also been reported. The

German Breast-Cancer Study Group trial (also referred to as the Bundesministerium für Forschung und Technologie [BMFT] 03 study) (18) found that 25% of RT patients had acute skin reactions, and 28% had long-term skin alterations (1-2 years after RT). Radiation pneumonitis in the MA.20 trial was reported in 1.3% of patients receiving RT and 0.2% without. In some older RT regimens there was a significant increase in contralateral breast cancer and non-cancer mortality rates, primarily from heart disease and lung cancer (15,19). Careful treatment planning is likely to reduce (but not eliminate) risks other than lymphedema and skin effects.

- The benefit of PMRT in patients with node-negative LABC (T3-4N0) is less clear because they have not been reported separately from smaller (T2N0) cancers. Additionally, in patients clinically T3N0 the rate of pathological node positivity exceeds 50% and these patients may be considered T3Nx unless deemed N0 by SLNB before NACT or by ALND. The EBCTCG fifth cycle analysis (16) found that patients with node-negative cancer (primarily early cancer) treated with mastectomy + ALND + RT had no difference in recurrence risk (3.0% RT vs 1.6%, p>0.1)due to RT but significantly higher overall mortality rate (47.6% vs 41.6%, p=0.03). Control patients (no RT) with node negative cancer in studies using mastectomy + axillary sampling had higher recurrence than in studies with ALND (17.8% vs 1.6%); RT in patients treated with axillary sampling resulted in significantly lower recurrence risk (3.7% vs 17.8%) and no difference in 20-year mortality (46.1% vs 49.9%, RR=1.0, p>0.1). Patients with T3N0 cancer remain a group with limited data and should be discussed individually with regards to risks and benefits.

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

Recommendation 2b

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

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

- The recommendation for breast/chest wall irradiation is based on several RCTs as summarized in the EBCTCG meta-analyses (10,15,20-23) and is discussed in Question 2a.
- A prospective nonrandomized study (24) in high-risk patients with Stage II-III breast cancer found improved disease-free survival (DFS) rates at median 77 months follow-up (73% with internal mammary (IM) node RT vs 52% without, p=0.02), whereas OS was 78% vs 64%, p=0.08. Subgroups at higher risk of recurrence may have greater benefit, as has been reported for patients with positive nodes.
- A meta-analysis of the role of RT to regional nodes included three trials (two abstracts and one full publication) in patients with early/LABC (25) and concluded that regional RT to IM and medial supraclavicular (MS) nodes improves DFS, OS, and distant metastasis-free survival (DMFS) in Stage I-III breast cancer. This analysis did not meet our inclusion criteria because only approximately 36% of patients had LABC; therefore, the results need to be confirmed when the trials are fully published including subgroup data.
- The recommendation to include local node-bearing areas is consistent with current practice and other clinical practice guidelines. The NCCN guideline (12) recommends that if IM lymph nodes are clinically or pathologically positive, RT should be administered to

the IM nodes; otherwise, treatment to the IM nodes should be strongly considered in patients with node-positive and T3N0 cancer. NCCN also states that RT to the infraclavicular region and supraclavicular area is recommended for patients with ≥4 positive nodes and should be strongly considered if 1-3 nodes are positive, and considered for patients with T3N0 cancer (especially if inadequate axillary evaluation or extensive lymphovascular invasion).

- The ACR (26) recommends PMRT for T1-2N2+ and T3-4N+, usually including ipsilateral supraclavicular fossa for patients with positive nodes. There is more variation for IM nodes, but IM RT is considered for patients at risk of IM involvement such as those with medial or centrally located tumours and positive axillary lymph nodes. PMRT treatment of T1-2N1 and T3NO is controversial and should be individualized.

Qualifying Statements

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

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

Recommendation 2c

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

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

- No prospective randomized studies were found in the literature review (see Section 2) that compared treatment with vs without RT in female patients with pathologically complete response (pCR) to neoadjuvant therapy. The consensus of the authors is that postoperative RT should therefore remain the standard of care.
- When examining the evidence, it is important for the clinician to be aware of the various definitions for pCR that have been used in clinical studies. These range from no microscopic evidence of viable tumour cells, only residual necrotic or nonviable tumour cells, or only residual intraductal tumour cells in the resected specimen. The MD Anderson Cancer Center requires the added disappearance of axillary lymph node metastasis for a pCR.
- Randomized trials such as those planned by the Athena Breast Cancer Network (34,35) and the NSABP B51/RTOG 1304 trial may provide data to re-evaluate the recommendation for specific subgroups in the future.

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

Recommendation 3-1

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

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

- The median sentinel lymph node (SLN) identification rates (SLN ID rates) for the trials in Section 2 were 88% overall, 93% in patients with cN0 cancer and 85% in patients with clinically positive nodes. SLN ID rates depend on the experience of surgeons and the techniques used (see Section 2 for details).
- The ACOSOG Z1071 trial (36,37) conducted with patients with positive nodes (>85% LABC) is one of the largest and most recent studies. It found a 93% SLN ID rate for cN1 cancer and 89% for cN2 cancer. This study found detection with radiolabeled colloid much better than blue dye alone (94% colloid + dye, 91% colloid, 79% dye).
- For the studies in Section 2, median false negative (FN) rates were 10% overall, 7% cN0, and 13% clinically node positive. The SN FNAC study (38,39) found the FN rate decreased with the number of sentinel nodes removed (FN rate 19% for 1 SN, 7% for 2+ SN) and is consistent with the SENTINA trial findings. Using radiolabelled tracer plus blue dye and removing at least 2-3 SLNs, the best teams achieved FN rates of 5-7%. The FN rate is not dissimilar to the FN rates of 5-10% for early breast cancer surgery (40-42).

- Although the studies indicate that SLNB is technically feasible in both early and locally advanced breast cancer, a small percentage of patients will be understaged using SLNB alone. This risk needs to be weighed against the increased adverse effects of ALND.
- This recommendation is based on the authors' valuing potentially increased survival rates with use of ALND over increased postoperative complications. Given the results of the Z0011 and EBCTCG studies for early or operable cancers, some patients may decide that for less advanced LABC (e.g, Stages 2b-3a) the adverse effects of ALND are greater than the benefits.

Qualifying Statements

- Although the SLNB technique in patients (mostly with LABC) receiving NACT is comparable to that in early breast cancer, the clinical implications of a FN SLNB is not known in these patients (see Discussion in Section 2).
- The benefit of ALND is that more nodes are removed and examined, giving more accurate staging for some patients. Provided that locoregional RT is to be administered in all patients, as recommended in Questions 2a and 2b, the staging may have no impact on treatment. However, some patients may value the additional prognostic information. If a patient is not going to receive locoregional RT, then ALND is recommended. Trials in patients with LABC are ongoing.
- More than 80% of female patients undergoing ALND have at least one postoperative complication in the arm and psychological distress is common (43). In the Z0011 trial (44,45) ALND added to SLNB resulted in more wound infections, axillary seromas, paresthesias, and subjective reports of lymphedema than SLNB alone.
- The NCCN guideline (12) (not specifically on NACT) indicates "in the absence of definitive data demonstrating superior survival [with axillary lymph node staging], the performance of ALND may be considered optional in patients who have particularly favourable tumours, patients for whom the selection of adjuvant systemic therapy is unlikely to be affected, for the elderly, or those with serious comorbid conditions". They recommend that cN0 plus SLN negative (including T3N0) need no further ALND. However, the authors of the current guideline note that most patients with LABC are pathologically node positive before neoadjuvant therapy, even those considered clinically negative; therefore, a high portion may still be pathologically node positive after neoadjuvant therapy.
- None of the studies included inflammatory breast cancer; therefore, these findings cannot be extrapolated to that cohort of patients.

Recommendation 3-2

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

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

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

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

- The SENTINA study (46) did not conduct ALND if the SLNB before NACT was negative so FN rates could not be determined for this subgroup. Arm B of the SENTINA trial included patients initially cN0 with a positive SLN ($pN1_{SN}$) before NACT and conducted a second SLNB plus ALND after NACT. SLN ID rate was 76% in the second SLNB and the FN rate based on the second SLNB was 61% compared with a SLN ID rate of 99% in patients with cN0 cancer when SLNB was performed before NACT. This suggests that SLNB should not be performed both before and after NACT.

Qualifying Statements

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

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

Recommendation 4-1

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

Recommendation 4-2

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

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

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

treatment but better tolerability and DFS; the other trial demonstrated some improved response but worse adverse effects and treatment delays. There is therefore insufficient evidence to switch chemotherapy mid-treatment.
- The recommendations are based on current practice and are consistent with the guidelines by NCCN (12), Health Canada (55), and the Consensus Panel for Neoadjuvant Chemotherapy (13).

Qualifying Statements (Recommendation 4-2)
- There is a body of literature including patients with locally advanced and metastatic disease (mostly single-arm case series, small pilot studies, or retrospective studies) that supports a variety of second-line single agent and multi-agent NACT and/or RT regimens to improve response (including pCR) and, thus, operability or survival. Although the data are limited and not within the rigorous inclusion criteria of the literature review, Table 8 of Section 2 lists some of these studies as examples of regimens in the medical literature that have been tried in this clinical scenario. These data are not systematically reviewed nor of quality sufficient to make a recommendation as to preferred regimens. It is advised that oncologists individualize the choice of therapy based on the patient and risk of adverse effects.

FUTURE RESEARCH

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

RELATED GUIDELINES

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

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

3. George R, Quan ML, McCready D, McLeod R, Rumble RB, and the Expert Panel on SLNB in Breast Cancer. Sentinel lymph node biopsy in early-stage breast cancer [Internet]. Toronto (ON): Cancer Care Ontario; 2009 Jul 14. [cited 2013 Jun 6]. 90 p. Program in Evidence-Based Care Evidence-Based Series No.: 17-5. Available from: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/571.

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Evidence-Based Series #1-19: Section 2

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

Locoregional Therapy of Locally Advanced Breast Cancer (LABC): Evidentiary Base

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

Report Date: September 29, 2014

INTRODUCTION

This evidence-based series addresses several questions related to locally advanced breast cancer (LABC). This systematic review and evidence summary developed by the Working Group of the Breast Cancer Disease Site Group (DSG) is the basis for recommendations in Section 1.

QUESTIONS

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

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

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

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

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

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

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

METHODS

The Evidence-Based Series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (56). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by a Working Group of five members of the PEBC Breast DSG and one methodologist. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ministry.

Literature Search Strategy

The literature was searched using the MEDLINE and EMBASE databases (1996 to December 2011) and the Cochrane Library. Several preliminary searches were conducted, before conducting the final overall search (see Appendix B) which included and provided an update to all the preliminary searches (except two which were considered not relevant). In addition, the proceedings of the meetings of the American Society of Clinical Oncology (ASCO) and the San Antonio Breast Cancer Symposium (SABCS) were searched for relevant abstracts in the past three years. An Internet search of Canadian and international health organizations was also conducted to identify existing clinical practice guidelines, systematic reviews, and health technology assessments relevant to our guideline questions. The MEDLINE/EMBASE searches were rerun August 2013 and December 11, 2013 to locate articles published or indexed since the December 2011 search.

Study Selection Criteria

The literature searches were designed to retrieve systematic reviews, meta-analyses, randomized control trials (RCTs), cohort studies, and clinical practice guidelines that studied locoregional therapy for LABC. Studies had to include at least 50 patients (except for Question 4), have a prospective design, and provide a statistical comparison of the interventions of interest. Systematic reviews and meta-analyses had to include a description of the review methods (literature search, study selection, and data extraction). Only the most recent versions of reviews or guidelines were retained. Abstracts were discarded if a full-publication was also available, and only the most recent updates of RCTs were included, provided sufficient study details were reported.

For purposes of this guideline, LABC includes Stages IIB and IIIABC (including inflammatory cancer), as defined in the *AJCC Cancer Staging Manual, 6th edition* (1). RCTs with Stage II (unspecified) were also included, as were studies with Stage IIA, as long as Stage I plus Stage IIA comprised less than half the patients, or there were subgroup results for Stage

IIB and/or Stage III. Studies in which the title and abstract only indicated "early breast cancer" with no mention of stage or other indication that they may include patients meeting our definition of LABC were excluded. An exception was made for RCTs located from another publication about LABC (review, guideline, or RCT); in this case the Methods and Results of the original RCT publication were reviewed to determine whether it did actually meet our definition of LABC despite the title and/or abstract indicating otherwise. Studies in which the cancer was described as metastatic were excluded, unless mention was made that metastasis was only to regional lymph nodes. RCTs were the preferred studies. Cohort studies were considered in the initial screening, but were included only if the groups compared were equivalent (e.g., a similar distribution of tumour stage). Cohort studies were excluded if the patients were assigned to treatment based on patient/disease factors instead of randomly, such that prognosis of the two groups (before the treatment being studied) was not equivalent.

All studies identified through the literature search were assessed against the selection criteria by a health research methodologist (CW or GF) from the Working Group. Studies with uncertainty regarding eligibility were discussed with the other authors.

For Question 2b regarding extent of radiation (whole breast/chest or locoregional) studies were excluded if they focused on partial vs whole breast irradiation (e.g., accelerated partial breast irradiation [APBI], brachytherapy, intensity-modulated radiation therapy [IMRT]); intraoperative techniques such as TARGIT or ELIOT; compared radiation techniques such as dose-density, boost, or hypofractionation; or focused on simulation/treatment planning.

Quality Appraisal of Evidence-Based Guidelines

The SAGE Inventory of Cancer Guidelines is a searchable database of more than 2200 cancer control guidelines and standards released since 2003, developed and maintained by the Canadian Partnership Against Cancer's Capacity Enhancement Program (http://www.cancerguidelines.ca/Guidelines/inventory/index.php). This inventory includes evaluation of the process of practice guideline development and the quality of reporting using The Appraisal of Guidelines for Research and Evaluation II (AGREE II) Instrument (57).

Synthesizing the Evidence

When two or more trials provided appropriate data on outcomes of interest, statistical pooling using meta-analysis was done using Review Manager software (RevMan 5.1) (58) provided by the Cochrane Collaboration. A random effects model was used for all pooling because it provides a more conservative estimate. Pooled results are expressed as relative risks (RRs) with 95% confidence intervals (CIs). A RR of less than one favours the drug/supplement and an RR of greater than one favours the placebo or control intervention.

RESULTS

Overview of Literature Search Results for Complete Project

The original searches in EMBASE and MEDLINE resulted in 6482 references, and the revised search (December 2011) found 23,629 additional references. The final updates (August and December 2013) found an additional 12,027 citations. Additional references

(mostly results of older trials on postmastectomy radiotherapy [PMRT]) were located from the reference lists of included studies and recent reviews. After applying the inclusion/exclusion criteria there were 143 publications of trials as well as 18 guidelines and 27 systematic reviews or meta-analysis that were relevant. Most studies included a mix of cancer stages. For example, for Question 2a, only two trials with PMRT were conducted exclusively with patients with Stage III breast cancer.

Clinical Practice Guidelines

Eight practice guidelines on radiotherapy (RT) for breast cancer were identified (11,26,59-65). An additional nine guidelines on treatment or management of breast cancer included a section on locoregional treatment of LABC and the questions of interest (12-14,55,66-70). All addressed RT, but only four addressed Question 1 (BCS vs mastectomy) (11,13,14,70), two briefly addressed Question 3 (sentinel lymph node biopsy [SLNB]) (12,13), and three addressed Question 4 (treatment in non-responders to neoadjuvant therapy) (12,13,55). The European Society for Medical Oncology (ESMO) has also published a guideline on cardiotoxicity of chemotherapy and RT (71) that makes recommendations in order to reduce cardiotoxicity. The coverage of each guideline with respect to our guideline questions is shown in Appendix C. The AGREE II scores for clinical practice guidelines from the SAGE Inventory of Cancer Guidelines are shown in Appendix D.

Other guidelines are considered by the PEBC for endorsement (in which case no literature search is conducted) only if they fully cover the question of interest, are based on a current systematic review of the literature, and are assessed to be of high quality. Although the guidelines found provide relevant background and consensus information, they did not meet our criteria for endorsement. This did not preclude them from being cited in the recommendations (see Section 1) for specific aspects of a question or to indicate consistency between guidelines.

Systematic Reviews and Meta-Analyses

Relevant systematic reviews and meta-analyses are listed in Appendix E (excluding those on SLNB) which are discussed with Question 3). Most of the guidelines in Appendix C are also based on a systematic review. Quality assessment of the systematic reviews using the AMSTAR tool (72) is provided in Appendix G.

Several publications are meta-analyses by the Early Breast Cancer Trialists Collaborative Group (EBCTCG, see www.ctsu.ox.ac.uk/research/meta-trials/ebctcg) which is an international collaboration formed in 1985 to evaluate studies on early (operable) breast cancer. Despite the name, the EBCTCG defines *early* as "breast cancer in which all clinically apparent disease can be removed surgically" (10) and therefore includes LABC. The EBCTCG obtain individual patient data for all relevant RCTs (studies conducted throughout the world except Japan and USSR in the initial analysis, but later expanded to include these countries). The initial analysis included hormonal and cytotoxic therapy, with updates every five years giving longer-term follow-up and with the scope expanded to include other aspects of early breast cancer management (chemotherapy, endocrine therapy, surgery, RT). Individual patient meta-analysis is considered the strongest evidence (73) and provides the most reliable and least biased means of addressing questions that are not answered in individual RCTs (74). This is reflected in the decision of the Cochrane Collaboration to withdraw instead of update several reviews on topics covered by the EBCTCG (75-77), stating that the EBCTCG reviews

are based on individual patient data, are of the highest quality, and represent the best available evidence on the effects of these treatments on relapse, second cancer, and death. Several of the EBCTG reports are referred to in the Question 2 of this guideline. Because the EBCTCG had strict inclusion criteria and protocols and included individual patient data for all studies, it was considered unnecessary and unfeasible to extract data from or evaluate the quality of the individual trials included by the EBCTCG. Some limitations of the EBCTCG data are discussed in the relevant sections subsequently.

Other RCTs

Many of the RTCs found in the literature search for PMRT were already included and assessed in the reviews, guidelines, or meta-analyses noted previously; therefore, there was no additional quality assessment of these studies. Because assessment of study quality is based primarily on design of the study, quality assessment is done per trial and, therefore, updates were not assessed for trial quality. A summary of study/trial design and quality characteristics is provided in Appendix H for new RCTs (i.e., RCTs not included in the cited guidelines, reviews, or meta-analyses).

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

Literature Search

Several guidelines covered broader topics related to breast cancer. Recommendations most relevant to Question 1 are summarized in subsequent subsections. None of the guidelines fully covered the question based on RCT evidence and they were not considered to be used (endorsed) instead of a literature search. However, they did confirm the lack of RCTs on this topic for LABC.

Twenty-nine articles that appeared to address this topic were identified in the initial screening. After further evaluation of the study designs, it was concluded that none met the inclusion criteria. The main reasons for exclusion were that treatment was not randomized but based on clinical factors instead, such as tumour size and location (e.g., patients with tumours >3 cm or near the nipple had a mastectomy whereas other patients had BCS), the comparison was surgery plus radiation vs radiation alone, or the trials included <50 patients.

Summary of Relevant Guidelines

1. <u>American College of Radiology (ACR) (11)</u>

Breast preservation is feasible in certain patients with LABC. Those with clinical N2/N3 disease and small primary tumours, whose nodal disease responds to neoadjuvant chemotherapy (NACT), should be offered breast-preserving therapy. Many patients with large primary tumours may also be treated with breast conservation if a good response to NACT is achieved. Patients with multicentric disease or extensive calcifications are not good candidates for BCS following NACT. All patients undergoing breast-conserving therapy (BCT) should receive adjuvant whole-breast irradiation. Patients with inflammatory breast cancer should not be considered candidates for BCT.

2. National Comprehensive Cancer Network (NCCN) (12)

If the patient desires breast preservation then image-detectable marker(s) should be placed before NACT. Patients initially candidates for BCS other than tumour size, such as Stage IIB or IIIA (T3N1 only), with partial or complete response such that lumpectomy is possible can be treated with lumpectomy plus RT (based on pre-NACT tumour characteristics). The recommendation for patients initially Stages IIIABC (except T3N1) with good response to NACT is to treat with mastectomy or consider lumpectomy. All patients should receive axillary lymph node dissection (ALND) and RT. For patients with skin and/or chest wall involvement (T4 non-inflammatory) before NACT, BCS may be performed in carefully selected patients based on multidisciplinary assessment of local recurrence risk. Exclusions for BCS include inflammatory disease (T4d) and incomplete resolution of skin involvement after NACT.

3. International expert panel on inflammatory breast cancer (14)

The only method of definitive surgery to be offered to female patients with inflammatory breast cancer following preoperative systemic treatment is a modified radical mastectomy.

4. Consensus Conference on Neoadjuvant Chemotherapy in Carcinoma of the Breast (13)

Locoregional treatment following NACT depends on an assessment of the degree of tumour response. In considering BCS, the same criteria should be used as in the initial evaluation without NACT; namely, the absence of multicentric tumour, the absence of widespread malignant-appearing calcifications, and the ability to excise the residual tumour completely with clear margins and a suitable cosmetic result. The various properties of the tumour, its geography within the breast, and the likely cosmetic outcome should be considered when choosing between BCS and mastectomy. Breast conservation is usually possible if there is clinically complete response (cCR). The site of the initial lesion must be excised and RT should follow. Resection of an area surrounding the marker placed at the beginning of NACT is recommended to ensure that no microscopic residual disease remains. Treatment of patients with a cCR exclusively by RT without surgery is associated with a higher incidence of local recurrence.

Patients with LABC must have responded to the extent that skin involvement has regressed and chest wall fixation, if initially present, has disappeared. Skin-sparing mastectomy usually is not indicated for patients with initial skin involvement, but it might be an appropriate choice for those with T2 or even T3 tumours after an excellent response to NACT. Breast conservation, except under unusual circumstances, is not indicated in patients who present with inflammatory carcinoma, irrespective of the apparent improvement in the clinical findings.

Go to Recommendations (Section 1)

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

This section is based on 42 publications from the literature search plus 37 publications cited in other articles. Most of the relevant trials have been extensively reported in meta-analyses (10,15-17,23,78). Several guidelines listed in Appendix C also have sections on

PMRT. A summary of all the 38 trials included in the meta-analyses or found in the literature search is provided in Appendix F. Details on the radiation treatment are summarized by the EBCTCG in the supplementary data (webtables) of the 2005 and 2014 meta-analyses (15,16) and have not been reproduced here. Table 1 summarizes the EBCTCG results. The EBCTCG meta-analyses are the most inclusive and are summarized in more detail; other reviews/meta-analyses address some of the EGCTCG limitations or include some more recent trials.

In early PMRT studies patients did not receive systemic treatment or received systemic treatment considered inferior by today's standards. Although PMRT and chemotherapy both may reduce recurrence rates, the additional benefit of PMRT when administered with optimal chemotherapy is unclear. To address this, we attempted separate analysis of studies using current chemotherapy. Table 2 and Figure 1 report in more detail the subset of studies using anthracycline-based chemotherapy.

Table 3 includes descriptions and outcomes for 10 RCTs (25 publications) evaluating PMRT found in the current literature search. It mainly includes recent updates (longer-term follow-up) and subgroup analyses of the trials in Appendix F; therefore, most of the individual studies are not discussed in detail. Several reviews considered the British Columbia study and the DBCG 82b&c trials to be most relevant and Zellars (86,94,95) stated that the DBCG 82b&c trials and the British Columbia trial are the first prospective RCTs using uniform modern radiation techniques to show both locoregional control advantage and survival rate advantage, including benefit in patients with 1-3 positive. Some subgroup data (see Table 3) for different molecular profiles is summarized subsequently. Only one study (79) was found that is not included in the EBCTCG or other meta-analyses. Because study details and design were assessed in the meta-analysis, no further quality assessment of the included studies was conducted. Analysis of the updated data did not generally change the conclusions of the following meta-analysis and systematic reviews; therefore, the individual studies are not discussed.

Meta-analyses

The **EBCTCG** performed a meta-analysis on individual patient data for all randomized trials of surgery ± RT for operable breast cancer. This would include Stages IIB and IIIA (T2N1-2 and T3N0-2), which are LABC in our definition (see Methods) and may sometimes be operable, as well as small node-negative cancers (T0-2N0, Stages I-IIA) or with limited nodal involvement (T0-1N1, Stage IIA) would be early cancer outside our LABC definition. They used only unconfounded trials in which there was no difference between groups in use of systemic therapy. They included 78 RCTs and 42,000 female patients who had either BCS or mastectomy (analyzed separately). The fourth cycle update published in 2005 (15) reported results up the year 2000 from trials that started up to the year 1995. The fifth cycle data for BCS ± RT was published in 2011. The corresponding mastectomy ± RT data was presented at the ASCO 2007 and American Society for Radiation Oncology (ASTRO) 2006 (21,22) conferences; the full results on RT after mastectomy with 10-year recurrence rates and 20-year breast cancer mortality rates were published when this guideline was almost complete (16).

The fourth cycle analysis (15) reported that most local recurrences occurred during the first few years, with approximately three-quarters during the first five years. Therefore, the main analyses used 5-year local recurrence and 15-year mortality rates. A summary of

the results in various groups is provided in Table 1. Recurrence rate data had many more events than survival rate data and, therefore, many more associations were statistically significant. Although trends are often similar for survival rates, significance was not reached in several subgroups. However these two outcomes are inter-related. There was an overall 4:1 relationship between recurrence rates and long-term survival rates. Approximately one breast cancer death over the next 15 years would be avoided for every four local recurrences avoided. For subgroup analysis, it was considered that any differences or similarities are more likely to be trustworthy for local recurrence than mortality rates. The 4:1 rule could then be applied to survival rates. For node-positive disease with axillary clearance, the five-year local recurrence risk was 6% with RT vs 23% without ($p<0.00001$), and 15-year breast cancer mortality risk was 54.7% vs 60.1% ($p=0.0002$). Radiotherapy resulted in a similar proportional reduction in local recurrence for all female patients, irrespective of age or tumour characteristics (estrogen receptor [ER] status, grade), systemic therapy, or recent or older studies. A large absolute reduction was observed only if the control risk was large. In some of the older RT regimens there was a significant excess of contralateral breast cancer and non-cancer mortality, primarily from heart disease and lung cancer.

For BCS or mastectomy data combined (15), RT gave no significant difference in mortality rates for the subgroup with a difference in five-year local recurrence risk (RT vs control) <10%. There was significant improvement in 15-year breast cancer mortality rates (44.6% vs 49.5%, $p<0.0001$) and overall mortality rates (51.4% vs 55.2%, $p=0.0002$) when the recurrence risk was >10%. Note that all mastectomy subgroups (which would mostly be considered as LABC) except node negative with axillary clearance fell into the >10% risk of recurrence category. For this low-risk group (node negative plus axillary clearance), RT reduced the local recurrence rate at five years to 2.3% compared with 6.3% without RT, and 3.1% vs 8.0% at 15 years; however, RT patients had higher breast cancer-specific and overall mortality rates at 15 years.

The results for the fifth cycle analysis (see Table 1) were similar to those for the fourth cycle for node positive patients, except that the benefit of RT for 20-year breast cancer mortality was now statistically significant for more subgroups (mastectomy + ALND: node positive and subgroups with 1-3 positive nodes, ≥4 positive nodes; mastectomy + axillary sampling; mastectomy only). Comparison of data by type of nodal surgery indicated (none, sampling, ALND) showed RT benefit in all groups, though the potential benefit is greater in patients with less extensive surgery due to higher risk of recurrence. For node negative patients, RT had no benefit for recurrence or breast cancer mortality and a statistically significant increase in overall mortality in patients with mastectomy + ALND, but had recurrence benefit in patients who had mastectomy + axillary sampling or mastectomy alone.

The previous EBCTCG analysis (23) had reported a two-third reduction in local recurrence rates and reduction in breast cancer mortality rates ($p=0.0001$), but an increase in other mortality rates, particularly vascular ($p=0.0003$), such that overall survival (OS) rates at 20 years were 37.1% with RT vs 35.9% in controls ($p=0.06$). When looking at proportional changes after the second year, RT reduced the annual mortality rate from breast cancer by 13.2% but increased it from other causes by 21.2%. The absolute benefit still favored RT overall, but the authors suggested this may not be the case in subgroups with particularly low risk of recurrence. The ratio of breast cancer mortality rates to other mortality rates was strongly affected by nodal status, age, and decade of follow-up.

Several reviews (17,62,78,80) point out some of the limitations of the EBCTCG analyses when relating to modern oncologic practice. The overviews combined studies that used diverse surgical treatments (BCS, simple mastectomy, modified radical mastectomy, and radical mastectomy), systemic therapies (no systemic therapy, or agents no longer considered optimal), and RT techniques and doses (not all included the chest wall, some trials delivered high doses to the heart when treating the internal mammary (IM) nodes, and several older trials used orthovoltage equipment and low doses of RT).

The following reviews/meta-analyses look at subsets of the trials based on factors such as radiation dose and fields, systemic therapy, and age of studies.

Gebski et al (78) noted that whether RT improves the survival rate is controversial and explored whether the dose and extent of RT may be responsible for different effects on breast cancer survival and OS. They reanalyzed data from 36 unconfounded trials of PMRT (all but three were included in the EBCTCG reports) using three predefined treatment categories for individual patient data, and also reanalyzed data from EBCTCG 2000 (23).

- Category 1, optimal RT: doses in the range of 40 – 60 gray (Gy) in 2-Gy fractions (where 50 Gy=5000 rads) or as a biologically equivalent dose (BED) to the chest wall, axillary lymph nodes, and the supraclavicular fossa with or without the IM lymph nodes.
- Category 2, inadequate or excessive RT: doses of <40 Gy in 2-Gy fractions (or, for other fractionation schedules, the calculated BED being <40 Gy) or of >60 Gy in 2-Gy fractions (or for other fractionation schedules the calculated BED being >60 Gy).
- Category 3, incomplete tissue coverage: restricted the target volume to areas of less than the area of the chest wall and regional lymph nodes.

They concluded that in the comparisons with optimal and complete RT, RT was associated with a 2.9% increase in the 5-year survival rate (odds ratio, OR=0.87, 95% confidence interval [CI] 0.79-0.96, p=0.006) and a 6.4% increase in the 10-year survival rate(OR=0.91, 95% CI=0.70-0.85, p<0.001), whereas category 2 and 3 studies showed no statistically significant change in survival rates (OR=0.91, 95% CI=0.75-1.11 and OR=0.97, 95% CI=0.61-1.55, respectively). Using the EBCTCG studies, the local recurrence was reduced most in category 1 studies (80%) compared with category 2 or 3 studies (70% or 64%, respectively), and odds of all-cause death were also lower in category 1 studies. Category 3 studies (incomplete coverage) found higher overall deaths with RT than without.

Van de Steene (81) explored reasons why the EBCTCG 1995 (10) did not find improved survival rate with PMRT in contrast to the DBCG 82b&c and British Columbia trials. They found a significant survival benefit for the RT arm for recent trials, large trials, and trials with standard fractionation. They concluded that survival rate is improved provided that current techniques are used and treatment is administered with standard fractionation.

Whelan et al (17) performed a meta-analysis of RCTs published between 1967 and 1999 on female patients with node-positive breast cancer who received systemic treatment (the group of most relevance to the current guideline) and were randomized to receive locoregional RT or not (see Appendix F). They included most of the studies reported by EBCTCG that gave systemic therapy, except those of ovarian ablation, although the follow-up

time was shorter. Most trials included pre and postmenopausal patients with node-positive breast cancer. They concluded that locoregional radiation after surgery in patients treated with systemic therapy reduced the risk of any recurrence (OR=0.69, 95% CI=0.58-0.83), local recurrence (OR=0.25, 95% CI=0.19-0.324), and mortality (OR=0.83, 95% CI=0.74-0.94).

Other Reviews

The **ASCO 2001 guideline** (64) analyzed studies on PMRT in patients who received systemic therapy. **Recht and Edge, 2003** (65) updated the trial results from the ASCO guideline and added some additional information. All trials showed PMRT reduced recurrence. The South Swedish study found that less than one-third of recurrences could be controlled by salvage therapy.

Harris (82) reviewed cardiac mortality and morbidity rates after breast cancer treatment and noted that excess deaths in early studies were directly related to radiation techniques that exposed excessive volumes of the heart. New techniques of tangential irradiation with three dimensional (3D) computed tomography (CT)-based planning have minimized radiation to the heart such that more recent studies do not show an increase in adverse cardiac effects with PMRT, although there may still be risk factors (e.g., hypertension) or interactions with systemic treatment.

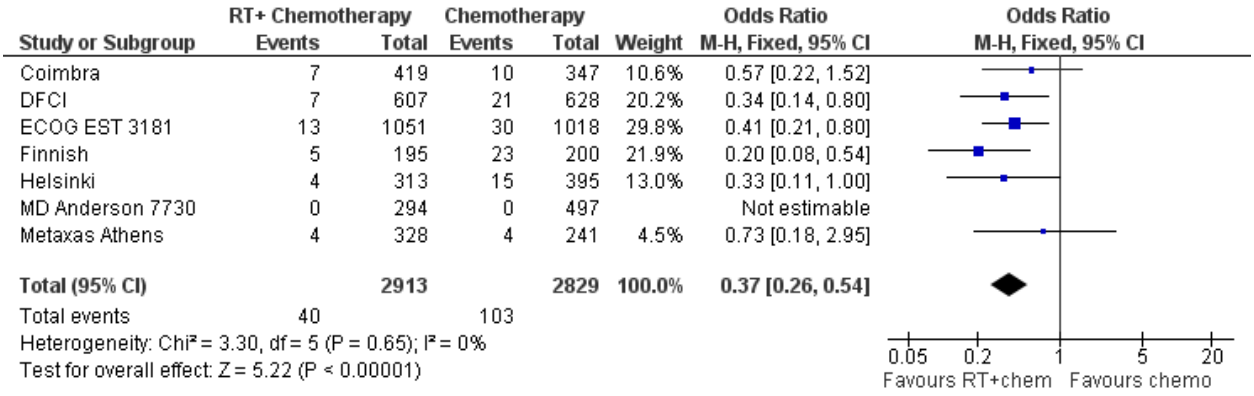
Based on nonrandomized studies, **Rowell, 2009** (83) found that baseline risk of LRR was higher with lymphovascular invasion (LVI), grade 3 tumour, tumours >2 cm, close resection margin, premenopausal, or age <50 years. Those without any risk factors had baseline LRR risk of ≤5%, whereas the risk was ≥15% with two or more risk factors. They concluded use of PMRT in patients with node-negative cancer needs re-evaluation and should be considered for female patients with ≥2 risk factors.

Radiation Plus Chemotherapy

Most of the earlier radiation studies did not use systemic treatment/chemotherapy, or used earlier generation chemotherapy agents which have been replaced by more effective regimens. Therefore, the EBCTCG meta-analysis could not directly answer the question of whether there is additional benefit of PMRT if the patient receives optimal chemotherapy. The analyses by Whelan (17) and ASCO (64,65) addressed PMRT in patients receiving systemic treatment, although they included older agents as well. Table 2 and Figure 1 give results for the subset of studies using anthracycline-based therapy. The meta-analysis of Figure 1 indicates there is still benefit of PMRT in these patients. No results were available for taxane-based chemotherapy.

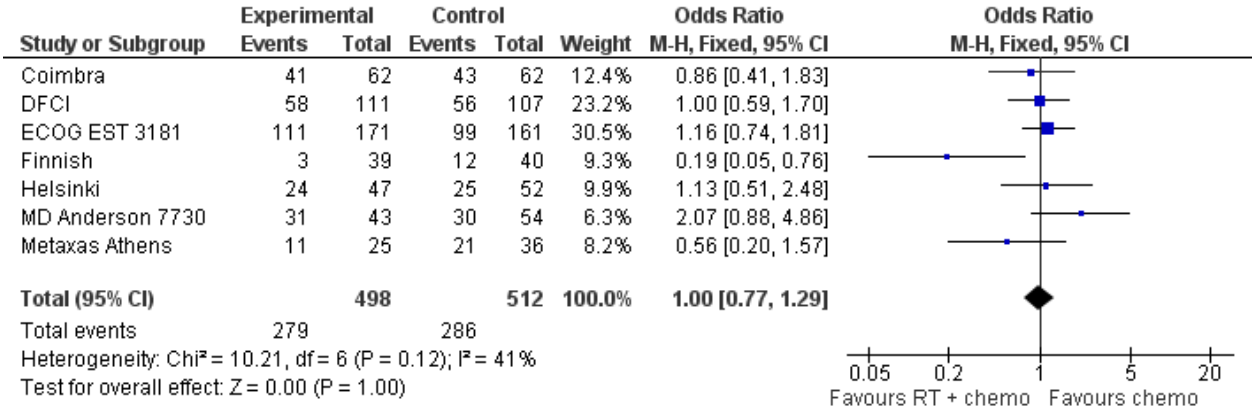
Figure 1. Meta-analyses of local recurrence and mortality rates for studies of postmastectomy radiotherapy plus anthracycline-based chemotherapy vs chemotherapy alone.

a) Local recurrence rate



Data from EBCTCG 2005 (15) except for the Finnish study (84). Totals are expressed in women-years.

b) Any Death



Data from EBCTCG 2005 (15) except for the Finnish study (84).

Molecular Subgroup Analysis

Some of the trial updates (see Table 3) report additional molecular subgroup analysis and looked for correlation with response or prognosis. Kyndi et al (85) performed tissue microarray analysis for ER, progesterone receptor (PR), and human epidermal growth factor 2 (HER2) for some of the specimens from the DBCG 82b&c trials and found RT gave significantly better OS and LRR for ER+, PR+, and HER2- subgroups. ER-, PR-, and HER2+ had improved LRR but not OS.

An abstract by Laurberg et al (86) reported on molecular analysis of patients in the British Columbia and DBCG 82b trials and found significantly better 20-year locoregional relapse-free survival (LRFS) for the luminal A subgroup for both trials (British Columbia trial: 94% vs 66%, p=0.05; DBCG 82b trial: 92% vs 25%, p=0.01). The basal-like subgroup had improved survival rate (92% vs 23%, p=0.004) in the British Columbia trial, but not in the DBCG 82b trial (54% vs 66%). No differences in OS were found for subgroups; however, the DBCG trial found improved survival for the overall population at 10 years (54% vs 45%, p<0.001). In an earlier abstract (87), they reported 10-year survival rates for the British Columbia trial by subtype and found improved breast cancer specific survival rates with RT in the luminal A group (82% vs 36%) but not in non-luminal A (54% vs 49%, p=0.69). Some of the same researchers [(88,89) abstract only] analyzed specimens from the DBCG82bc cohort and derived a seven-gene signature to form a weighted index of local control. The combined lower three quartiles benefited from PMRT (85% vs 31% local control, $p=2.5x10^{-8}$), whereas those with a high index had no further improvement with PMRT (86% vs 90% local control, p=0.93).

Differential benefit of PMRT for specific subgroups was also found in retrospective studies comparing patients with or without PMRT (not randomized). Lee et al (90) identified 104 locally advanced or high-risk patients (Stage T3/4 disease, any Stage N2/3, positive <1 mm resection margins, or skin/nipple/pectoral invasion) and reported benefit of PMRT overall (p=0.029) and for patients with luminal A (p=0.07) and non-p53 overexpression (p=0.026), but not triple negative and patients with p53 overexpression. Wu et al (91) included 774 patients with ≥4 positive nodes and reported improved LRFS, distant metastasis-free survival (DMFS), and mortality rates for luminal A subtypes (all p<0.001) and reduced LRFS for luminal B subtype, but no effect for HER2+ or basal subtypes.

The preceding data are limited by the retrospective nature of the studies, exploratory subgroup analyses, small sample numbers, and preliminary reporting, but suggest stronger benefits of PMRT for specific molecular subgroups. The benefit on luminal A subtype appears consistent in these studies.

Go to Recommendations (Section 1) Go to Discussion (Section 2)

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

Three RCTs in seven publications (see Table 4) (28,29,32,33,92-94) evaluated the role of radiation to regional nodes. The studies included 7170 patients, both early and LABC. It is estimated that approximately 36% were LABC. Two of the trials were only published as

abstracts and may be considered ongoing. Results available were not subdivided by stage and therefore they did not meet the inclusion criteria (>50% LABC or with LABC subgroups reported); however, the large number of patients suggests subgroups representing LABC may be reported in the final publications and these studies need to be followed. A meta-analysis of these three studies (25) was based on the full publication of one trial and abstracts plus presentations of the other two trials and concluded that regional RT to IM and medial supraclavicular (MS) nodes improves disease-free survival (DFS), OS, DMFS in Stage I-III breast cancer. It was limited by lack of full publication of the data and therefore could not comment on subgroups. It notes that due to the relatively small average survival advantage, individual patient data meta-analysis may help identify subgroups with more benefit. Literature reviews for the meta-analysis and by the authors of this guideline located no other RCTs on this topic for either early or LABC.

The study by Stemmer et al (24) was a prospective nonrandomized study designed to treat patients with high-risk Stage II-III cancer with high dose chemotherapy and locoregional RT. For 20 months during the study the electron-beam facility was not available; therefore, 33 patients did not receive planned IM node irradiation. These patients were compared with 67 patients who received IM node RT. DFS at median 77 months follow-up was 73% with IM node RT vs 52% without (p=0.02), whereas OS was 78% vs 64%, p=0.08.

Guidelines and Reviews

Fourteen guidelines (12-14,26,55,59-64,66,68,70) relevant to the extent of radiation treatment were found; the more recent are summarized in Table 5. The NCCN guideline (12) is the most recent and comprehensive. ESMO has also published a guideline on cardiotoxicity of chemotherapy and RT (71) that makes recommendations to reduce cardiotoxicity. Most of the guidelines recommend irradiation of some nodes for all patients covered by the guidelines with node-positive disease, or those with ≥4 positive nodes. Nodes to include vary, the most common being supraclavicular and infraclavicular, with internal mammary chain (IMC) also included in some.

Two systematic reviews (95,96) deal with irradiation of IM nodes in breast cancer, and are listed in Appendix E. These reviews may be consulted for background information, and a summary of retrospective studies plus ongoing RCTs in early breast cancer, including some patients with LABC. No RCTs specifically on IMC RT in LABC are included.

Moran and Haffty wrote a review "Radiation techniques and toxicities for locally advanced breast cancer" which discusses some of the technical aspects and concerns with specific reference to LABC (97). Several other reviews have been published (e.g., (98-100)) concerning cardiotoxicity and other complications of breast cancer RT.

Go to Recommendations (Section 1) Go to Discussion (Section 2)

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

Various definitions for pathologically complete response (pCR) have been used in clinical studies. Mukai et al (101) compared the pCR rate in 141 patients using different definitions and found pCR ranged from 5% to 14%. The Japan Breast Cancer Society defines pCR as no remaining cancer cells (or only necrotic or nonviable residual cells), the German Prospective Adriamycin–Docetaxel (GEPARDO) trial defines pCR as no microscopic evidence of

viable tumour cells in the resected specimen, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 definition allows intraductal tumour cells, and the MD Anderson Cancer Center trials requires complete response of the primary lesion plus disappearance of axillary lymph node metastasis. Some definitions require complete disappearance of viable tumour cells (Japanese and German/GEPARDO trials) and others allow intraductal residual cells NSABP B-18, MD Anderson). Of these, only MD Anderson evaluates lymph nodes.

No prospective studies were found that compared treatment with and without RT in female patients with pCR to neoadjuvant therapy. The recent systematic review by Fowble et al (35) on the role of PMRT after NACT in Stage II-III breast cancer also indicated there were no prospective randomized trials. They therefore summarized the retrospective studies and did a consensus study of treatment appropriateness ratings for hypothetical clinical scenarios. They concluded that patients clinically Stage II (T1-2N0-1) with pCR had <10% risk of LRF without radiation and that limited data support patients with Stage IIIA cancer with pCR as being low risk.

Go to Recommendations (Section 1) Go to Discussion (Section 2)

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

Table 6 summarized 30 studies (7 only reported as abstracts) from 33 publications. Of these, three full reports and one abstract were located from the lists of trials included in six recent systematic reviews including four with meta-analyses (102-107). These reviews did not deal specifically with LABC; therefore, they are not included in the current systematic review results.

Sentinel lymph node (SLN) identification (SLN ID) and false negative (FN) rates were the most commonly reported outcomes. Negative predictive value (NPV) and accuracy were sometimes reported and have been calculated where possible if not reported in the publications. Control data are included if reported; however, most studies did not have controls. Control data have been omitted when obtained from patients with a greatly different distribution of tumour grade compared with those with SLNB plus ALND. Only prospective studies with at least 50 patients who received NACT, SLNB, and ALND are included. Prospective/retrospective design could not be determined for a few studies, and these have been included with a notation to this effect. Because most of the studies are nonrandomized, non-controlled, non-comparative, short-term surgical studies, most of the quality assessment fields do not apply and the studies have not been included in the evaluation in Appendix H.

Timing of SLNB

Only three of the studies in Table 6 (46-48) compared timing of SLNB (before or after NACT) and one additional study (49) performed SLNB before neoadjuvant therapy. The rest of the studies performed SLNB and ALND after completion of NACT. Vazquez Guerrero et al (49) conducted SLNB before NACT and found an SLN ID rate of 99% and accuracy of 95%. Zhao et al (48) found that pre-NACT SLNB had a lower FN rate (8% vs 24%) and better accuracy (95% vs 84%) than post-NACT SLNB; however, the study is published in Chinese and therefore tumour

stage and study design are unknown and we are unable to ascertain whether all the inclusion criteria were met. Papa et al (47) also found that in patients with cN0 cancer (T2/T3) the SLN ID rate was higher (97% vs 87%) and the FN rate lower (0% vs 16%) when SLNB was performed before NACT. This was a small study and although the authors indicated it was in patients with LABC, the mean tumour size was 4.0 cm; therefore, less than half the patients are likely to be T3N0.

The SENTinel NeoAdjuvant (SENTINA) study (46) was a four-arm trial conducted primarily with patients with T2 tumours (70%-80% T2). Arm B included patients initially cN0 with a positive SLN (pN1sn) before NACT and conducted a second SLNB plus ALND after NACT. The SLN ID rate was 76% in the second SLNB using radiocolloid + dye (61% without dye) and the FN rate was 61% (52% without dye), compared with an SLN ID rate of 99% in patients with cN0 cancer when SLNB was before NACT. It must be noted that a median of two SLN were removed before NACT; therefore, in the second operation the "SLN" would not originally be considered a SLN. It is often thought that SLN removal may disturb lymphatic drainage at least in the short term; therefore, the results are not unexpected. Arm C was conducted in patients with clinically positive nodes and performed SLNB and ALND after NACT only in patients converted to clinically node negative (ycN0) after NACT. In this group the SLN ID rate was 88% and the FN rate was 9% using radiocolloid plus dye (80% and 14% respectively, without dye). The FN rate depended on the number of nodes removed (1 node 24%, 2 nodes 18%, ≥3 nodes 5%). There were no arms in the study that made a direct comparison of SLNB before or after NACT in patients of the same stage.

SLNB After NACT

SLN ID rate and FN rate were the primary outcomes. Eleven of the studies were conducted in patients with positive nodes, two were in patients with cN0 cancer, six reported some separate data patients with for N+ and N0 cancers, and six combined data for N+ and N0 patients. In the studies that reported on patients with cN+ and cN- cancers separately, detection tended to be higher in patients with cN0 cancer, although patients with node-negative cancer are less likely to be LABC. The median SLN ID rate was 88% overall, 93% for patients with cN0 cancer, and 85% in patients with clinically positive nodes. Corresponding median FN rates were 10%, 7%, and 13%, respectively. The ID rate was higher in the subset of studies which reported data by initial nodal status, with a median SLN ID rate of 93% overall, 95% in cN0, and 89% in patients with clinically positive nodes. After NACT, an average of 47% of patients initially with cN0 cancer were found to be pN+, whereas for patients with clinically positive nodes an average of 62% were pN+.

Go to Recommendations (Section 1) Go to Discussion (Section 2)

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

Only three RCTs (four publications) were found (see Table 7) that randomized patients with LABC to additional treatments if they did not respond to initial NACT. The GeparTrio study randomized patients with low response to two cycles of docetaxel + doxorubicin + cyclophosphamide (TAC) (<50% decrease in tumour size) to four additional cycles of either

TAC or vinorelbine + capecitabine (NX) (53,108). They found similar efficacy but better tolerability with NX. They considered pCR marginal for both groups (5.3% and 6.0%). After further follow-up, early non-responders had better DFS for TAC-NX than TAC×6 (hazard ratio, HR=0.59, 95% CI=0.49-0.82, p=0.001).

The GeparQuinto trial (109) compared paclitaxel ± everolimus in patients not responding to epirubicin + cyclophosphamide (EC) and found everolimus did not improve response. Unfortunately there was no control group without paclitaxel.

The study by Qi et al (54) randomized patients with low response to two cycles of cyclophosphamide + pirarubicin + fluorouracil (<50% decrease in tumour size or an increase in size/progression) to four additional cycles of paclitaxel plus carboplatin, with the paclitaxel either weekly or every three weeks. Weekly treatment had higher response but also more treatment delays and hematoxicity.

In cases meeting the criteria for BCS other than tumour size, the current NCCN guideline (12) recommends that mastectomy (followed by any remaining cycles of the preoperative chemotherapy) be performed if there is progressive disease or partial response insufficient for BSC. This is in contrast to earlier versions of the guideline (110) which recommended considering alternative chemotherapy before surgery. For other Stage IIIA-IIIC cancers if there is no response to preoperative chemotherapy then consider additional systemic chemotherapy and/or preoperative radiation. If there is sufficient response then perform a mastectomy/BCS; if still no response then use individualized treatment. This also applies to inflammatory cancer except that mastectomy (not BCS) is recommended. It is noted that preoperative systemic therapy for HER2+ tumours should include trastuzumab, whereas endocrine therapy and chemotherapy may be administered to patients with HR+ cancer. Endocrine therapy alone may be considered for postmenopausal patients.

The Health Canada guideline on LABC (55) was written when taxanes were not routinely used and recommended that inoperable tumours (Stages IIIB or IIIC) not responding to primary anthracycline-based chemotherapy could be treated with taxanes or proceed directly to irradiation followed by modified radical mastectomy, if feasible.

A guideline based on the Consensus Conference on Neoadjuvant Chemotherapy in Carcinoma of the Breast (Philadelphia, PA, 2003) written around the same time (13) indicated that as many as 90% of female patients who are administered NACT will manifest a clinical response either to the first courses of chemotherapy or a second non-cross-resistant therapy. Patients receiving anthracycline-based regimens benefit from cross-over to alternate non-cross-resistant regimens, most frequently a taxane. Patients with hormone receptor-positive breast carcinoma should also receive hormonal therapy. Patients who do not respond should have surgery if feasible to remove all macroscopic evidence of tumour; if unresectable, then preoperative RT or exclusive RT might be employed. The radiation approach in non-responders should be a course of 45–50 Gy over 4.5–5 weeks (sometimes with an additional boost of 10 Gy in 1 week to the site of the macroscopic tumour). For tumours still unresectable, additional radiation using brachytherapy or shrinking fields may be indicated.

There is a wide range in rates of clinical or pathological response to NACT reported in studies that were retrieved and initially screened in the literature search. Except as noted previously, these studies did not meet the inclusion criteria, were not systematically reviewed and they did not form the basis of specific recommendations. Some of these studies, however, suggested that selection of chemotherapeutic agent is important and may

vary depending on patient characteristics. Table 8 includes some of the various treatments explored for second-line neoadjuvant therapy to increase the rate of response and allow resection. Most studies were small, nonrandomized exploratory or phase II trials and are included to illustrate some of the various approaches, but are not sufficient to select optimal treatment. Some studies used RT concurrently or after NACT. These studies indicated further response with second-line chemotherapy (or RT).

There were several studies of other chemotherapeutic agents (e.g., ixabepilone, lepatinib, letrozole, platinum compounds) conducted in patients with advanced or metastatic disease and therefore outside the scope of the review. There may be a role for some of these agents in patients with LABC who do not respond to standard regimens.

Go to Recommendations (Section 1) Go to Discussion (Section 2)

DISCUSSION

Question 1. BCS vs Mastectomy after NACT

Neoadjuvant therapy may result in change in the extent or distribution of tumour, or complete disappearance (clinically or pathologically complete response). However, it is considered necessary to completely excise the tumour as well as any tissue previously involved (i.e., the tumour bed) even when there is complete response to NACT. It should be noted that the actual volume of tissue to remove will be decreased if there is response to neoadjuvant therapy. To ensure complete excision of the original tumour, marking the original tumour extent (e.g., by clips or needles) is recommended. Although the optimal method of marking was not evaluated in this guideline, the consensus reached at the Canadian Consortium for Locally Advanced Breast Cancer (COLAB) in 2011 was that clips should be inserted at the time of diagnosis to mark tumour location and this should be considered the standard of care (7). Use of clips can improve surgical outcomes, allowing more accurate identification of the tumour site (especially if complete response), resection of all (previously) cancerous tissue with adequate margins, pathologic diagnosis of the most appropriate area of specimens, and better accuracy of molecular analyses. Marking of the tumour may be more critical to the surgeon when performing BCS compared with mastectomy, but for the pathologist identification of the affected areas is essential in either situation.

As indicated in Results, no RCTs were located that randomized only patients with LABC to either mastectomy or BCS following NACT. In the absence of such data, the authors' opinion is that mastectomy should remain the standard of care in LABC generally, with BCS considered for some patients with good response to NACT or strong preference for breast conservation.

When deciding between mastectomy and BCS for patients who meet BCS criteria, the following issues should be considered. Mastectomy has greater detrimental effect on body image, self-esteem, and sexuality for some female patients, results in loss of sensation, and is more complex and aggressive surgery. With BCS there is usually no need for additional reconstructive surgery. Conversely, in some cases of BCS positive margins may require re-excision. The risk of recurrence and breast cancer mortality may be higher with BCS than mastectomy. There were no RCTs found to either prove or disprove this. In cases or recurrence after BCS, further surgery may be needed, and some patients would rather reduce this possibility by having mastectomy as initial treatment.

Some patients may prefer BCS even when informed of the lack of long-term data supporting its use. It should be noted that patients with less-involved LABC (e.g., Stage IIB

tumours) have been included in guidelines on early breast cancer which concluded that BCS plus RT is equivalent to mastectomy, and BCS may also be appropriate for these patients. In determining BCS vs mastectomy, planned adjuvant treatment needs to be taken into account. Although RT is addressed in Question 2 and is recommended for all patients (whether BCS or mastectomy), studies indicate mastectomy may provide better outcomes in patients who will not receive RT.

Guidelines by the American College of Radiology (ACR) (11), National Comprehensive Cancer Network (NCCN) (12), and the Consensus Conference on Neoadjuvant Chemotherapy in Carcinoma of the Breast (13) indicate BCS after NACT is appropriate for some patients with LABC. This may include patients with small N2/N3 tumours with nodal response, or large (T3N0 or T3N1) tumours with good response. NCCN recommends patients initially Stages IIIABC (except T3N1) with good response be treated with mastectomy or consider lumpectomy (plus ALND plus RT). BCS may be performed in carefully selected patients with T4 non-inflammatory cancer (12,13) provided that there is complete resolution of skin involvement, but it should not be used for inflammatory cancer (11-14).

Huang et al (111) developed a prognostic index score to predict rates of LRR after neoadjuvant therapy for mastectomy and BCS. All patients received RT after surgery and most received adjuvant chemotherapy (77% BCS, 95% mastectomy). On average, the mastectomy patients had more advanced cancers; therefore, a direct comparison of the overall groups was not warranted. One point was assigned for each of clinical N2-N3 disease, LVI, pathologic size >2 cm after NACT, and multifocal residual disease. The 10-year LRR were very low and similar in the two groups if the index score was 0-1, trended toward being lower for mastectomy if the score was 2 (12% vs 28%, p=0.28), and was significantly lower with mastectomy if the score was 3-4 (19% vs 61%, p=0.009). The index is based on retrospective data and needs to be confirmed in randomized studies, but suggests patients with good/complete response to NACT are candidates for BCT provided there are no high-risk factors.

Go to Recommendations (Section 1)

Question 2a. Postmastectomy Radiotherapy

The effectiveness of PMRT in reducing locoregional recurrence is well-established. The EBCTCG found benefit overall and in all early and LABC subgroups (N0, N1, N2+, T1, T2, T3/4, with or without systemic treatment). PMRT either alone or with older chemotherapy regimens such as CMF, using optimal dosing and modern techniques to minimize cardiotoxicity and other adverse effects, was also found to improve breast cancer specific and OS in patients with node-positive cancer.

Lymphedema is more likely when surgery includes ALND and/or when RT includes the nodal areas. Comparing groups with RT to without RT, the BC study (112,113) found 9% vs 3% arm edema, the DBCG 82b&c trials (114) found lymphedema rates of 14% vs 3% (NS) by objective assessment and 43% vs 17% (p=0.02) by subjective assessment, and the South Sweden study (115) found 6.8% vs 3.9% lymphedema. The DBCG 82b&c trials also reported a significant decrease in shoulder mobility (objective assessment 45% vs 15% slight and 5% vs 0% moderate/severe, p=0.004; symptomatic 17% vs 2%, p=0.001). Decreased strength (14% vs 2%), arm weakness (28% vs 19%), and paresthesia/hypesthesia (21% vs 7%, NS) were also reported.

The ECOG EST3181 study (116) found 7.5% severe adverse effects in the RT patients (2.7% skin/mucosa, 2% hematologic, 0.7% infections/respiratory/hepatic/other) vs 3% without RT. The BMFT 03 German study (18) found that 25% of patients who received RT had acute

skin reactions, and 28% had long-term skin alterations (1-2 years after RT). Radiation pneumonitis has been reported in approximately 1-4% of patients (33,115,117), although this increased to 23% (p=0.008) when RT and anthracycline chemotherapy were both used. Note that the higher rates were in older trials (enrolment 1978-85) and the more recent MA.20 trial reported grade ≥2 pneumonitis of 1.3% with RT vs 0.2% without RT (p=0.01). There is also a very low risk of rib fracture or brachial plexopathy (18,115). In some of the older RT regimens there was a significant excess of contralateral breast cancer and non-cancer mortality, primarily from heart disease and lung cancer (15). The Stockholm study reported higher risk of second primary tumours (12% vs 5%, p=0.01), especially lung cancers after 10 years (3.7% vs 0.3%) (19). Other than lymphedema and early (often transient) effects on the skin, careful treatment planning is likely to reduce (but not eliminate) the other risks.

As observed in Figure 1, the conclusion that RT added to chemotherapy reduces local recurrence is still valid when considering only the subset of trials with anthracycline-based chemotherapy. Addition of RT to chemotherapy had no effect on survival rate. The data are limited by the fact that all the trials had a relatively small number of patients. The DFCI (118,119) and Metaxas Athens studies (120) had high rates of patients not adhering to the randomized treatment. None of the RCTs included in these tables address whether there is benefit to adding RT to taxane-based chemotherapy or current chemoendocrine therapies. It is expected that with optimal chemotherapy the absolute risk of recurrence for some patients would be lower; therefore, the absolute benefit of RT (in addition to chemotherapy) would also be lower. The relative benefit of RT would still exist but for patients with very low risk of recurrence, the benefits may not outweigh RT risks. Note though that the risk of non-breast cancer deaths is much lower when using modern RT planning and techniques than for RT as administered in the many of the studies in the EBCTCG meta-analyses which started almost 30 years ago [1964-1986 for the latest analysis (16)].

Some have suggested that recurrence but not survival benefit is due to careful follow-up and that recurrence was treated by additional treatment (re-excision, chemotherapy, RT). This was not supported by the South Swedish trial (121) which found salvage therapy was successful in treating recurrence in less than one-third of cases. Outside of clinical trials there may be less intense follow-up; therefore, recurrence may lead to worse survival rates than in RCTs. Even if increased recurrence rates do not lead to differences in survival solely due to the ability to re-treat the patient, there may be a psychological value (e.g., peace of mind) to doing more treatment at the time of initial surgery. This must be weighed against adverse effects of radiation treatment.

Alternatively, the EBCTG authors suggest that recurrence is a much more sensitive analysis because it requires shorter follow-up to reach sufficient events for statistical significance. In many of the comparisons there were not enough events for trends to be statistically significant. In trials of RT after BCS (both N0 and N+ cancers), one breast cancer death was avoided in the first 15 years for every four recurrences (20). The latest meta-analysis refined this for node positive cancers in female patients with mastectomy (generally with more advanced cancers and extensive RT than the earlier BCS meta-analysis) and found RT avoided one death in the first 20 years for every 1.5 recurrences avoided during the first 10 years (16).

In patients with node-positive cancer the fourth cycle EBCTCG analysis (15) found statistically significant benefit recurrence and survival benefit for patients with node-positive cancer overall. By the fifth cycle with longer follow-up there was also significant RT benefit

for subgroups with 1-3 positive nodes and ≥4 positive nodes (16). Radiotherapy improved survival rate for all T stages (T1, T2, T3/4).

Survival benefit in patients with node-negative cancer LABC is less clear as the EBCTCG analysis did not subdivide the data and patients likely had smaller early stage cancers (not LABC). The recent EBCTCG update (16) found that for female patients that were N0 and received ALND, RT resulted in no significant difference on locoregional or overall recurrence or breast cancer mortality rates, but RT increased the overall mortality rate (RR=1.23, p=0.03). There appears to be a small but positive effect of RT on survival that is masked by cardiotoxicity and inadequate RT in the older RCTs. For female patients with axillary sampling, RT reduced locoregional and overall recurrence rates (p<0.00001 and p=0.0003 respectively) but had no significant effect on breast cancer mortality or overall mortality rates. In patients with mastectomy alone or with axillary sampling, recurrence and survival in controls (no RT) was much worse than in the ALND groups, suggesting that many of these patients may have been clinically but not pathologically node negative.

There may be subgroups of patients with node-negative cancer, such as those with large tumours (T3N0) or with other risk factors for which RT is beneficial. The meta-analysis by Rowell (83) of female patients with node-negative cancer who had mastectomy with axillary clearance and optimal RT included the Stockholm A and DBCG 82b&c studies. It found that PMRT resulted in 83% reduction in risk of LRR (p<0.00001) and 14% improvement in survival rate (p<0.16). They concluded that the use of PMRT in patients with node-negative cancer needs re-evaluation and should be considered for female patients with ≥2 risk factors (LVI, grade 3 tumour, tumours >2 cm, close resection margin, premenopausal, or age <50 years). Those without any risk factors had baseline LRR risk of ≤5%, whereas the risk was ≥15% with two or more risk factors.

Retrospective exploratory subgroup analyses suggest stronger benefits of PMRT for specific molecular subgroups. The greater benefit on luminal A subtype appears to be consistent. The review by Blitzblau and Horton (122) concluded that biologic subtype is an important predictor of locoregional recurrence and should be considered along with TNM parameters in determination of benefit of PMRT. The review also suggested that subtype be incorporated into future radiation clinical trials.

Go to Recommendations (Section 1)

Question 2b. Locoregional Radiotherapy vs Breast/Chest Wall Irradiation

Although the role of postoperative radiation is well-established in female patients with LABC, the optimal extent of radiation is less clear. Available data are limited. Techniques of breast/chest wall irradiation may provide some dose to adjacent lymph nodes in the axillary and IMC, limiting the ability of trials to detect the contribution of benefit of radiation to each component region.

The prospective nonrandomized study by Stemmer et al (24) found better survival rates for patients who received IM node RT (DFS 73% vs 52%, p=0.02; OS 78% vs 64%, p=0.08).

The three main RCTs investigating extent of radiation are MA.20 (32,33,94), EORTC 22922/10925 (29-31,92,93), and a French study by Hennequin et al (28) (see Table 4). The studies evaluated the role of IM node irradiation (and MS in some trials) in breast cancer (early or locally advanced). Improvements in survival rates of approximately 3% were found, although these were often not statistically significant. Olson et al (27) suggested that a

randomized trial of approximately 8000 female patients would be needed to enable identification of a statistically significant 3% difference in OS. A meta-analyses of these three studies (25) concluded regional RT to IM and MS nodes improves DFS, OS, and DMFS in Stage I-III breast cancer. Whether or not this is clinically relevant may depend on individual patient factors and baseline risk.

A total of 7170 patients were included in the three studies, of which it was estimated that approximately 36% of the patients met our definition of LABC. These studies do not therefore meet our inclusion criteria based on the proportion of patients with LABC compared to those with early cancer. However, we consider the positive benefit relevant as typically the relative benefit of radiation is the same regardless of risk stratum. The absolute benefit increases with increased risk. It is reasonable to conclude that the subgroup of patients with LABC would likely have even greater benefit than that found for early plus LABC combined. It is hoped that full publication of the trials will include sufficient detail to confirm this. Both the meta-analysis and the literature search for this guideline did not locate any other trials on this topic (regardless of cancer stage) so it is unlikely that we have introduced selection bias by commenting on these trials.

Adverse effects of RT are as indicated in Question 2a, although lymphedema may be more severe when locoregional radiation is used. The need for 3D treatment planning is likely greater with locoregional radiation than with breast/chest wall irradiation in order to minimize cardiovascular and pulmonary adverse effects. In the absence of 3D planning, these adverse effects may outweigh benefits in lower risk patients.

Go to Recommendations (Section 1)

Question 2c. Radiotherapy Following Pathologically Complete Response

No prospective RCTs addressed this question. A systematic review of retrospective studies (35) concluded Stage II (T1-2N0-1) with pCR had <10% risk of LRF without radiation. The studies summarized in this section, although not prospective, are considered the major studies relevant to LABC and are often cited in discussions on this topic (sometimes without referring to the retrospective design).

The study at the MD Anderson Cancer Center by McGuire et al (123) included 226 patients with pCR who were treated by mastectomy ± RT. PMRT was decided by the patient and physician. Although retrospective and nonrandomized, data are reported for the subgroup of 74 patients with pCR who were clinically Stage III at initial presentation. Of these, 62 received PMRT and 12 did not. PMRT was associated with a significantly lower 10-year rate of locoregional recurrence (7.3% vs 33.3%, p=0.04), and significantly higher DMFS (88% vs 41%, p=0.0006), cause-specific survival (CSS, 87% vs 40%, p=0.0014), and OS (77% vs 33%, p=0.0016). A retrospective review (124) at the same centre included 109 female patients with pCR (29% Stage IIA, 29% Stage IIB, 27% Stage IIIA, 6% Stage IIIB, 6% Stage IIIC) treated by BCS plus RT (breast conserving therapy, BCT). It found 2.7% LRR at median 6.6 years follow-up (LRR 3.1% Stage IIB, 4.8% Stage III) and a ten-year survival rate of 92%. The difference in recurrence/survival rates between the mastectomy plus RT and BCT studies may be partially due to the different distribution of patients with Stage III cancers.

The abstract by Fasola et al (125) reported on 32 patients with pCR (22 PMRT, 10 non-PMRT) and stated that RT appears to improve local control (100% vs 89%, p=0.3) and DMFS

rate (100% vs 78%, p=0.08) at three years. In the overall trial, most patients were Stage IIA, IIB or IIIA, although the distribution for those with pCR was not stated.

The recent NSABP B-18 and B-27 retrospective analysis (51) analysis found >10% ten-year risk of LRR for mastectomy patients without PMRT with residual nodal involvement (ypN+), whereas the risk was <10% for patients with pCR in both the breast and lymph nodes. LRR for subgroups with pCR was 6.2% T3N0 (N=16), 0% T1-2N1 (N=21), and 0% T3N1 (N=11) compared with 12.3% overall and 22.5% for T3N1 that remained N+ (N=128). They caution that the study had small numbers for some of the mastectomy subgroups and only included operable breast cancer (T1-3N0-1M0). LRR are expected to be higher for more advanced cancers (T4, N2).

These studies suggest a value to RT even in cases of pCR. In the absence of RCTs to the contrary, RT should not be discontinued solely because of pCR.

A meta-analysis of seven German neoadjuvant studies by von Minckwitz et al (126) and a review based on the experience of the German Breast Group (127) suggest that the prognostic value of pCR depends on subtype. pCR is associated with better outcome for hormone receptor negative (HR–: HER2+/HR- or HER2-HR- [TN]), and some more aggressive HER2-/HR+ tumours. The review by Blitzblau and Horton (122) concludes that biologic subtype is an important predictor of locoregional recurrence and should be considered along with TNM parameters in determination of benefit of PMRT. The review also suggests that subtype be incorporated into future radiation clinical trials.

The NSABP B51 study will address the question for patients initially cN1 who become ypN0; however, it will not be completed until 2028.

Go to Recommendations (Section 1)

Question 3. SLNB or Axillary Dissection for Staging after Neoadjuvant Chemotherapy

SLN ID rates depend on the experience of surgeons and technique used. Breslin et al (128) found SLN ID rates improved from 65% with the earlier patients to 94% later in the study. In the B-27 trial (129) (not in Table 6 because of the apparently retrospective design) the SLN ID rate increased from 82% in 1996 to 90% in 2000. The ACOSOG Z1071 trial (36,37) is one of the largest and most recent studies and was conducted in patients with node-positive cancer (>85% LABC). They found 93% SLN ID rate for cN1 tumours and 89% for cN2 tumours. This study found detection with radiolabelled colloid much better than blue dye alone (94% colloid plus dye, 91% colloid, 79% dye). B-27 also confirms this finding (89% vs 78% with dye). The SN FNAC study (38,39) found the FN rate decreased with the number of SLN removed (FN rate 19% for 1 SN, 7% for ≥2 SN) and was consistent with the SENTINA trial findings.

Timing of SLNB

Four studies (46-49) reported SLN ID rates of 98%-99% in patients with cN0 cancer when SLNB was performed before NACT. This is higher than for most of the studies in which SLNB was performed after NACT; for these the median ID rate was 93% for patients with cN0 cancer and 88% overall. The SENTINA study (46) found that in patients with SLNB before NACT, repeat SLNB after NACT had only 76% SLN ID rate and 61% FN rate. Therefore SLNB should not be performed both before and after NACT in the same patient. The SENTINA study also found lower SLN ID rates for patients initially cN+ converted to clinically ycN0 than for patients cN0 at the start (80% vs 99%), although Papa et al (47) found lower ID rates in

patients with cN0 cancer after NACT therapy than before (87% vs 98%). There is some concern about the SLNB results in the SENTINA study; however, as the post-NACT results are lower than for most other studies in Table 6 (80% vs median 88% for all studies).

The disadvantage of performing SLNB before NACT is that a separate operation would be required; however, results may more accurately reflect pretreatment characteristics. The data suggest the identification rate may be higher before NACT in patients with cN0 cancer. There is some concern that NACT may eliminate disease in the SLN but not all the nodes, such that the FN rate may be higher after NACT. The included studies indicated that most trials have been designed to perform SLNB after NACT. This may be based on an assumption that nodal status after NACT is more important than before NACT, or solely because it is easier to do one operation. The studies in the literature review do not address differential treatment decisions based on nodal SLN status.

As discussed in the next subsection, SLNB is feasible after NACT, but there are no completed trials designed to determine whether SLNB should be before or subsequent to NACT. Although the ongoing trials listed may address this timing issue, no conclusions can be made regarding the most appropriate timing of SLNB.

SLNB after NACT

The studies in Table 6 had a median SLN ID rate of 88% and FN rate of 10%. The identification rate in some studies is lower than is recommended in the SLNB guideline (40). There are differences in levels of proficiency in performing SLNB, with some centres having results considered unacceptable. Most of the studies were summarized in four meta-analyses, in which the SLN ID rate ranged from 90-94% for patients with clinically node-negative cancer and 88% for patients with clinically node-positive cancer. The FN rates for pooled data from studies including both patients clinically node negative and node positive (determined before NACT administration) ranged from 7%-10.5%, which is not dissimilar to the recommended FN rates for early breast cancer surgery (40). The meta-analysis by Tan et al (104) included only patients cN0 after NACT and found an ID rate of 94% (86%-100%), a FN rate of 7%, and accuracy of 95% for this subset of patients. Although the studies in the meta-analysis included patients with T1-4 N0-2 cancers, and did specifically focus on LABC, results are similar to those for patients with cN0 cancer in Table 6. In the current review, the median ID rate for patients with cN0 cancer was 93% (81%-98%), or 95% (87%-98%) after exclusion of two studies that did not use radiotracer for SLN ID. In patients with clinically positive nodes SLN detection was slightly lower, with the median SLN ID rate for the included studies being 85% (89% in the subset of studies that had subgroups of patients with clinically negative and clinically positive nodes).

The data support the feasibility of SLNB in patients who are clinically node negative or node positive before NACT. Although there is still some controversy, several recent reviews (130-132) suggest that that completion ALND might be omitted in patients clinically node negative and with negative SLN after NACT ($ypN0_{SN}$). For LABC, this would apply to T3N0 cases. However, it should be noted that most patients with LABC are pathologically node positive before NACT, even those considered clinically negative; therefore, a high proportion may still be pathologically node positive after neoadjuvant therapy.

ALND results in more complete removal of lymph nodes and therefore there are fewer nodes left that could contain residual cancer. As indicated previously, training and proficiency of surgeons plays a large role in whether SLN ID rate is acceptable.There is no

evidence as to whether this has clinical impact on treatment or survival. In early breast cancer (T1-2N0), the Z0011 trial (44) found ALND did not improve survival rates in patients with positive SLN who received lumpectomy plus whole-breast irradiation plus adjuvant systemic therapy. ALND is more invasive surgery than SLNB, there is higher risk of surgical complications, and higher risk of lymphedema occurring or being more severe. More than 80% of female patients undergoing ALND have at least one postoperative complication in the arm and psychological distress is common (43). In the Z0011 trial (44,45) ALND added to SLNB resulted in more wound infections, axillary seromas, paresthesias, and subjective reports of lymphedema than SLNB alone. Schrenk et al (133) reported significant increase in upper and forearm circumference, higher subjective lymphedema, pain, numbness, and motion restriction for ALND compared with SLNB. Lymphedema is associated with cosmetic deformity, discomfort, infection, reduction in arm function, and emotional distress (134). Some people have allergies to blue dye used in SLNB.

Although the SLNB technique is comparable in patients receiving NACT (the bulk of whom have LABC), the clinical implications of a FN SLNB are not known in these patients. In patients with early breast cancer, a FN rate of <10% is considered acceptable (40) given that high-risk patients who may be falsely deemed node negative are likely to receive further treatment in the form of systemic chemotherapy. This, in addition to local or regional radiation, may provide the axillary sterilization of residual disease and confer a low rate of axillary recurrence. This is not the case in patients who would have already received all their systemic chemotherapy preoperatively; therefore, residual disease may be untreated and become clinically relevant. Additionally, residual disease (in the axilla or elsewhere) following NACT is presumably resistant to first-line systemic chemotherapy and this residual disease may be very different than disease present in the axilla de novo. In the absence of long-term safety or locoregional outcome data, axillary node dissection remains the standard of care.

Go to Recommendations (Section 1)

Question 4. Treatment of LABC Nonresponsive to NACT

The GeparTrio study (53,108) found early non-responders to two cycles of TAC had better DFS for TAC×2→NX than TAC×2→TAC×4 (HR=0.59, 95% CI=0.49-0.82, p=0.001). This study suggests a role for second-line chemotherapy, at least for particular subgroups of patients. Response-guided therapy (TAC×8 or TAC-NX) was better than TAC×6 for DFS overall (HR=0.71, p<0.003) and for subgroups HR+ (luminal A, luminal B) but not HR- or TN, whereas pCR predicted improved DFS in TN, HER2+ (nonluminal), and luminal B (HER2-).

Several RCTs and reviews indicate that different subgroups of patients may benefit from different neoadjuvant treatments. The NCCN guideline (12) lists several neoadjuvant/adjuvant regimens and notes that preoperative systemic therapy for HER2+ tumours should include trastuzumab along with chemotherapy, whereas patients with HR+ cancer may be administered endocrine therapy and chemotherapy (or consideration of endocrine therapy alone in postmenopausal patients). For patients with HER2+ cancer, a meta-analysis reported 46% pCR with trastuzumab plus NACT vs 25% with NACT alone (135). Several of the most recent RCTs (136-144) reported pCR of 52%-74% for HER2+ disease treated with chemotherapy plus trastuzumab. Dual blockade is also being investigated. The NeoALTTO study (145) found higher pCR rates for lapatinib + trastuzumab + paclitaxel than

for trastuzumab + paclitaxel or lapatinib + paclitaxel (pCR 47%, 28%, 20%, respectively). The NeoSphere trial (146) found higher pCR rate (measured in breast only) with pertuzumab + trastuzumab + docetaxel compared with trastuzumab plus docetaxel (56% vs 29%). The studies have been included in the recent systematic review on HER2-targeted therapy in neoadjuvant trials (147). Rates are reportedly higher in patients with HER2+ HR- cancer than HER2+ HR+ cancer [e.g., 89% vs 37% (137), 70% vs 57% (144)]. Triple-negative cancers commonly have higher response to chemotherapy alone than other cancer subtypes; a meta-analysis found pCR of 33% for TN and for HR-/HER2+ (no anti-HER2+ therapy) compared with 16% for HR+HER2+ (no anti-HER2+) and 9% HR+HER2- (135). A small study by Frasci et al (148) reported 98% clinical response and 62% pCR in TN cancer using cisplatin, epirubicin and paclitaxel. Masuda et al (149) reported 28% pCR in TN cases, although this varied according Lehmann subtype determined by gene expression microarrays from 0% for basal-like 2 to 52% for basal-like 2. A systematic review on neoadjuvant hormonal therapy in HR+ cancer (150) found hormonal therapy demonstrated similar efficacy to NACT, aromatase inhibitors were superior to tamoxifen, and tumour response rates increased when administration was extended beyond 3-4 months. A recent review (151) discussed some of the issues in management of inflammatory breast cancer, including chemo-radiotherapy and radical RT.

The guideline by Health Canada (55) recommends that patients who progress on an anthracycline-based regime proceed to taxane chemotherapy, whereas the Consensus Panel for Neoadjuvant Chemotherapy (13) suggests that patients who progress on the first-line chemotherapy (generally anthracycline-based) benefit further from crossover to an alternate, non-cross-resistant therapy, most frequently a taxane. Because these guidelines were published in 2004 when taxane-anthracycline combinations were not routine, a current interpretation would be that patients who progress on the anthracycline component of anthracycline/taxane chemotherapy administered as part of the first-line regimen should then proceed to the second part of this first-line regimen (proceed to taxane).

Our overall conclusion is that patients whose tumours do not respond to first-line chemotherapy (plus HER2-targeted agents or endocrine therapy if appropriate) may proceed to surgery if the disease is operable or to additional systemic chemotherapy and/or preoperative radiation. The failure to respond to NACT is considered a poor prognostic sign and clinical trials should be designed for this patient cohort, evaluating novel treatment modalities such as concurrent chemotherapy and radiation, which is currently being done on an individual basis (i.e., concurrent cisplatin radiation for progressive triple-negative disease).

Go to Recommendations (Section 1)

OTHER TRIALS PLANNED OR IN PROGRESS

Table 9 indicates some other trials the authors are aware of that may address the questions in this review in the future. This list is not meant to be exhaustive and other trials are likely ongoing or planned.

CONFLICT OF INTEREST

Information regarding conflict of interest declarations can be found at the end of Section 3.

JOURNAL REFERENCE

The recommendations of this EBS have been published in the journal *Current Oncology* in a supplement on breast cancer:

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A complete list of the members of the Breast DSG and the Working Group with their affiliations is provided in Appendix A.

Table 1. Results of fourth cycle and fifth EBCTCG meta-analyses.

a) Fourth Cycle (15)

Nodal surgery	Nodal status	N	5-year local recurrence risk (RT vs no RT)	15-year breast cancer mortality (RT vs no RT)	15-year mortality, any death (RT vs no RT)
Mastectomy +axillary clearance (25 trials)	Positive or negative	9933	5.2% vs 20.2%, p<0.0001	51.1% vs 55.2%, p=0.006	57.1% vs 60.2%, p>0.1
	Negative	1428	2.3% vs 6.3%, p=0.0002	31.1% vs 27.7%, p=0.01	42.4% vs 38.2%, p=0.0002
	Positive	8505	5.8% vs 22.8%, p<0.00001	54.7% vs 60.1%, p=0.0002	59.8% vs 64.2%, p=0.0009
	• 1-3 positive	1890	4.0% vs 15.5%, p<0.00001*	43.3% vs 47.7%, p=0.24	51.1% vs 52.7%, p>0.1
	• ≥4 positive	1868	11.6% vs 26.3%, p<0.00001*	68.0% vs 70.3%, p=0.14	70.8% vs 72.4%, p>0.1
	• T1	Not reported	4.8% vs 22.1%, p<0.00001*	47.8% vs 56.8%, p=0.007*	50.1% vs 57.7%, p=0.003*
	• T2		5.9% vs 30.3%, p<0.00001*	65.0% vs 68.4%, p=0.09*	64.5% vs 69.7%, p=0.09*
	• T3/T4		8.4% vs 35.6%, p<0.00001*	70.8% vs 78.2%, p=0.25*	70.1% vs 75.8%, p=0.20*
	• Systemic†	Not reported	6.4% vs 24.8%, p<0.00001*	57.2% vs 63.5%, p<0.001*	58.8% vs 63.6%, p=0.0002*
	• No systemic		4.1% vs 17.3%, p<0.00001*	48.6% vs 51.1%, p=0.46*	70.3% vs 68.5%, p=0.73*
Mastectomy + axillary sampling (4 trials)	Negative	449	6.1% vs 24.5%, p<0.00001*	32.9% vs 40.2%, p=0.4*	48.0% vs 49.6%, p=0.8*
	Positive	198	13.8% vs 22.5%‡, p<0.00001*	66.3% vs 68.9%, p=0.3*	72.6% vs 69.9%, p=0.4*
Mastectomy only (7 trials)	Negative	3904	5.6% vs 23.3%, p<0.00001*	45.4% vs 47.3%, p=0.8*	67.5% vs 65.7%, p=0.3*
	Positive	1673	11.6% vs 33.5%, p<0.00001*	54.3% vs 58.6%, p=0.2*	73.1% vs 74.5%, p=0.2*

b) Fifth Cycle (16)

Nodal surgery	Nodal status	N	10-year local recurrence risk (RT vs no RT)	20-year breast cancer mortality (RT vs no RT)	20-year mortality, any death (RT vs no RT)
Mastectomy + axillary dissection to at least level II (14 trials)	Negative	700	3.0% vs 1.6%, p>0.1 (NS)	28.8% vs 26.6%, RR=1.18, p>0.1 (NS)	47.6% vs 41.6%, RR=1.23, p=0.03
	Positive	3131	8.1% vs 26.0%, p<0.00001	58.3% vs 66.4%, RR=0.84, p=0.001	65.4% vs 70.4%, RR=0.89, p=0.01
	1-3 positive	1314	3.8% vs 20.3%, p<0.00001	42.3% vs 50.2%, RR=0.80, p=0.01	53.5% vs 56.5%, RR=0.89, p>0.1 (NS)
	• + systemic§	1133	4.3% vs 21.0%, p<0.00001	41.5% vs 49.4%, RR=0.78, p=0.01	52.6% vs 55.5%, RR=0.86, p=0.08
	≥4 positive nodes	1772	13.0% vs 32.1%, p<0.00001	70.7% vs 80.0%, RR=0.87, p=0.04	75.1% vs 82.7%, RR=0.89, p=0.05
	• + systemic§	1677	13.6% vs 31.5%, p<0.00001	70.0% vs 78.0%, RR=0.89, p=0.08	74.9% vs 82.0%, RR=0.90, p>0.1 (NS)
Mastectomy + axillary sampling (9 trials)	Negative	870	3.7% vs 17.8%, p<0.00001	32.0% vs 35.8%, RR=0.97, p>0.1 (NS)	46.1% vs 49.9%, RR=1.00, p>0.1 (NS)
	Positive	2541	6.3% vs 37.2%, p<0.00001	55.6% vs 68.2%, RR=0.74, p<0.00001	63.1% vs 71.8%, RR=0.79, p<0.00001
Mastectomy only (4 trials)	Clinically negative	2896	16.1% vs 35.4%, p<0.00001	50.8% vs 53.1%, RR=0.97, p>0.1 (NS)	62.8% vs 61.8%, RR=1.06, p>0.1 (NS)
	Clinically positive	1481	18.0% vs 45.0%, p<0.00001	56.6% vs 63.3%, RR=0.86, p=0.03	67.1% vs 71.5%, RR=0.91, p>0.1 (NS)

Abbreviations: N, number of patients; NS, not significant

Notes: 1. Tumours that are T3/4 (any nodal status), with ≥4 positive nodes (any size), or T2 with positive nodes are considered as LABC in the current guideline and thus most relevant. Most patients categorized as node negative or T1 will not be LABC, although T2 will have large portions of both early and LABC cancers.

2. Full data for PMRT was published in March 2014 (16) when the guideline was undergoing final editing before internal review.

3. PMRT in the fifth cycle analysis included the chest wall plus supraclavicular and/or axillary fossa plus internal mammary chain

* Values are from forest plots (Webfigures 6b, 8a, 8b) throughout the entire period of follow-up (both during and after the first 15 years), and are slightly different than in Webfigures 2a-e which give mortality at 15 years. Significance values use the entire follow-up.

† Chemotherapy or tamoxifen

‡ **D**ata inconsistent: Webfigure 8b and Figure 4 report values of 22.5% and 50.1% respectively

§ Usually cyclophosphamide, methotrexate, and fluorouracil (CMF) or tamoxifen in both trial groups. Tamoxifen given to ER- women in both groups is considered as no systemic therapy.

Go to Recommendations (Section 1) Go to Results (Section 2) Go to Discussion (Section 2)

Table 2. Subset of postmastectomy radiotherapy trials using anthracycline-based systemic therapies.

Study Name, Reference, Enrolment period	N	Patient characteristics (stage, nodes)	Surgery	Radiotherapy	Systemic therapy	Follow-up	Recurrence or survival outcomes (RT vs no RT) (OR from meta-analyses)	Other adverse effects
DFCI Boston Griem, 1987 (119) Odds ratios (OR) from (17,119) 1974-1984	206	Stage II-III, T1-3N+ or T3N0 Randomized to type of chemo, and then to RT or not	RM (MRM) +ALND	BW, AF RT administered after chemo to chest wall (tangent fields) and nodal regions, including supraclavicular and upper axillary nodal regions. IM not routinely treated. Lower axilla treated only if ≥50% of axillary nodes were involved.	CMF, MF, or AC, see below	35 pts withdrew after randomization (34 refused RT, 1 in observation arm received RT)	RT + chemo vs chemo, ITT analysis: Local failure first: 5% vs 14%, p=0.03 Local Failure: 7% vs 17%, p=0.03 (OR=0.30) Any failure: 39% vs 38%, p=0.57 (OR=1.03) OS: 66% vs 72%, p=0.20 (OR=1.17; OR=1.00 at latest follow-up)	
	83	Moderate risk subgroup N1or T3N0; median 1.5 positive nodes, median 3.1 cm		4050-5000 cGy, median 4500 cGy	8 cycles CMF vs MF then randomized to RT	Median follow-up 53 m	ITT analysis: local failure first: 2% vs 5%, p=0.61 any failure: 21% vs 25%, p=0.71 OS: 77% vs 85%, p=0.39 (OR=1.04 at 5 y)	
	123	High-risk subgroup N2-3 or ≥1 nodes in axillary apex Median 9.1 positive nodes, median 3.6 cm		2250-5400 cGy, median 4500 cGy	AC 15 vs 30 w (5 or 10 cycles) then randomized to RT	Median follow-up 45 m	ITT analysis: Local failure first: 6% vs 20%, p=0.03 Distant failure first: 44% vs 27% Any distant failure: 48% vs 38% Any failure: 51% vs 47%, p=0.22 OS: 59% vs 63%, p=0.27 (OR=1.18 at 5 y) Analysis by Treatment received: Local recurrence 2% vs 20%, p=0.007 cardiotoxicity: 4.5% vs 5.1%, p>0.99	cardiotoxicity: 4.5% vs 5.1%, p>0.99

Study Name, Reference, Enrolment period	N	Patient characteristics (stage, nodes)	Surgery	Radiotherapy	Systemic therapy	Follow-up	Recurrence or survival outcomes (RT vs no RT) (OR from meta-analyses)	Other adverse effects
DFCI Boston Shapiro, 1998 (118) See also Griem, 1987 (119); 1974-1985	276	≥4 positive axillary lymph nodes or at least 1 positive axillary apical level III lymph node; median tumour size 4 cm (<1 to 16 cm), median 7 positive nodes (0-41); 7% Stage I, 72% Stage II, 21% Stage III	96% mastectomy, 4% BCS	chest wall and regional lymph nodes; of those receiving RT, 91% had breast or chest wall RT and included supraclavicular and axillary nodes in most pts, breast tangents only included mammary nodes in 51 pts and did not include them in 19 pts, unclear in 20 pts. Retrospectively categorized cardiac RT dose as low (right-sided cancers with tangential fields), moderate (left-sided cancers with tangential fields), or high (separate anterior field for IM nodes)	Randomized to AC for 5 or 10 cycles then secondary randomization to RT or observation; some pts who did not participate in randomization received RT	Median 6 y follow-up		Risk of cardiac events per patient RT vs no RT (5 cycles AC): 1.5% vs 6.9% RT vs no RT (10 cycles AC): 14.8% vs 9.8% RT is protective with 5 cycles AC but negative cardiac effect with 10 cycles AC (this appears to be inconsistent); there may be interaction between AC and RT or due to low number of events
Coimbra Gervasio , 1998 (152,153) [abstracts] Cited in (17,64,78) 1980-1983	112	Node positive, Stage II	MRM	BW, AF, IMC chest wall, supraclavicular lymph nodes, axillary lymph nodes, IM nodes; 36-45 Gy in 12 fractions, 4 w.; megavoltage/ orthovoltage, prechemo	AC, 6-11 cycles Arm A: AC alone, Arm B: AC+RT	Arm B (AC+RT) vs Arm A (AC)	OS: 32.7% vs 35.1% (OR=1.00 from EBCTCG 2000; OR=1.11, 95% CI=0.51-2.43 in Whelan) Any recurrence: 43.6% vs 57.9% (OR=0.56, 95% CI=0.27-1.19) Recurrence time lapse 44.4 m vs 38.6 m, not significant	Cardiotoxicity: 23.6% vs 19.2%, p>0.05
MD Anderson 7730B Buzdar, 1984 (154) 1977-1980	97	Operable, node positive; included N2-3 and inflammatory if operable. 60% Stage II, 25% Stage III, 15% Stage IV; 31% N1, 39% N2, 30% N3	29% RM, 54% MRM, 15% ext simple	BW, AF, IMC, S postoperative	FAC ± BCG for ≈ 8 cycle then CMF ± BCG continued for 2 y, also randomized to RT starting in 1978	Median follow-up of 33 m	No significant difference in DFS ± BCG (p=0.21) and ± RT (p=0.99) 3y DFS: 64% vs 69%, p=0.79 (OS 35% vs 56% in Recht; OS at 5 y 28% vs 44% in EBCTCG)	
Helsinki Blomqvist, 1992 (117)	199 (99 for group	Inclusion criteria was N+ Stage II (T1-2N1) Group 3: 62% N1, 34% N2+, 4% unknown;	MRM + axillary evacuation	BW, AF, IMC RT between second and third chemo cycles 45 Gy in 15 fractions to	CAFt (cyclophosphamide, doxorubicin, futrafur) for 8 cycles	5-y and 8-y results	Comparison of Group 3 (RT + chemo) vs 2 (chemo).	• Grade III/IV hematological adverse effects: 0% RT, 32% RT +

Study Name, Reference, Enrolment period	N	Patient characteristics (stage, nodes)	Surgery	Radiotherapy	Systemic therapy	Follow-up	Recurrence or survival outcomes (RT vs no RT) (OR from meta-analyses)	Other adverse effects
1981-1984	2+3) 51% age <50 Group 2: 73% N1, 17% N2+, 10% unknown; 62% age <50		operative area (oblique field); supraclavicular, axillary, parasternal areas (anterior fields); supplemented with 30 Gy in 10 fractions from a posterior axillary field	1. RT (N=50) 2. CAFt (N=52) 3. RT + CAFt (N=47) 4. RT+ CAFt + TAM (N=50)		Local control, 5 y, 93% vs 76%, p=0.14 OS: 72% vs 87% @ 5 y, 65% vs 69% @ 8 y DFS: 64% vs 65% @ 5 y, 56% vs 56% @ 8 y Distant relapse-free survival: 64% vs 73% @ 5 y, 54% vs 59% @ 8 y For local control: RT≈ chemo but RT+ chemo better; For OS or DFS: chemo better than RT, chemo + RT ≈ chemo	chemo, 6% chemo, p=0.0001 • Radiation pneumonitis: 4% RT vs 23% RT + chemo • Discontinued due to adverse effects (mainly GI): 0% RT, 36% RT+ chemo, 23% chemo • Chemo dose reduction: 28% RT + chemo, 17% chemo • CAFt associated with considerable adverse effects
ECOG EST3181 Olson, 1997 (116) 1982-1987	312	Technically resectable, non-inflammatory LABC. Stage III Included T1 or T2 lesions fixed to the underlying muscle or having N2 LN disease, T3N1-2 or T3 with muscle involvement, T4N0-2 (except T4d). By 1992 AJCC-TMN system, 2% IIA, 5% IIB, 53% IIIA, 40% IIIB 42% cN0, 44% cN1, 14% cN2; 96% pN+, median 7 positive LN	MRM or RM, AD with 8+ LN removed (median 17)	Chest wall, supraclavicular LN, ax LN, IM nodes 46 Gy in 23 fractions over 4.5 w using 2 Gy/fraction on chest wall (1 cm of bolus used on chest wall every other day starting first day) and regional LN areas (ipsilateral axillary apex, supraclavicular fossa,IMC). Compensating filters used for tangential fields. N2 or N1 + extranodal microscopic extension received additional boost to midplane of axilla to total dose of 50 Gy Energy: megavoltage, Cobalt-60, 4 MV or 6 MV photons	CAF +H + TAM 6 cycles chemo/ hormonal therapy (CAF + TAM + fluoxymesterone) Prophylactic RT vs observation at end of chemo if still disease free. For the observation group, RT administered only if locoregional recurrence	Median 9.1 y follow-up, RT vs observation Submission of pathology slides for eligibility review was required for all pts.	Median 9.1 y follow-up, RT vs observation • Relapse rate (all relapses): 60% vs 56%, p=0.68 • OS: 46% vs 47%, p=0.94 From Whelan 2000 meta-analysis (17): Any recurrence (RT vs no RT): OR=1.19 (95% CI=0.76-1.87) Locoregional recurrence: OR=0.38 (95% CI=0.19-0.76) Mortality: OR=1.01 (95% CI=0.65-1.58)	• 7.5% severe adverse effects (2.7% skin and mucosa; 2.0% hematologic; 0.7% infectious, respiratory, hepatic, other) vs 3% • 3 vs 7 mild to moderate cardiac toxicities • 3 vs 0 severe grade 3 cardiac toxicities • At 12 m, 12% lymphedema and limited range of motion, 10% sequelae involving the lungs and pleura, 10% involving the heart

Study Name, Reference, Enrolment period	N	Patient characteristics (stage, nodes)	Surgery	Radiotherapy	Systemic therapy	Follow-up	Recurrence or survival outcomes (RT vs no RT) (OR from meta-analyses)	Other adverse effects
Finnish Grohn, 1984 (155) Klefstrom, 1987 (84) 1976-81 Note: timing of chemo and RT compared with surgery is different in the two reports	120	Operable Stage III, T3N0-2 (37 N0, 82 N1-2); after pathologic re-examination, 79N+ of which 47 N2+ RT (N=40), chemo (N=40), or combined RT & chemo (N=39)	MRM, leaving the pectoral fasciae and muscles intact. Axillary fat including lymph nodes removed in all cases	BW, AF, IMC RT 45 Gy in 15 fractions over 3 w, starting 3-4 w (9-10 w) after surgery, with fields covering supraclavicular and intraclavicular regions, axilla, parasternal regions, and chest wall. Posterior ax portal was irradiated with 30 Gy over 2 w in 10 fractions. Midline dose in axilla was ≈ 50 Gy at 5 w. Total RT treatment time 5 w Energy: Co60 (megavoltage)	VAC (+ levamisole immunotherapy to all groups in early years; first 60 pts) 6 cycles of chemo starting an average of 7-8 w after surgery; when combined with RT started 2 w after discontinuation of RT	5-y follow-up results Staging of the disease was based on postsurgical pathologic assessment of the tumour and ax LNs.	<u>Recurrent disease</u> RT + chemo: 5 pts (13%) RT alone: 27 pts (68%) Chemo: 21 pts (53%) Combined therapy had higher DFS and OS DFS: RT + chemo vs RT ($P<0.001$); RT + chemo vs chemo ($P<0.001$) OS: RT + chemo vs RT ($P<0.001$); RT + chemo vs chemo:($P<0.01$) First site of recurrence predominantly local in chemo group but metastatic in those with RT Levamisole appeared to increase DFS and OS in all 3 arms ($p=0.035$ and $p=0.019$) From Whelan 2000 meta-analysis: Any recurrence (RT + chemo vs chemo): OR=0.21 (95% CI=0.08-0.55) Locoregional recurrence: OR=0.11 (95% CI=0.04-0.34) Mortality: OR=0.17 (95% CI=0.04-0.67)	Radiotherapy was well tolerated. Only two pts had mild leukopenia, and two had mild thrombocytopenia All pts treated by chemotherapy developed total but transient alopecia. Most chemo pts experienced nausea and vomiting. Three pts had nonlethal transient arrhythmias and one skin rash due to chemotherapy

Study Name, Reference, Enrolment period	N	Patient characteristics (stage, nodes)	Surgery	Radiotherapy	Systemic therapy	Follow-up	Recurrence or survival outcomes (RT vs no RT) (OR from meta-analyses)	Other adverse effects
Metaxas Athens Papaioannou, 1983 (120) 1978-1981	105	Stage IIB-III; most Stage III LABC. Pts ≤75 y with tumours ≥5 cm. Included T3, T4a, and some T4b, all N categories, but only M0. Control group was not equivalent in number of positive lymph nodes Histological diagnosis established after open biopsy or needle aspiration. Open biopsy done at another institution was accepted, after review of histological sections, only if protocol treatment could begin within 2 w from biopsy	Total mastectomy including pectoralis fascia but not necessarily the muscles, plus complete axillary dissection , including resection of all three levels of axillary lymph nodes	BW, AF, IMC RT vs no RT. RT doses to regional LN bearing areas & chest wall were 4500 to 5000 rad for 5 w beginning 2-3 w after mastectomy. Energy: megavoltage	Vincristine +AC (day 1)+MF (day 2); 2 cycles before surgery and 10 cycles afterwards (cycles every 3-4 w) Pts received 10 cycles of chemo after RT (RT group) or directly after mastectomy (no RT group). Premenopausal pts had bilateral oophorectomy just before mastectomy. Postmenopausal pts (at least 1 y after menopause) received antiestrogens (Nolvadex) daily starting at the beginning of chemo. Premenopausal pts started Nolvadex the day after mastectomy. Novaldex continued to the end of chemo	205 pts enrolled, 78 disqualified, reported on 105 pts with at least 6 m follow-up, mean 23 m follow-up	Local recurrence: 8.3% vs 10.5%, p=NS All failures: 27% vs 21%, p=NS DFS of recurring pts: 17.4 m vs 20.1 m (P>0.1) Survival of recurring pts: 21.7 m vs 28.7 m (P<0.05)	• No serious local sequelae were encountered from mastectomy or RT, but complications of chemo were numerous, particularly in irradiated pts. • Moderate myelotoxicity was observed in 15% of pts, delaying chemo up to one m; occurred in 80% of chemo pts

Abbreviations: AC (or CA), cyclophosphamide + Adriamycin® (doxorubicin); AF, axilla and supraclavicular fossa; BCG, Bacillus Calmette-Guérin; BW, breast/chest wall; CAF, cyclophosphamide + doxorubicin (Adriamycin®) + 5-fluorouracil; CAFt, cyclophosphamide + doxorubicin + futrafur; chemo, chemotherapy; CMF, cyclophosphamide + methotrexate + fluorouracil; DFS, disease-free survival; H, halotestin; IM, internal mammary; IMC, internal mammary chain; ITT, intention to treat; M, mastectomy (type not further specified); MF, methotrexate + fluorouracil; MRM, modified radical mastectomy (includes level I and II dissection); OR, odds ratio; RM, radical mastectomy (breast, chest wall muscles, and level I-III ALND); S, boost to scar; SM or TM, simple or total mastectomy (no ALND); VAC, vincristine + doxorubicin + cyclophosphamide

Go to Recommendations (Section 1) Go to Results (Section 2) Go to Discussion (Section 2)

Table 3. Postmastectomy radiotherapy vs no radiotherapy: Studies from the literature search.

Study name, reference, enrolment period	# patients	Patient characteristics	Intervention	Follow-up	Recurrence or survival outcomes (RT vs no RT)	Other adverse effects, comments
Eastern Cooperative Oncology Group (ECOG) Olson , 1997 (116) 1982-1987	312	Non-inflammatory, technically resectable LABC, undergone MRM or standard radical mastectomy +AD <6 w before study entry, no recurrence during 6 cycles of systemic therapy Included T1 or T2 lesions fixed to the underlying muscle or having N2 LN disease, T3N1-2 or T3 with muscle involvement, T4N0-2 (except T4d). By 1992 AJCC-TNM system, 2% IIA, 5% IIB, 53% IIIA, 40% IIIB 42% cN0, 44% cN1, 14% cN2; 96% pN+, median 7 positive LN	Prophylactic RT vs observation (RT only if locoregional recurrence) 6 cycles chemo/hormonal therapy (CAF + TAM +fluoxymesterone), then randomized to RT (N=164) or observation (N=148) (plus RT if recurrence) 46 Gy in 23 fractions over 4 ½ w using 2 Gy/fraction on chest wall (1 cm of bolus used on chest wall every other day starting first day) and regional LN areas (ipsilateral axillary apex, supraclavicular fossa, IMC). Compensating filters used for tangential fields. N2 or N1 + extranodal microscopic extension received additional boost to midplane of axilla to total dose of 50 Gy RT: chest wall, supraclavicular LN, AX LN, IM nodes; Energy: megavoltage, Cobalt-60, 4 MV or 6 MV	Median 9.1 y follow-up	• Relapse rate (all relapses): 60% vs 56%, p=0.68 • OS: 46% vs 47%, p=0.94 From Whelan 2000 meta-analysis (17): Any recurrence: OR=1.19 (95% CI=0.76-1.87) Locoregional recurrence: OR=0.38 (95% CI=0.19-0.76) Mortality: OR=1.01 (95% CI=0.65-1.58)	Submission of pathology slides for eligibility review was required for all pts. 7.5% severe adverse effects (2.7% skin and mucosa; 2.0% hematologic; 0.7% infectious, respiratory, hepatic, other) vs 3% 3 vs 7 mild to moderate cardiac toxicities 3 vs 0 severe grade 3 cardiac toxicities At12 m, 12% lymphedema and limited range of motion, 10% sequelae involving the lungs and pleura, 10% involving the heart

British Columbia Randomized Trial
1979-1986
 	
Ragaz, 2005 (112)
Ragaz, 1997 (113)
	318	Premenopausal, Stage I or II with positive LNs after MRM + AD of level I & II nodes, median 11 nodes removed
		
		58% 1-3 LN+,
		35% ≥4 LN+,
		7% unknown
			Chemo ± RT
			• CMF chemo + RT (N=164) or chemo alone (N=154).
			• CMF (500 mg/m^2, 40 mg/m^2, 600 mg/m^2) intravenously every 21 days for 12 m (N=80) or changed to 6 m after 1981
			• 16 daily RT treatments over 3-4 w, administered between the fourth & fifth chemo cycles, total dose 35-37.5 Gy
			RT: 5-field technique
			Site: chest wall (2 tangential fields), mid axilla through a supraclavicular-axillary field with posterior axillary boost, IM field; covered locoregional
				Median 249 m follow-up, 20-y survival data according to number of positive LNs
				
				RT + chemo vs chemo
					• Event-free survival
					  • All: 35% vs 25%, RR=0.70 (95% CI=0.54-0.92), p=0.009
					  • 1-3 nodes: 44% vs 32%, RR=0.71 (95% CI=0.49-1.03)
					  • ≥4 nodes: 26% vs 12%, RR=0.68 (95% CI=0.45-1.03), P for interaction=0.8
					• Breast cancer-free survival
					  • All: 48% vs 30%, RR=0.63 (95% CI=0.47-0.83), p=0.001
					  • 1-3 nodes: 57% vs 41%, RR=0.64 (95% CI=0.42-0.97)
					  • ≥4 nodes: 34% vs 12%, RR=0.59 (95% CI=0.38-0.91), P for interaction=0.7
					• Systemic breast cancer-free survival
						• Long-term adverse effects, including cardiac deaths, were minimal for both arms.
						• Cardiac deaths 1.8% (3/164) vs 0.6% (1/154)
						• Non-breast cancer deaths 8.5% (14/164) vs 3.8% (6/154), p=0.11.
						• Other adverse effects similar except arm edema 9% (15/165) vs 3% (5/154)

Study name, reference, enrolment period	# patients	Patient characteristics	Intervention	Follow-up	Recurrence or survival outcomes (RT vs no RT)	Other adverse effects, comments
			lymph nodes including bilateral IMCs Energy: megavoltage, cobalt-60 CMF is now used infrequently, changes in RT technique		• All: 48% vs 31%, RR=0.66 (95% CI=0.49-0.88), p=0.004 • 1-3 nodes: 58% vs 44%, RR=0.68 (95% CI=0.45-1.04) • ≥4 nodes: 33% vs 11%, RR=0.63 (95% CI=0.41-0.97), P for interaction=0.7 • Breast cancer specific survival • All: 53% vs 38%, RR=0.67 (95% CI=0.49-0.90), p=0.008 • 1-3 nodes: 64% vs 53%, RR=0.67 (95% CI=0.42-1.06) • ≥4 nodes: 35% vs 17%, RR=0.66 (95% CI=0.43-1.01), P for interaction=0.9 • OS • 47% vs 37%, RR=0.73 (95% CI=0.55-0.98), p=0.03 • 1-3 nodes: 57% vs 50%, RR=0.76 (95% CI=0.50-1.15) • ≥4 nodes: 31% vs 17%, RR=0.70 (95% CI=0.46-1.06), P for interaction=0.7	• The incidence of second cancers and the associated mortality were distributed evenly between the two groups
British Columbia Randomized Trial (see above) Voduc, 2012 [Abstract] (87)	318	See above 34% Luminal A subtype (HR+, HER2-, Ki67 <14%)	See above Determined intrinsic subtype in 144 archival samples	Survival outcomes at 10 y	•BCSS, Luminal A: 82% vs 36%, p<0.001 •BCSS, non-Luminal A: 54% vs 49%, p=0.69 •LRFS, Luminal A: 88% vs 61%, p=0.005 •LRFS, non-Luminal A: 68% vs 57%, p=0.15	
British Columbia Randomized Trial (see above) and DBCCG 82b (see below) Laurberg, 2013 (86)	215	See above for BC trial and below for DBCCG 82b trial	Determined intrinsic subtype in 128 samples from BC trial and 87 samples from DBCCG 82b trial	LRFS outcomes at 20 y	LRFS outcomes, BC-trial •Luminal A: 94% vs 66%, p=0.05 •Luminal B: 60% vs 40%, p=0.66 •HER2-enriched: 65% vs 69%, p=0.70 •BLBC (basal-like): 92% vs 23%, p=0.004 LRFS outcomes, DBCG 82b trial •Luminal A: 92% vs 25%, p=0.01 •Luminal B: 86% vs 89%, p=0.82 •HER2-enriched: 90% vs 76%, p=0.42 •BLBC (basal-like): 54% vs 66%, p=0.33	
Danish Breast Cancer cooperative Group [DBCG]82b Overgaard, 1997 (156)	1708	Premenopausal, total mastectomy +AD, Stage II or III=high risk (one or more of: N+, T3-4, invasion to skin or pectoral fascia) AD=removal of central	8 cycles CMF chemo with RT started within 1 w of first chemo cycle (N=852) or 9 cycles CMF alone (N=856). 50 Gy in 25 fractions over 5 w or 48 Gy in 22 fractions over 5.5 w. Anterior photon field against the supra & infraclavicular regions & ax	Median 114 m follow-up, survival data at 10 y RT + chemo vs chemo	Locoregional recurrence: 9% vs 32%, p<0.001 DFS: • All: 48% vs 34%, P<0.001 • N0: 74% vs 62% • N1 (1-3 nodes): 54% vs 39% • N2+ (>3 nodes): 27% vs 14%	

Study name, reference, enrolment period	# patients	Patient characteristics	Intervention	Follow-up	Recurrence or survival outcomes (RT vs no RT)	Other adverse effects, comments
1982-1989		axillary nodes involving level I and part of level II, median 7 nodes 8% N0, 62% N1, 30% N2+ 40% T1, 45% T2, 14% T3	regions & and anterior electron field against the IM nodes & chest wall. RT: Site: chest wall, supraclavicular LN, ax LN, IM nodes Energy: megavoltage/electrons		• T1: 57% vs 45% • T2: 43% vs 28% • T3: 37% vs 22% OS: • All: 54% vs 45%, P<0.001 • N0: 82% vs 70% • N1: 62% vs 54% • N2: 32% vs 20% • T1: 67% vs 58% • T2: 47% vs 38% • T3: 40% vs 33% All subgroup differences significant	
Danish Breast Cancer Cooperative Group [DBCG]82c Overgaard, 1999 (157) 1982-1990	1375	Postmenopausal, total mastectomy +AD, Stage II or III=high risk (one or more of: N+, T3-4, invasion to skin or pectoral fascia) AD=removal of central axillary nodes involving level I and part of level II, median 7 nodes 10% N0, 58% N1, 33% N2+ 38% T1, 49% T2, 12% T3	RT + TAM (N=686) or TAM alone for 1 y (N=689). 50 Gy in 25 fractions in 35 days or 48 Gy in 22 fractions in 38 days. Anterior photon field against the supra & infraclavicular regions & ax regions & and anterior electron field against the IM nodes & chest wall. RT: Site: chest wall, supraclavicular LN, ax LN, IM nodes Energy: megavoltage/electrons Histopathologic examination was done according to a standardized procedure by the 30 participating pathology departments.	Median 123 m follow-up, survival data at 10 y RT + TAM vs TAM	Locoregional recurrence: 8% vs 35%, P<0.001 DFS • 36% vs 24%, P<0.001 • N0: 43% vs 40% • N1: 44% vs 31% • N2+: 18% vs 6% • T1: 43% vs 28% • T2: 31% vs 21% • T3: 29% vs 22% OS • 45% vs 36%, p=0.03 • N0: 56% 55% • N1: 55% vs 44% • N2+: 24% vs 17% • T1: 52% vs 44% • T2: 42% vs 32% • T3: 30% vs 29%	
DBCG 82b&c Højris, 1999 (158)	3083	Same as above (156,157)	Same as above (156,157)	Median of 10 y follow-up	Breast cancer mortality 44.2% vs 52.5%	Ischemic heart disease deaths, 0.8% vs 0.9%, HR=0.84 (95% CI=0.4-1.8)
DBCG 82b&c Højris, 2000 (114)	84	Same as above (156,157) 94% N+	Late treatment-related morbidity in a subgroup from one centre still alive and without previously treated local recurrence, measured by structured interview and physical exam, RT vs no RT	Assessment at single visit at median of 9 y after surgery		Lymphedema • Objective assessment: 14% vs 3% (NS) • Subjective assessment: 17% periodic and 26% constant vs ≈ 12% and

Study name, reference, enrolment period	# patients	Patient characteristics	Intervention	Follow-up	Recurrence or survival outcomes (RT vs no RT)	Other adverse effects, comments
						5% (p=0.02) • Impact on lives/ activities: 17% vs 9% Decreased shoulder mobility • Objective: slight: 45% vs 15%; moderate/ severe 5 % vs 0%, p=0.004 • Symptomatic: 17% vs 2%, p=0.001
DBCG 82b&c Nielsen, 2006 (159)	3083	Same as above (156,157)	RT (N=1538) vs no RT (N=1545)	Median 18 y follow-up	• First breast cancer event: 59% vs 73%, RR=0.68 (95% CI=0.63-0.75), P<0.001 • LRR: 14% vs 49%, RR=0.23 (95% CI=0.19-0.27), P<0.001 • Distant metastasis: 53% vs 64%, RR=0.78 (95% CI=0.71-0.86), P<0.001	
DBCG 82b&c Subgroup analysis Overgaard, 2007 (160)	1152	Subgroup of LN+ female pts with ≥8 nodes removed. Analysis of 1-3 positive nodes vs ≥4 positive nodes. N1 subgroup: 47% T1, 48% T2, 4% T3 N2+ subgroup: 28% T1, 52% T2, 21% T3	1-3 positive nodes: RT (N=276) vs no RT (N=276) ≥4 positive nodes: RT (N=287) vs no RT (N=313)	Median 18 y follow-up, 15-y LRR and survival results	Locoregional recurrence • 4% vs 26% (actuarial 6% vs 37%), RR=0.12 (95% CI=0.07-0.19), p<0.001 • N1: 4% vs 27%, RR=0.10 (95% CI=0.05-0.22), P<0.001 • N2+: 10% vs 51%, RR=0.17 (95% CI=0.10-0.28), P<0.001 • T1: 4% vs 29% • T2+: 7% vs 43% OS • 39% vs 29%, RR=0.63 (95% CI=0.49-0.81), p=0.015 • N1: 57% vs 48%, RR=0.69 (95% CI=0.50-0.97), p=0.03 • N2+: 21% vs 12%, RR=0.49 (95% CI=0.31-0.76), p=0.03 • T1: 50% vs 36% • T2: 33% vs 25%	
DBCG 82b&c Overgaard, 2011 (161) [abstract]	3083	Same as above (156,157)		25-y actuarial probabilities:	LRR: 14% vs 46%, HR=0.23 (95% CI=0.22-0.24), p<0.0001 OS: 24% vs 18%, HR=0.81 (95% CI=0.75-0.88), p<0.0001	
DBCG 82b&c Kyndi, 2008 (85)	1000	Same as above (156,157)	Randomly selected subgroup, tissue microarray analysis for ER, PR, HER2 to investigate whether response to PMRT differs according to these	Median follow-up 17 y for pts alive	• ER+, PR+, HER2-: significantly better OS (p=0.002, P<0.001, p=0.007) and LRR (P<0.001 for all) • ER-, PR-, HER2+: no improvement in OS	

Study name, reference, enrolment period	# patients	Patient characteristics	Intervention	Follow-up	Recurrence or survival outcomes (RT vs no RT)	Other adverse effects, comments
			biological markers		(p=0.8, p=0.9, p=0.96), but improved LRR (p=0.001, P<0.001, p=0.001) • HR+/HER2-: OS HR=0.78, p=0.009; LRR HR=0.09, p<0.001 • HR+/HER2+: OS HR=0.65, p=0.07; LRR HR=0.06, p<0.005 • HR-/HER2-: OS HR=0.85, p=0.4; LRR HR=0.33, p=0.001 • HR-/HER2+: OS HR=1.35, p=0.14; LRR HR=0.53, p=0.2	
Stockholm Breast Cancer Study Group Rutqvist, 2006 (19) 1976-1990	1226	Two trials: Pre- (N=545) & post-menopausal (N=679) high-risk pts with node positive disease or tumour size >30 mm treated with MRM. 12% pN0, 56% pN1, 24% pN2+, 7% N+ but number of positive nodes unknown. 42% pT1, 53% pT2, 4% pT3	RT vs CMF-type chemo Premenopausal: RT (N=256) vs chemo (N=291) Postmenopausal (factorial design): RT alone (N=148), RT plus TAM (N=160), chemo alone (N=182), chemo plus TAM (N=189). Chemo = chlorambucil + MF for first 18 m of the trial (12 courses at 6 w intervals); switched to CMF in 1978 (12 courses with 28 day cycles, switched to 6 courses of CMF in 1988) RT was begun 4-6 w after surgery: 46 Gy with 2 Gy/fraction 5 days/w for 4.5 w. Target volume included chest wall, axilla, supraclavicular fossa, and ipsilateral IM nodes (down to the fifth intercostal space). Energy: high-voltage technique (chest wall 7-14 MeV electrons, nodes Co60 or 4-6 MV photons) All hormone receptor assays were done in 1 laboratory. Tamoxifen (40 mg/d) administered for 2 y starting 4-6 w after surgery; in 1983 disease-free pts at 2 y started random allocation to continue to 5 y or stop	Median 18.4 y follow-up; RT vs Chemo	Premenopausal • Locoregional recurrence, HR=0.67 (95% CI=0.44-1.0), p=0.048 • Distant recurrence, HR=1.68 (95% CI=1.3-2.2), p<0.001 • OS: HR=1.21 (95% CI=0.96-1.51), p=0.10 • RFS: HR=1.25 (95% CI=1.10-1.54), p=0.037 Postmenopausal • Locoregional recurrence, HR=0.43 (95% CI=0.30-0.63), P<0.001 • Distant recurrence, HR=1.05 (95% CI=0.81-1.35), p=0.72 • OS: HR=0.92 (95% CI=0.77-1.11), p=0.38 • RFS: HR=0.91 (95% CI=0.77-1.08), p=0.28	<u>Premenopausal</u> The number of non-breast cancer deaths (3% vs 3%) was too small to permit meaningful conclusions <u>Postmenopausal</u> Non-breast cancer deaths 19% vs 12%, p=0.13; non-cardiovascular 13% vs 7% (p=0.64); no difference in cardiovascular deaths (6% vs 5%, p=0.94) Higher risk of a second primary malignancy (12% vs 5%, p=0.01), especially lung cancers occurring after 10 y (3.7% vs 0.3%)

				Cumulative incidence of events at 15 y	• Locoregional recurrence:
					  • Premenopausal:
					  • All: 14% RT vs 24% Chemo
					  • 1-3 nodes: RT: 12%, Chemo: 18%
					  • ≥4 positive nodes: RT: 19%, Chemo: 34%
					  • Postmenopausal:
					  • All: 12% RT vs 26% Chemo, HR=0.43 (95% CI=0.30-0.63), p<0.001
					  • 1-3 nodes: RT: 9%, Chemo: 25%
					  • ≥4 positive nodes: RT: 15%, Chemo: 30%
					• Death:
					  • Premenopausal:
					  • All: 56% RT vs 50% Chemo
					  • 1-3 nodes: RT: 52%, Chemo: 41%	

Study name, reference, enrolment period	# patients	Patient characteristics	Intervention	Follow-up	Recurrence or survival outcomes (RT vs no RT)	Other adverse effects, comments
					• ≥4 positive nodes: RT: 73%, Chemo: 70% • Postmenopausal: • All: 60% RT vs 62% Chemo • 1-3 nodes: RT: 51%, Chemo: 55% • ≥4 positive nodes: RT: 79%, Chemo: 80% • No statistically significant interaction between RT & chemo and nodal involvement for any type of first event or cause of death.	
South Sweden Breast Cancer Group Killander, 2007 (115) 1978-1985	713	Postmenopausal pts (age <71 y), Stage II, with MRM Median tumour size 25 mm Median 10 nodes examined 41% pN0, 40% pN1, 18% pN2+ MRM + en bloc AD of level 1 & 2 axilla, included pectoral fascia of major pectoralis muscles Only Stage II but presents results by # of positive nodes, including ≥4 positive nodes	Radiotherapy and/or Tamoxifen (median 12 m) RT (N=235) or RT + TAM (N=230) or TAM (N=248). Site: chest wall, LN of supra and infraclavicular fosse, axilla, ipsilateral parasternal mammary nodes Dose: 38-48 Gy in 20 fractions administered daily with a 3 w interval after the first 12 fractions Energy: electrons or photons (orthovoltage, megavoltage) Surgical and pathological procedures standardized by extensive guidelines in the protocol. HR measurements were performed on all properly frozen tumour samples at the research laboratory of Lund University's Oncology Department	Median 23 y follow-up, 20-y estimates	• Locoregional recurrence as first event • All: 6.7% RT, 5.3% RT + TAM, 18.5% Tam, p<0.001 • N0: 3.5% RT, 5.9% RT + TAM, 6.7% TAM • 1-3 nodes: 8.1% RT, 2.6% RT + TAM, 25.9% TAM • ≥4 positive nodes: 11.4% RT, 9.4% RT + TAM, 25.5% TAM • Cumulative incidence of systemic disease • N0: 27% RT, 30% RT + TAM, 25% Tam (NS) • 1-3 nodes: 58% RT, 36% RT + TAM, 51% TAM • RT vs RT + TAM p=0.007 • RT + TAM vs TAM p=0.047 • ≥4 positive nodes: 88% RT, 67% RT + TAM, 74% TAM; • RT vs RT + TAM p=0.021 • Mortality • N0: 61% RT, 58% RT + TAM, 53% TAM (NS) • 1-3 nodes: 74% RT, 65% RT + TAM, 64% TAM (NS) • ≥4 positive nodes: 92% RT, 84% RT + TAM, 85% TAM (NS)	Lymphedema 6.8% (73/435) vs 3.9% (9/233) Radiation pneumonitis requiring treatment 3.9% Brachial plexopathy was found in 2 pts (0.5%) 4-6% contralateral breast cancer, no difference between arms No difference in endometrial cancer or any other cancer types
South Sweden Breast Cancer Group Killander, 2009 (121) 1978-1983	387	Stage II. Premenopausal pts (median age 47 y). Median tumour size 25 mm. 33% pN0, 43% pN1, 20% pN2+. Undergone MRM + level I & II AD	RT (N=130) or RT + C (cyclophosphamide; N=124) or C (N=133). RT as in Killander, 2007 (115)	Median 24 y follow-up, 20 y estimates	• Locoregional recurrence • N0: 0% RT, 0% RT+C, 7.1% C • 1-3 nodes: 8.9% RT, 3.9% RT+C, 14.8% C • ≥4 positive nodes: 9.3% RT, 8.3% RT+C, 23.1% C • Cumulative incidence of systemic disease • N0: 29% RT vs 28% RT+C vs 19% C	Cardiac effects in subgroup identified retrospectively: more ECG changes in those with left-side RT (11/34) or right-side RT (6/33) vs no RT (1/23),

Study name, reference, enrolment period	# patients	Patient characteristics	Intervention	Follow-up	Recurrence or survival outcomes (RT vs no RT)	Other adverse effects, comments
Gustavsson, 1999 (162) (cardiac effects)					• 1-3 nodes: 41% RT, 35% RT+C, 38% C • ≥4 positive nodes: 58% RT, 58% RT+C, 69% C • Mortality • N0: 27% RT vs 37% RT+C vs 16% C (p=0.04 for RT+C vs C) • 1-3 nodes: 44% RT, 33% RT+C, 50% C • ≥4 positive nodes: 70% RT, 62% RT+C, 69% C	p=0.03; no serious cardiac sequelae
German Breast-Cancer Study Group (GBSG) BMFT 03 Germany Schmoor, 2000 (18) 1984-1989	199	Stage T1a-3a, N+ MRM (Patey) with en bloc axillary dissection with at least 6 identifiable lymph nodes 38% premenopausal CMF group: 57% N1, 32% N2, 11% N3; 28% T1, 41% 20-30 mm, 31% >30 mm CMF +RT group: 64% N1, 23% N2, 13% N3; 33% T1, 40% 21-30 mm, 27% >30 mm	CMF ± RT 6 cycles CMF (modified Bonnadonna regimen, 500, 40, 600 mg/m^2, IV) or 6 cycles CMF +RT RT between second and third cycle of CMF Target volume included chest wall, parasternal and supraclavicular nodes, axilla 4-6 MV photons or telecobalt Conventional fractionation, 2 Gy 5/w Chest wall irradiated by tangential fields up to 50 Gy, nodes/axilla included in an anterior field (hockey stick) with total dose 44 Gy. Parasternal region: half dose administered with electrons if available Histopathologic classification re-examined and grading performed centrally in one histopathologic reference centre. Quality control for hormone-receptor analysis performed centrally	Median follow-up for EFS was 8.2 y, OS was 9.9 y; CMF +RT vs CMF alone	• EFS: RR=0.82 (95% CI=0.55-1.21), p=0.312 • EFS (5 y): 58% vs 53% • Locoregional recurrence as first event: RR=0.35 (95% CI=0.14-0.91), p=0.030 • Locoregional recurrence (10 y): 6.6% vs 17.5% • OS: RR=0.93 (95% CI=0.62-1.40), p=0.733 • OS (5 y): 70% vs 67% • Adjusted analyses found no significant effect of RT on EFS and OS	Acute adverse effects in RT pts: 25% had skin reactions 8% had WBC <3000/μL and 1% had platelets <75000/μL Long-term adverse effects 1 or 2 y after RT: 28% skin alterations, 4% rib osteolysis, 4% pulmonary
Tianjin Medical University, China Shi, 2003 (79) [Chinese] 1985-1986	162	Operable breast cancer 33% N0, 25% N1, 41% N2 25% IIIA	Randomly administered RT according to clinical stage and involving condition of axillary lymph nodes RT vs control RT included supraclavicular area and/or IM area to 50 Gy. Co60 + 10 MeV β	5-, 10-, and 15-y survival, RT vs control	• All: 72%, 56.1%, 54.3% vs 66.3%, 51.3%, 49.4%, p>0.05 • No difference in clinical Stage I-IIIA or LN+ vs LN- • N2+ (>=4 nodes): 55.6%, 38.9%, 37.1% vs 29.0%, 16.1%, 16.1%, P<0.05	
Glasgow Trial	322	LN+, mastectomy for	Conventional postoperative RT vs CMF	Median 27-y	Multivariate analysis	

Study name, reference, enrolment period	# patients	Patient characteristics	Intervention	Follow-up	Recurrence or survival outcomes (RT vs no RT)	Other adverse effects, comments

McArdle, 2010 (163)
 	
McArdle, 1986 (164)
1976-1982
		operable breast cancer
		
		32% >3 nodes positive
			vs RT→CMF
			
			CMF as described by Bonadonna
				follow-up	• Cancer-specific HR, compared with RT+CMF
					  • RT: HR=1.24 (95% CI=0.81-1.90), p=0.32
					  • CMF: HR=1.43 (95% CI=0.96-2.13), p=0.082
					• Overall HR, compared with RT+CMF
					  • RT: HR=1.02 (95% CI=0.70-1.48), p=0.921
					  • CMF: HR=1.28 (95% CI=0.90-1.81), p=0.169
					No difference in all-cause or cancer-specific survival between pts in each of the 3 treatment arms	

Stockholm Trial (Stockholm A) Arriagada, 1995 (165) Arriagada, 2010 (166) [abstract] Gyenes, 1998 (167) 1971-1976	960	Early (operable, unilateral) breast cancer, MRM Stage I-III postoperative RT: 63% N-, 13% 1 node, 23% ≥2 node positive; 60% T1, 28% T2, 8% T3 surgery alone: 62% pN-, 13% 1 node, 25% ≥2 nodes; 54% T1, 34% T2, 8% T3 preoperative RT: 79% N-, 9% 1 node, 12% ≥2 nodes; 18% T0, 61% T1, 18% T2, 2% T3	Pre or post-operative locoregional RT (Co60) vs MRM alone (control) Irradiated volumes included chest wall, axilla, supraclavicular and IM lymph nodes, dose 45 Gy/25fractions/5 w Preoperative RT group not equivalent in stage (T or N status) so excluded from this table	Median 32 y follow-up	pts with positive nodes, postop RT vs control LRR: HR=0.24, p<0.0001), absolute risk (15 y) reduced from 47%-15% Distant metastases: HR=0.65, p=0.009 Overall death: HR=0.82, p=0.17, 8% benefit at 15 y N- pts, postop RT vs control LRR HR=0.27, absolute 15-y reduction from 23%-5% No significant effect on other outcomes Results confirm major LRR reduction in the RT group without an increase of second malignancy	Patients receiving high dose-volumes to the heart (pts with left-sided tangential fields) had increased mortality of ischemic heart disease (HR=2.5, p=0.03) but not myocardial infarction (HR=1.3, not significant)

Abbreviations: AD, axillary dissection; AX, axillary node; BCSS, breast cancer specific survival; CMF, cyclophosphamide + methotrexate + fluorouracil; ER, estrogen receptor; DFS, disease-free survival; EFS, event-free survival; HER2, human epidermal growth factor receptor 2; HR, hazard ratio (95% confidence interval); HR-, hormone receptor negative (ER- and PR-); HR+, hormone receptor positive (ER+ and/or PR+); IM, internal mammary; IMC, internal mammary chain; LRFS, locoregional relapse-free survival; LRR, locoregional recurrence; MRM, modified radical mastectomy; N0, node negative; OS, overall survival; PR, progesterone receptor; RFS, recurrence-free survival; RR, relative risk; SM, simple mastectomy; TAM, tamoxifen; TN, triple negative (HR-HER2-)

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Table 4. Studies of locoregional radiation.

Study name, reference, enrolment period	# patients	Patient characteristics	Intervention	Follow-up	Recurrence or survival outcomes (RT vs no RT)	Other adverse effects, comments
Randomized Trials [included a mixture of patients with early cancer and LABC]						
EORTC 22922-10925 NCT00002851 Poortmans, 2013 [abstract] (92,93) Matzinger, 2010 (29) 1996-2004 46 institutions in 13 countries	4004	Involved axillary LN (56%)and/or centrally/medially located primary tumour Stage I-III 34% Stage I, 32% Stage IIA, 19% Stage IIB, 14% Stage III Recruited after breast and axillary surgery. No restrictions on use of adjuvant systemic treatment : 42% received NACT, 23% adjuvant chemo, 60% adjuvant hormonal therapy 99% of N+ and 66% of N0 patients received adjuvant system treatment [33% LABC]	Randomized to receive IM and MS lymph node irradiation, 50 Gy in 25 fractions of 2 Gy; 26 Gy with photons (min energy of Co60 and max 10 MV) and 24 Gy with electrons; standardized treatment to have one anterior field BCS (76%): 85% had RT boost to primary tumour bed Mastectomy (24%): 73% in both arms had chest wall irradiation Axillary RT administered to 6.8% in no IM-MS group and 7.8% in IM-MS group	Survival outcomes at 10 y (average 10.9 y follow-up), Adverse effects within 3 y IM-MS vs none	• OS: 82.3% vs 80.7%, HR=0.87 (95% CI=0.76-1.00), p=0.056; p=0.0496 after adjusting for stratification factors • DFS: 72.1% vs 69.1%, HR=0.89 (95% CI=0.80-1.00), p=0.044 • MFS: 78.0% vs 75.0%, HR=0.86 (95% CI=0.76-0.98), p=0.020 Causes of death (382 vs 429) similar in both groups except for breast cancer (259 vs 310)	•Few adverse effects in both arms, most frequent was edema (8.1% vs 7.8%), skin fibrosis (8.5% vs 8.3%), telangiectasia (2.3% vs 1.5%), lung fibrosis (2.8% vs 0.9%) •Lymphedema 3.8% vs 3.6%, NS •No significant difference in cardiac fibrosis or cardiac disease (0.3% vs 0.4%, p=0.55) •Any lung adverse effects higher in IM-MS (4.3% vs 1.3%, p<0.0001) corresponding to 57 additional cases. •Any late adverse effects 25.5% vs 21.8%, p=0.006 •Conclude IM-MS well tolerated, did not impair WHO performance status at 3 y
Hennequin, 2013 (28) 1991-1997 13 French centres	1334	Stage I and III (stated as Stage I-II but patient characteristics do not match this) with either positive axillary lymph nodes (pN+, 75%) or central/medial tumour location (with or without pN+) Enrolled after modified radical mastectomy + ALND (levels 1 and II) Randomization stratified by tumour location (medial/central or lateral),	PMRT to chest wall and supraclavicular nodes (and apical axillary nodes if pN+), irradiation was 50 Gy or equivalent Randomized to with or without IMC-RT • IMC-RT included first 5 intercostal spaces, 2/3 of dose (31.5 Gy) administered by electrons	Median 11.3 y follow-up among survivors (8.6 y overall)	• 10-y OS 62.6% IM node vs 59.3 non-IM node (p=0.8) • Differences in preplanned subgroups (factors stratified for) were not statistically significant • pN0 pts (internal/medial	• Grade 3-4 late adverse effects of radiation were roughly the same order of magnitude in both groups, and there was no significant excess of late cardiac events (2.2% vs 1.7%, NS)

Study name, reference, enrolment period	# patients	Patient characteristics	Intervention	Follow-up	Recurrence or survival outcomes (RT vs no RT)	Other adverse effects, comments
		nodal status (pN0 or pN+), adjuvant chemo vs none 36% lateral, 64% medial/internal 24% pN0, 44% pN1, 19% pN2, 13% pN3 33% T1, 53% T2, 9% T3 [≈ 35% LABC]	• The authors indicated the study was designed to find a 10% difference and therefore underpowered to find small differences in survival. • They used 2-dimensional techniques and could not rule out small benefits with more modern conformal techniques to a higher risk population.		tumours) had better OS without IM node RT (not statistically significant) • pts with pathologically positive nodes had better OS with IM node RT, with a larger benefit for internal/medial tumours ≈7% improvement) than lateral tumours (≈4% improvement (both not statistically significant)	caused by including IM nodes. •Grade ≥2 late effects 3.1% vs 2.3%, NS Concluded they could not recommend for or against IM node irradiation after mastectomy.
NCIC-CTG MA.20 Whelan, 2011 [abstract] (33,94) Olivotto, 2003 [trial description] (32) 2002-2007, Canada, USA, Australia	1832	N+ or high risk N0 (≥5 cm; or ≥2 cm and <10 axillary nodes removed with either ER-, grade 3 or LVI) treated with BCS and SLNB or ALND (ALND for all N+) and adjuvant chemo and/or endocrine therapy Stratified by positive nodes (0, 1-3, >3), axillary nodes removed (<10, ≥10), chemo (anthracycline, other, none) and endocrine therapy (yes, no) 10% N0, 85% N1, 5% N2+; 45% of WBI pts had tumours >2 cm although 50% of WBI+RNI pts had tumours >2cm. 91% received adjuvant chemo and 77% endocrine therapy [≈ 45% LABC]	Randomized to WBI + RNI vs WBI alone after BCS RNI included supraclavicular, infraclavicular, and ipsilateral IMC nodes in the first to third interspaces, includes level 3 AX nodes, 45Gy/25 fractions WBI: CT planning recommended, 4-18 MV, 50 Gy/25 fractions, boost of 10 Gy/5 fractions permitted	Median 62 m follow-up WBI+RNI vs WBI	• DFS: 89.7% vs 84.0%, HR=0.67 (95% CI=0.52-0.87), p=0.003 • OS: 92.3% vs 90.7%, HR=0.76 (95% CI=0.56-1.03), p=0.07 • Isolated Locoregional DFS: 96.8% vs 94.5%, HR=0.58 (95% CI=0.37-0.92), p=0.02 • Distant DFS: 92.4% vs 87.0%, HR=0.64 (95% CI=0.47-0.85), p=0.002 • Concluded pts with large primary tumours or more than 3 positive nodes should be offered RNI and that it be also offered to those with 1-3 positive nodes provided they are made aware of associated adverse effects	More grade ≥2 pneumonitis (1.3% vs 0.2%, p=0.01), grade ≥2 radiation dermatitis (50% vs 40%, p<0.001), and lymphedema (7% vs 4%, p=0.004), and adverse cosmetic outcome at 5 y (36% vs 29%, p=0.047)

Study name, reference, enrolment period	# patients	Patient characteristics	Intervention	Follow-up	Recurrence or survival outcomes (RT vs no RT)	Other adverse effects, comments
Meta-analysis						
Meta-analysis of above 3 trials Budach, 2013 (25)		See above	See above Regional RT of the MS-LN and the IM-LN (MA.20 and EORTC) vs none		OS: HR=0.85 (95% CI=0.75-0.96) DFS: HR=0.85 (95% CI=0.77-0.94) DMFS: HR=0.82 (95% CI=0.73-0.92) OS including French study: HR=0.88 (95% CI=0.80-0.97) Conclude regional RT to IM and MS nodes improves DFS, OS, DMFS in Stage I-III breast cancer	
Prospective nonrandomized cohort study						
Stemmer, 2003 (24) 1994-1998 Israel	100	High-risk Stage II-III pts treated with lumpectomy + ALND or mastectomy, then chemo and locoregional RT no difference between groups for prognostic parameters including tumour size, number of positive axillary lymph nodes (median 10 for IM node RT and 11 for no IM node RT)	IM node RT (N=67) vs no IM node RT (N=33) pts because the electron-beam facility was not available for 20 m of the study (1996-1997) All received breast/chest wall RT with tangential 6-8 MV photon beams (plus boost to tumour bed for BCS pts), axilla and supraclavicular node RT with 6-8 MV photo. IM node group also received IM RT with anterior 9-12 MeV electron beam	median 77 m follow-up IM node RT vs without	DFS: 73% vs 52%, p=0.02 OS: 78% vs 64%, p=0.08	Grade 2 skin adverse effects 22% vs 15% Grade 3 skin adverse effects 10% vs 6% Radiation pneumonitis in 2 IM node pts No long-term organ adverse effects or secondary leukemia.

Abbreviations: BCSS, breast cancer specific survival; DFS, disease-free survival; DMFS, distant metastasis-free survival; D-RFS, distant relapse-free survival; IM, internal mammary; IMC, internal mammary chain; MFS, metastasis-free survival; MS, medial supraclavicular; NACT, neoadjuvant chemotherapy; OS, overall survival; RNI, regional nodal irradiation; WBI, whole breast irradiation

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Table 5. Summary of guideline recommendations for extent of radiotherapy.

Group/Location, year published	Review years	Patient characteristics	Radiation
NCCN, 2013 (12)		Any	If IM lymph nodes are clinically or pathologically positive, RT should be administered to the IM nodes; otherwise, treatment to the IM nodes is at the discretion of the treating radiation oncologist. Computed tomography (CT) treatment planning should be used in all cases in which RT is delivered to the IM lymph node field
		cT2N1 or cT3N0-1	BCS: • ≥4 nodes (pN2+): RT to whole breast ± boost to tumour bed, infraclavicular region, and supraclavicular area; RT to IM nodes if clinically or pathologically positive; otherwise, strongly consider RT to IM nodes • 1-3 nodes (T2N1 or T3N1): RT to whole breast ± tumour bed, strongly consider RT to infraclavicular region and supraclavicular area; RT to IM nodes if clinically or pathologically positive; otherwise, strongly consider RT to IM nodes • T3N0: RT to whole breast ± boost to tumour bed or consider partial breast irradiation PMRT: • ≥4 nodes (pN2+): PMRT to chest wall + infraclavicular region and supraclavicular area; RT to IM nodes if clinically or pathologically positive; otherwise, strongly consider RT to IM nodes • 1-3 nodes (T2N1 or T3N1): strongly consider RT to chest wall + infraclavicular region and supraclavicular area; RT to IM nodes if clinically or pathologically positive; otherwise, strongly consider RT to IM nodes • T3N0 or positive margins: consider RT to chest wall ± infraclavicular and supraclavicular nodes especially if inadequate axillary evaluation or extensive lymphovascular invasion. Strongly consider IM node RT
		Initially inoperable LABC, Stage IIIA (T0-3N2, excludes T3N1) or IIIB (cT4N0-2 or N3)	RT after NACT decided based on pre-chemotherapy tumour characteristics After response to NACT • Mastectomy +AD: as for ≥4 nodes above; also applies to inflammatory cancer • BSC +AD: RT to breast + infraclavicular and supraclavicular nodes (plus IM nodes if involved)
Alberta, 2012 (59)	1966-2008 revised consensus in 2012 but no new search	T2, SN+, no AD T2, SN+, completion AD T3-4 Any after NACT (except T1/T2N0 with mastectomy)	Chest wall + RNI individualized based on risk assessment Chest wall + RNI Chest wall + RNI Chest wall + RNI
ACR, 2012 (26)	MEDLINE to 2011 (2012?)	PMRT for T3N1, T4N1, T4N2 and for T1-2 with ≥4 positive lymph nodes	Chest wall, occasionally boost to scar especially if positive margins, hypofractionation often used in Canada and Europe Usually include ipsilateral supraclavicular fossa for LN+, more variation for IM nodes but consider for pts at risk of IM involvement such as medial or centrally located tumours and positive axillary LNs. Use 3D treatment planning to minimize dose to lung and heart
Nice/Saint-Paul de Vence (France), 2011 (60)	1980-2009 (or 2010 for MEDLINE)	Invasive nonmetastatic adenocarcinomas	Administer PMRT for N0 if at least one risk factor for relapse (age <40 y, T3-T4 [size ≥pT3], grade III, multifocality, lymphovascular/muscular/cutaneous invasion). PMRT for N+ and ≥4 nodes positive
		• After NACT	Base RT on initial tumour status (before NACT)
		• BCS	RT to whole breast + boost to the tumour bed
		• PMRT, N- *or*	• If administered, include chest wall, IMC, ipsilateral supraclavicular areas. Apart from cases with insufficient lymph node dissection irradiation of the axilla should not be carried out systematically.

Group/Location, year published	Review years	Patient characteristics	Radiation
		• PMRT, isolated cells and axillary micrometastases	• For tumours in external quadrants, systematic irradiation of the nodal areas is not recommended. • Routine irradiation of axilla is not justified. Take into account number of nodes dissected, other local and general prognostic factors
		• PMRT, N+	Supraclavicular, subclavicular, and IMC nodes. IMC RT is particularly indicated in pts with internal-central pts with node-positive cancer and those with >4N+. For axilla, take into account ratio of positive nodes to total number removed.
ESMO, 2011 (66)	Based on EBCTCG 2005 (15)		RT after AD is not routinely recommended unless there is suspicion of residual tumour. Supraclavicular lymph nodes should be considered for inclusion in the case of extensive (N2+) involvement of axillary and supraclavicular lymph nodes Intermammary lymph nodes should be included in cases of metastatic spread to this area
International panel, 2011 (14)	2008 consensus	Inflammatory breast cancer	Modified radical mastectomy + PMRT including supraclavicular regions and IM lymph nodes
Belgium, 2010 (68)	Up to Jan 2010	PMRT	RT to chest wall in early invasive breast cancer and a high risk of local recurrence including ≥4 positive axillary lymph nodes or involved resection margins Until data from a large ongoing randomized trial become available, RT after mastectomy should be offered to pts with 1-3 positive nodes Axillary RT and IMC RT are to be discussed in the multidisciplinary team meeting (expert opinion)
NICE, 2009 (70)	1950-July 2008	Early breast cancer (includes LABC)	• RT after BCS; offer boost to excision site if high risk of recurrence • PMRT if high risk of local recurrence, including ≥4 positive axillary nodes or involved margins; • Enter intermediate-risk pts (1-3 nodes, lymphovascular invasion, grade 3, ER-, age <40 y) into clinical trial of PMRT • No PMRT if low risk of recurrence (most N0 pts) • Do not offer adjuvant RT to the axilla or supraclavicular fossa to pts with early breast cancer if pN0 • Do not offer adjuvant RT to the axilla after ALND for early breast cancer. • If ALND is not possible following a positive axillary SLNB or four-node sample, offer adjuvant RT to the axilla to pts with early breast cancer. • Offer adjuvant RT to the supraclavicular fossa to pts with early breast cancer and four or more involved axillary lymph nodes. • Offer adjuvant RT to the supraclavicular fossa to pts with early breast cancer and one to three positive lymph nodes if they have other poor prognostic factors (e.g., T3 and/or histological grade 3 tumours) and good performance status. • Do not offer adjuvant RT to the IMC to pts with early breast cancer who have had breast surgery
DEGRO, 2008 (61)	Updated to 2008	PMRT	• PMRT recommended for pT3-4, incomplete resection, or ≥4 positive axillary nodes; also for 1-3 positive axillary nodes and intermediate risk of locoregional recurrence • Supra/infraclavicular irradiation mandatory if ≥4 positive nodes, individual patient decision for 1-3 positive nodes • RT to axilla if no axillary dissection, if residual tumour, inadequate axillary clearance, or positive SNB without axillary dissection • No routine use of IMC, but consider for ≥4 positive nodes and large tumours especially with medial/central tumours

Abbreviations: AD, axillary node dissection; BCS, breast-conserving surgery; IM, internal mammary; IMC, internal mammary chain; NACT, neoadjuvant chemotherapy; RNI, regional nodal irradiation

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Table 6. Sentinel lymph node biopsy (pre- or post-chemotherapy) vs axillary dissection.

Author and Year	Study details (comparison, exclusions)	Outcome measures	Results, % (number/total)
Clinically node negative before NACT (see also studies reporting cN0 subgroup)			
Papa, 2008 (47) 2002-2005, Israel	Group 1 (N=31) NACT → SLNB (dye + ^{99}Tc) → ALND Group 2 (N=58) SLNB → NACT → ALND cN0, T2/3, mean ± SD: 4.0 cm±1.2 cm (<half were T3)	SLN ID, Group 1 (NACT first) SLN ID, Group 2 (SLNB first) FN rate, Group 1 FN rate, Group 2 NPV, Group 1 NPV, Group 2 Accuracy, Group 1 Accuracy, Group 2	87% (27/31) 98% (57/58) 16% (3/19) 0% (0/37) 73% (8/11) 100% (20/20) 89% (24/27) 100% (57/57)
Vazquez Guerrero, 2010 (49) [abstract] France	SLNB → NACT → ALND N=89; Stage T2-T3 not allowing BCS; cN0, mean 3.1 cm (<half were T3) blue dye used, radiotracer unknown	SLN ID FN rate NPV Accuracy	99% (88/89) 8% (4/48) 91% (40/44) 95% (84/88)
Yu, 2007 (168) 1998-2005, Taiwan	NACT → SLNB (dye) → intraoperative ultrasound → ALND N=127; T3 LABC; excluded those with initially palpable lymph nodes and tumours that did not shrink with NACT	SLN ID FN rate NPV Accuracy	91% (116/127) 7% (5/69) 90% (47/52) 96% (111/116)
Clinically node negative after NACT			
Rubio, 2010 (169) [Abstract] 2005-2009, Spain	NACT →SLNB (^{99}Tc)→ALND N=71, T1-3N0-1; clinically negative axilla after NACT; IHC if negative by H&E	SLN ID FN rate NPV Accuracy	96% (68/71) 4% (1/23) 98% (45/46) 98% (67/68)
Sun, 2009 (170) [Chinese, data from abstract] China	NACT → SLNB (dye +^{99}Tc-sulphur colloid)→ ALND N=60, cN0 axillary nodes after NACT stage and design unknown	SLN ID FN rate Accuracy	90% (54/60) 10% 92%
Clinically node positive and node negative, cN0 and cN+ subgroups			
Kuehn, 2013 (46) 2009-2012, Germany/Austria, 103 institutions **SENTINA** (substudy of the German Geparquinto trial)	Arm A: cN0 and SLN- (radiocolloid ± dye) → NACT Arm B: cN0 and SLN+ → NACT→ second SLN →ALND Arm C: cN+ → NACT, ycN0 → SLN →ALND N=2131; 1146 Arms A+B SLNB, 360 Arm B who followed protocol (second SLNB + ALND), 592 Arm C; Arm A 75% T2, Arm B 71% T2, Arm C 80% T2 Radiocolloid in all (not used in 1%), dye was optional Median 2 SLN removed in A/B before NACT	SLN ID, arm A/B (cN0, SLNB first) arm B after NACT (cN0→ypN+$_{SN}$) - radiocolloid + dye used arm C (cN+ →ycN0) - radiocolloid + dye used FN rate arm A/B FN rate arm B based on second SLNB after NACT - radiocolloid + dye used FN rate, arm C (cN+ →ycN0) - radiocolloid + dye used -1 node removed -2 nodes removed -3+ nodes removed	99% (1139/1146) 61% (219/360) 76% (80/105) 80% (474/592) 88% (144/164) Not determined 0% (by protocol) 52% (33/64) 56% (14/25) 14% (32/226) 9% (6/70) 24% (17/70) 18% (10/54) 5% (5/102)
Takahashi, 2012 (171) 2001-2010, Japan	NACT→SLNB (^{99m}Tc + dye)→ALND N=96, Stage II-III, 57% cN+, mean tumour size 3.5 cm Concluded successful in pts with cN0 cancer (Stage	SLN ID cN0 cN+ FN rate, cN0 cN+	88% (84/96) 88% (36/41) 87% (48/55) 24% (12/49) 6% (1/18) 35% (11/31)

Author and Year	Study details (comparison, exclusions)	Outcome measures	Results, % (number/total)
	IIA)	cN+ →ycN0 (N=46)	27% (6/22)
		NPV	78% (42/54)
		Accuracy	86% (72/84)
		cN0	97% (35/36)
		cN+	77% (37/48)
Gimbergues, 2008 (172) 2001-2006, France	NACT → SLNB (^{99m}Tc) → ALND N=129; 2% T1,71% T2, 27% T3; 64% cN0, 36% N1-2, non-operable conservatively at the time of diagnosis.	SLN ID, overall	94% (121/129)
		• T1-2 tumours	93% (87/94)
		• T3 tumours	97% (34/35)
		• cN0	94% (77/82)
		• cN+	94% (44/47)
		FN rate, overall	14% (8/56)
		• T1-2	6% (2/35)
		• T3	28% (6/21)
		• cN0	0% (0/29)
		• cN+	30% (8/27)
		NPV, overall	89% (65/73))
		• cN0	100% (48/48)
		• cN+	68% (17/25)
		Accuracy	93% (121/129)
		• cN0	100% (77/77)
		• cN+	82% (36/44)
Rebollo-Aguirre, 2012 (173) 2008-2011, Spain	NACT (+ trastuzumab if HER2+) →SLNB (^{99m}Tc)→ALND N=88, T1-3, N0-1: 42% cN+, 89% T2, 9% T3 Axillary status by physical exam + biopsy	SLN ID	92% (81/88)
		cN0	98% (50/51)
		cN1	84% (31/37)
		FN rate	8% (3/36)
		NPV	94% (45/48)
		Accuracy	96% (78/81)
Kinoshita, 2007 (174) 2003-2005, Japan	NACT → SLNB (dye + ^{99m}Tc)→ ALND N=104; Stage II to III; 61 T2 (59%), 35 T3 (34%), 8 T4 (8%) 52% cN0 (N=54), 48% cN+ (N=50); all cN0 after NACT	SLN ID, overall	93% (97/104)
		• T2	97% (59/61)
		• T3/T4	88% (38/43)
		• cN0	96% (52/54)
		• cN+	90% (45/50)
		FN rate, overall	10% (4/40)
		• T2	13% (2/16)
		• T3/T4	8% (2/24)
		• cN0	14% (2/14)
		• cN+	8% (2/26)
		NPV, overall	93% (57/61)
		• T2	86% (43/45)
		• T3/T4	88% (14/16)
		• cN0	95% (38/40)
		• cN+	90% (19/21)
		Accuracy, overall	96% (93/97)
		• T2	97% (57/59)
		• T3/T4	71% (27/38)
		• cN0	96% (50/52)
		• cN+	96% (43/45)
Lang, 2004 (175) 1997-2003, USA (California)	NACT → SLNB (6 dye, 38 ^{99m}Tc, 9 both) → ALND N=53; Stage II or III; median tumour size 4.5 cm 43% cN+ (N=23) Design unclear (prospective or retrospective)	SLN ID	94% (50/53)
		FN rate	4% (1/24)
		NPV	96% (26/27)
		Accuracy	98% (49/50)

Author and Year	Study details (comparison, exclusions)	Outcome measures	Results, % (number/total)
	Subgroup: cN0 at presentation	SLN ID FN rate NPV Accuracy	97% (29/30) 0% (0/12) 100% (17/17) 100% (29/29)
	Subgroup: cN+ at presentation	SLN ID FN rate NPV Accuracy	91% (21/23) 9% (1/11) 91% (10/11) 95% (20/21)
Shigekawa, 2012 (176) 2007 –2010, Japan	NACT → SLNB (dye and/or radioisotope)→ ALND N=87; AJCC Stage II or III breast cancer; axillary ultrasound before and after NACT, included pts N+ or >3 cm in size; 5% T1, 59% T2, 20% T3, 17% T4; 76% N+	Overall, SLN ID cN0 cN+ cN+ to cN+ cN+ to cN0 FN rate cN0 after NACT, N=68 cN0 before and after NACT, N=21 cN+ converted to cN0, N=47	76% (66/87) 81% (17/21) 74% (49/66) 53% (10/19) 83% (39/47) 23% (7/31) 0% (0/7) 29% (7/24)
Zhao, 2012 (48) [Chinese, data from abstract] 2005-2011, China	SLNB→NACT→ALND, N=150 cN0 and cN+ [design unknown]	SLN ID, cN0 cN+ FN rate, overall cN0 cN+ Accuracy cN0 cN+	98% 93% 8% 7% 8% 95% 98% 92%
	NACT→SLNB→ALND, N=102	FN rate Accuracy	24% 84%
Clinically node positive before NACT (see also studies reporting cN+ subgroup)			
Boughey, 2013 (36) Boughey, 2014 (37) Accrue 2009-2011, follow to 2015 USA, 136 institutions **ACOSOG Z1071 trial**	NACT → SLNB (radiotracer and/or dye*)→ ALND cN1, confirmed by FNA or core needle biopsy before NACT, N=649; 0.8% T0, 13% T1, 56% T2, 26% T3, 4% T4 non-inflammatory cN2, N=38; 5% T0, 13% T1, 34% T2, 26% T3, 21% T4 *4% dye only, 17% radiotracer only, 79% both	cN1 SLN ID FN rate NPV Accuracy cN2 SLN ID FN rate NPV Accuracy SNL ID, blue dye only SLN ID, radiolabelled colloid SLN ID, dye + radiolabelled colloid	 93% (603/649) 15% (56/364) 81% (239/295) 91% (547/603) 89% (34/38) 0% (0/18) 100% (16/16) 100% (34/34) 79% (22/28) 91% (106/116) 94% (511/545)
Rebollo-Aguirre, 2013 (177) 2008-2012, Spain	NACT (+ trastuzumab if HER2+) →SLNB (^{99m}Tc)→ALND N=53, T1-T3, N1, M0, HER2+; 9% Stage IIA, 79% Stage IIB, 11% IIIA	SLN ID FN rate NPV Accuracy pCR nodes	85% (45/53) 8% (2/24) 91% (21/23) 96% (43/45) 42%
Yagata, 2013 (178) 2007-2009, Japan	NACT→SLNB (^{99}Tc + dye)→ALND N=95, cN+ (cytologically proven), partial or complete response in breast to NACT; 22% T1, 59% T2, 16% T3	SLN ID FN rate NPV Accuracy pCR axilla	85% (81/95) 16% (8/51) 79% (30/38) 90% (73/81) 33%

Author and Year	Study details (comparison, exclusions)	Outcome measures	Results, % (number/total)
Boileau, 2013 (38,39) [abstract] 2009-2012 Canada (multicentre trial, Ontario + Quebec) SN FNAC Study	NACT → SLNB (^{99}Tc ± dye)→ ALND N=145, N+ (biopsy proven): T0-3, N1-2, M0 Clinical examination and axillary ultrasound after NACT. 17% N0, 74% N1, 6% N2; 50% T2, 40% T3 SLN negative by H&E were re-examined with IHC to determine status and yPN0i+, ypN1Mi, and ypN1 SNs were considered positive; pathology centrally reviewed ^{99}Tc mandatory, dye optional	SLN ID FN rate 1 SLN ≥2 SLN if ypN0(i+) considered N0 NPV Accuracy, SLNB Accuracy, axillary ultrasound Accuracy, clinical exam pCR in axilla	88% (127/145) 8% (7/83) 19% (4/21) 7% (4/61) 13% (11/83) 86% (44/51) 94% (120/127) 63% 46% 34% (49/145)
Canavese, 2011 (179) 2005-2009, Italy	NACT → SLNB (^{99m}Tc) → ALND N=64, cN+, large infiltrating tumour (>2 cm), Stage IIB or higher, exclude inflammatory 73% T3, 84% N1, 16% N2+, 78% Stage IIIA ID rate, FN rate, accuracy similar (slightly better) than in an earlier RCT the group conducted in early breast cancer	SNL ID FN rate NPV Accuracy pCR	94% (60/64) 5% (2/43) 91% (21/23) 97% 22%
Kang, 2004a (180) 2001-2003, Korea (same authors as Lee, 2007 (181))	NACT → SLNB (^{99m}Tc ± dye)→ ALND N=80; cN+ or tumour size >3 cm 100% N+; 18% T1, 59% T2, 18% T3, 5% T4 11 dye alone, 51 ^{99m}Tc alone; 18 both (dye added only when not identified by ^{99m}Tc alone)	SLN ID Dye only ^{99m}Tc ± dye FN rate NPV Accuracy	76% (61/80) 55% (6/11) 80% (55/69) 7% (3/41) 87% (20/23) 95% (58/61)
Kang, 2004b (182) 2001-2003, Korea	NACT → SLNB (^{99m}Tc and/or dye*)→ ALND N=54; cN+ or tumour size >3 cm 100% N+; 12% T1, 55% T2, 14% T3, 8% T4 9 dye alone, 33 ^{99m}Tc alone; 12 both (dye added only when not identified by ^{99m}Tc alone)	SLN ID Dye Radioisotope Radioisotope + dye if needed FN rate NPV Accuracy	72% (39/54) 44% (4/9) 67% (30/45) 78% (35/45) 11% (3/27) 80% (12/15) 92% (36/39)
	without NACT: SLNB → ALND (N=230); 2% T0, 47% T1, 48% T2, 2% T3	SLN ID FN rate NPV Accuracy	97% (222/230) 10% (10/101) 92% (121/131) 96% (212/222)
Lee, 2007 (181) 2001-2005, Korea	NACT → SLNB (^{99m}Tc and/or dye)→ ALND N=219; T1 (N=42, 19%), T2 (N=133, 61%), T3 (N=23, 11%), T4 (N=15, 7%); mean tumour size 3.4 cm all cN+ dye + ^{99m}Tc when SLN not identified by ^{99m}Tc alone	For pts receiving NACT: SLN ID FN rate NPV Accuracy	78% (170/219) 6% (7/124) 87% (46/53) 96% (163/170)
Ozmen, 2009 (183) [Abstract] 1992-2008, Turkey	NACT →SLNB (dye ± radiocolloid) → ALND N=69; LABC, IIB (46%), IIIA (22%), IIIB (32%); clinically or radiologically positive axilla (N1 or N2) Prospective (?)	SLN ID FN rate NPV Accuracy	85% (58/69) 17% (8/46) 60% (12/20) 86% (50/58)
Shen, 2007 (184) 1994-2002, USA (Texas)	NACT→ SLNB (dye and/or ^{99}Tc) → ALND N=69; N+ (verified by FNA), T1 to T4; Stage IIA (16%), Stage IIB (50.7%), Stage IIIA (13%), Stage IIIB (11.6%), Stage IIIC (8.7%) 8 pts refused ALND Prospective (?)	SLN ID FN rate NPV Accuracy pCR in axilla	93% (64/69) 25% (10/40) 62% (16/26) 82% (46/56) 29%
Brown, 2010 (185) 1994-2007, USA (Texas)	NACT → SLNB (dye and/or ^{99}Tc)→ ALND N=86, operable T1-T3 cN+ (N1-N3) confirmed by ultrasound-guided FNA	FN rate ≤3 nodes SLN ≥4 SLN	22% (13/60) 33% 5%

Author and Year	Study details (comparison, exclusions)	Outcome measures	Results, % (number/total)
	Prospective; retrospective re-analysis of SLN For pts initially N+, the absence of a treatment effect in negative SLN is sensitive in predicting a false-negative SLN	NPV Accuracy	67% (26/39) 85% (73/86)
Clinically node positive and node negative (results combined)			
Kinoshita, 2010 (186); Kinoshita, 2012 (187) [Abstracts] 2003-2008, Japan	NACT →SLNB (dye + radiocolloid)→ ALND N=200; Stage II and III, >3 cm or cN+ [possibly update of Kinoshita 2007]	SLN ID FN rate NPV Accuracy	94% (189/200) 13% (11/85) 90% (104/115) 94% (178/189)
Hino, 2008 (188) 2002-2003, Japan	NACT → SLNB (^{99m}Tc)→ ALND N=55, >3cm; 60% T2, 40% T3 40% cN+, 60% cN0 13/16 with unsuccessful mapping had no radioactivity uptake to axilla	SLN ID FN rate NPV Accuracy	71% (39/55) 0% (0/118) 100% (21/21) 100%
	Subgroup, N0 and tumour <3 cm after NACT, N=29	SLN ID FN rate	93% 0%
Breslin, 2000 (128) 1994-1999, USA (Texas)	NACT → SLNB (dye till 1997, dye + ^{99}Tc after 1997)→ ALND N=51, Stage II to III; T1N1 or T2-3N0-1; median tumour size 5 cm (range 1-13); 49% Stage IIA, 24% IIB, 27% IIIA, 37% cN+ Prospective (?)	SLN ID First pts, 1994-1996 N=17 Group 2, 1996-1997 N=17 Later pts, 1997-1999, N=17 FN rate NPV Accuracy	84% (43/51) 65% (11/17) 94% (16/17) 94% (16/17) 12% (3/25) 90% (18/21) 93% (40/43)
Chiesa, 2010 (189) [abstract] 2003-2009, Italy	NACT → SLNB (dye) → ALND N=50, Stage IIB-IIIAB (N+ or >5 cm)	SLN ID FN rate NPV Accuracy	92% (46/50) 6% (2/31) 9% (15/17) 98% (44/46)
Tio, 2004 (190) [abstract] Germany	NACT→SLNB (dye ± radiotracer)→ALND N=89, LABC Dye in all, 29 both dye + radiotracer [design unknown]	SLN ID Dye alone Dye + radiotracer FN rate NPV Accuracy	93% (83/89) 90% (54/60) 100% (29/29) 6% (2/35) 96% (48/50) 98% (81/83)
Pan, 2012 (191) [Chinese, data from abstract] 2004-2012, China	NACT→SLNB→ALND N=241, LABC Method of lymphatic mapping significantly related to SLN ID rate [design unknown]	SLN ID FN rate NPV Accuracy	86% (208/241) 15% (22/147) 74% (61/83) 89% (186/208)

Note: All studies were prospective unless otherwise indicated. Nodal status was determined prior to NACT unless indicated otherwise.
Abbreviations: ALND, axillary lymph node dissection; cN+, clinically node positive; cN0, clinically node negative; FN rate, false negative; NACT, neoadjuvant chemotherapy; NPV, negative predictive value; SLNB, sentinel lymph node biopsy; SLN ID, Sentinel lymph node identification rate

Definitions

- FN rate=the number of pts with no evidence of cancer in the SLN and at least one positive lymph node by ALND, divided by the total number of pts with at least one positive node by SLNB and/or ALND
- NPV=(TN/(TN+FN)), where TN=true negative and FN=false negative
- Accuracy=(TP+TN)/total=1-(FN/total), where TP=true positive, TN=true negative, and FN=false negative

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Table 7. Treatment for patients with LABC who progress after neoadjuvant therapy.

Author, year	Study design (Group)	Patient characteristics	# patients	Intervention	Outcomes
von Minckwitz, 2008 (53)	GEPARTRIO study TAC vs NX if poor response to TAC	Tumour ≥2 cm, 61% T2, 19% T3, 12% T4a-c, 5% T4d; median 40 mm by palpation and 29 mm by sonography; 42% N0	622	2 cycles TAC then evaluated response. Early responders randomized to 4 (N=704) or 6 (N=686) additional cycles TAC If no sonographic response (reduction in product of 2 largest perpendicular diameters was <50%) then randomized to 4 additional cycles TAC (N=321) or vinorelbine + capecitabine (NX; N=301); excluded those with disease progression	• Sonographic response: 50.5% TAC, 51.2% NX (significant for non-inferiority of NX) • pCR (no invasive or in situ residual tumour masses in breast and lymph nodes): 5.3% TAC vs 6.0 NX • BCS: 57.3% TAC vs 59.8% NX • adverse effects: NX had more hand-foot syndrome and sensory neuropathy but less hematological adverse effects, mucositis, infections, nail changes • Concluded similar efficacy but better tolerability of NX
von Minckwitz , 2013 (108)	GEPARTRIO, see above (53)				Median 62 m follow-up • Early responders: DFS better for TAC×8 than TAC×6 (HR=0.78, 95% CI=0.62-0.97,p=0.026) • Early non-responders: DFS better for TAC-NX than TAC×6 (HR=0.59, 95% CI=0.49-0.82, p=0.001); • DFS for non-responders administered TAC-NX similar to early responders administered TAC×8 • Response-guided therapy (TAC×8 or TAC-NX) better than TAC×6 for DFS overall (HR=0.71, p<0.003) and for subgroups HR+ (luminal A, luminal B) but not HR- or TN • pCR predicted improved DFS in TN, HER2+ (nonluminal) and luminal B (Her2-)
Huober, 2013 (109)	GeparQuinto (GBG 44)	HER2-operable or locally advanced, ≥1cm by ultrasound or ≥2 cm by palpation; must be cT3/4, or HR-, or HR+ N+ (cN+ for cT2 or pN_{SLN}+ for cT1)	403	4 neoadjuvant cycles EC (± bevacizumab) Those without clinical response (no change or progressive disease) were randomized to paclitaxel or paclitaxel + everolimus weekly for 12 w	Overall response 52.2% paclitaxel + everolimus and 61.7% paclitaxel alone (p=0.063). pCR 4.6% overall, 3.6% P + everolimius, 5.6% P alone Conclude everolimus does not improve response. No control group without paclitaxel.

Author, year	Study design (Group)	Patient characteristics	# patients	Intervention	Outcomes
Qi, 2010 (54)	Weekly vs every-3-w paclitaxel to see if better pCR rate in those with poor response to CTF	T1-3, N0-2, M0 invasive breast cancer, histologically confirmed by CNB; 66% ≤2 cm, 22% 2-3 cm, 13% >3 cm after CTF	144	2 cycles CTF and <75% reduction in diameter of tumour by ultrasound → randomized to 4 cycles Pq3wC (Arm A) or Pq1wC (Arm B) → surgery Stratified by partial or no clinical response to CTF: • Partial: ≥50% reduction in diameter and no progression or new disease (N=77) • No response: stable (<50% reduction, or <25% increase) or with progression: ≥25% increase or new lesions (N=144)	Subgroup with no response to CTF: Arm A 62% response and 36% excellent response; Arm B 83% response and 53% excellent response; Treatment delays due to toxicity: 12% Arm A vs 61% Arm B Hematotoxicity 9% Arm A vs 54% Arm B

Abbreviations: CNB, core needle biopsy; CTF, cyclophosphamide + pirarubicin + fluorouracil; EC, epirubicin + cyclophosphamide; Pq3wC, paclitaxel 175 mg/m^2 day 1 + carboplatin (AUC 6 d1) with cycles every 3 w; Pq1wC, paclitaxel 60 mg/m^2 (days 1, 8, 15) + carboplatin (AUC 6 day 1) with cycles every 3 w; TAC, docetaxel + doxorubicin + cyclophosphamide; NX, vinorelbine + capecitabine; pCR, pathologically complete response

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Table 8. Selected studies not meeting inclusion criteria: Second-line neoadjuvant treatments after poor response to initial neoadjuvant therapy.

Study, # patients	Patient Characteristics	Treatment	Assessment	Response

Heys, 2002 (192)
Smith, 2002 (193)
Hutcheon, 2003 (194)
 	
N=162 (55 poor response)
	Aberdeen Study large (≥3 cm) or LABC (T3, T4, or TxN2)	4 cycles CVAP;
		Pts with clinical response randomized to 4 cycles CVAP or docetaxel, rest (stable or progressive disease, N=55) 4 cycles docetaxel
			Partial clinical response is ≥50% reduction in the product of the two max perpendicular diameters of the tumour
			Clinical response after 8 cycles compared with a baseline measured after 4 cycles CVAP; for those with initial response (cCR or cPR) this represents further response; for those without initial response this is the same as total response
				• After 4 cycles CVAP: 66% clinical response
				• Randomized pts:
				  • 8 cycles CVAP: 15% pCR and 64% clinical response
				  • CVAP→ docetaxel: 31% pCR and 85% clinical response
				• Nonrandomized: 2% pCR, 47% clinical response

Xu, 2009 (195) N=19 [Chinese, data from abstract]	Operable breast cancer in pts previously nonresponsive to neoadjuvant anthracycline and taxane-containing regimen	2 cycles vinorelbine + cisplatin (NP)	Nonresponsive defined as those without complete or partial remission Clinical objective response evaluated by MRI	53% clinical response (CR+PR) 90% pathological response (grade 2-5)
Alvarez, 2010 (196) N=88	LABC, Stage IIB, IIIABC; neoadjuvant doxorubicin + docetaxel (DT)	CMF if insufficient response to DT (N=14) (Phase II study)	Partial clinical response is ≥50% reduction in the product of the two max perpendicular diameters of the tumour; assessed by physical exam, ultrasound, and mammography	90% clinical response to DT (3% cCR, 86% cPR); 84% response adequate for surgery After CMF 36% became operable
Amat, 2006 (197) N=53	Bulky operable breast cancer	Sequential neoadjuvant docetaxel then TNCF (Phase II study)	Average of clinical, mammographic and ultrasound measurements of tumour and nodes, evaluated decrease in tumour and node volumes (product of the two max perpendicular diameters); independent blinded pathology review	64% clinical response after docetaxel 81% clinical response rate (13% cCR) after docetaxel→ TNCF 11% pCR in breast and axilla
Gaui, 2007 (198) N=28	Inoperable LABC refractory to first-line anthracycline-based treatment	Radiotherapy plus concomitant capecitabine (Phase II study)	Physical examination before each cycle of chemo and before surgery. The product of the 2 greatest perpendicular diameters of the breast tumour was calculated. Complete response if no clinical evidence of tumour, partial response if reduction in tumour size ≥50% , stable if reduction but <50%, progressive disease if new suspicious lesion or tumour growth	82% became operable Median decrease in tumour size from 80-49 cm^2, 1 patient (4%) pCR, 3 pts (13%) with microscopic residual disease

Study, # patients	Patient Characteristics	Treatment	Assessment	Response
Heller, 2007 (199) N=88 (21)	LABC, primary tumours without metastasis that were too extensive for conservative surgery, failed to respond to neoadjuvant FEC (N=21)	FEC →docetaxel; docetaxel administered if response to FEC was insufficient	cCR is resolution of all target lesions, cPR is ≥30% decrease in sum of the longest diameter of target lesions pCR is no invasive tumour on histological exam (carcinoma in situ allowed) in the breast and no tumour whatsoever in surgically removed lymph nodes	FEC: 27% cCR, 51% c PR, 10% pCR FEC→ docetaxel subgroup: 14% cCR, 48% cPR%, 9.5% pCR Overall clinical response rate of 90% for FEC ± docetaxel
Huang, 2002 (200) N=38	Inoperable anthracycline-resistant breast cancer, T3 or Stage III-IV (only supraclavicular lymph node metastasis)	Radiotherapy to breast and surrounding lymphatic regions immediately after primary chemo	Retrospective study of pts with insufficient response to neoadjuvant chemo. Complete response is total resolution assessed by physical or radiological exam. Partial response is ≥50% reduction of the product of the 2 largest perpendicular dimensions of the mass	Primary chemo: Overall clinical tumour response 18% Overall clinical nodal response 23% 84% operable after RT (31% still needed myocutaneous reconstruction)
Ueno, 2006 (201) N=42	Inoperable breast cancer refractory to neoadjuvant chemo; less than PR to doxorubicin or taxane regimen and then crossover to the other; 13 pts still inoperable	High-dose chemo (HDCT) with cyclophosphamide, carmustine, thiotepa + autologous peripheral blood stem cell transplant	PR defined as a reduction >50% of the sum of the products of 2 greatest perpendicular diameters of each measurable lesion; response determined by both physical exam and radiographic studies	54% of inoperable pts became operable after HDCT
Untch, 2010 (202) N=1509	Operable N+ or locally advanced (cT3 or cT4); HER2+ (N=445); control group HER2- (N=1058) GeparQuattro Study	Epirubicin/ cyclophosphamide →docetaxel ± capecitabine; and trastuzumab if HER2+	pCR defined as no invasive or in situ residual tumours in the breast clinical response assessed preferably by ultrasound, or if not possible, by mammography or physical exam	32% pCR HER2+ 16% pCR HER2- Subgroup without response to EC: pCR 17% HER2+ and 3% HER2-
Wenzel, 2005 (203) N=13	Patients that failed to respond to first-line preoperative chemo	Epidoxorubicin + docetaxel → CMF (as second line; N=8) FEC→ paclitaxel or docetaxel as second line (N=5)	Tumor size determined clinically and by mammography, sonography, or MRI and monitored radiologically by the must suitable method cCR defined as disappearance of all measurable disease cPR was at least 50% decrease in tumour size pCR defined as disappearance of all signs of invasive tumour confirmed by the pathologist (yT0 or yDCIS) Failed to respond was stable disease (<50% reduction in size)	77% major response, 8% pCR (1 patient), 69% partial response

Study, # patients	Patient Characteristics	Treatment	Assessment	Response
Wang, 2013 (204) [Chinese, data from abstract] N=33	Pts nonresponsive to anthracycline + taxane	Vinorelbine + cisplatin (NP)	Clinical objective response evaluated with dynamic contrast-enhanced MRI according to RECIST 1.1, pathological response evaluated by Miller-Payne grading	48.5% clinical response (partial remission) Pathological response: 30% G3 (30%- 90% reduction in tumour cells), 27% G4 (>90% loss), 6% G5 (pCR)
Halim, 2012 (205) N=70	LABC, not suitable for BCS, no early response to 2 cycles TAC	Vinorelbine + gemcitabine	Objective response evaluated clinically with breast sonography, pathological response determined postoperatively	50% clinical response, 5.7% pathological response
Carmona Vigo, 2012, 2013 (206,207) [abstracts] N=184	LABC, Stage IIIB, unresponsive to systemic therapy; 99% T4, 46% inflammatory (T4d), 48% N0	Radical RT at high dose, hyperfractionated	Median follow-up of survivors was 106 m	88% response rate, 82.5 complete response, 6.2% partial response local DFS 81.5% at 15 y, cause-specific survival 37.1%
Lee, 2012 (208) [abstract] N=12	TN, LABC, progressed during neoadjuvant chemo (N=6) or rapid recurrence (N=3)	Salvage XRT ± cisplatin	Tumour response by physical assessments and imaging	11/12 pts had partial or complete clinical response 4/8 pts with surgery had pCR
Shaw, 2011 (209) [abstract] N=287	LABC, Stage IIB, IIIAB, poor response to neoadjuvant chemo	Preoperative concurrent chemoradiotherapy		at average 64 m follow-up was 37% relapse and 55% disease free, 10-y survival probability 60%

Note: Clinical response is the sum of clinically complete response and clinically partial response (cCR + cPR)
Abbreviations: cCR, clinically complete response; cPR, clinically partial response; CR, complete response; CVAP, cyclophosphamide + doxorubicin + vincristine + prednisolone; FEC, fluorouracil + epirubicin + cyclophosphamide; pCR, pathologically complete response; PR, partial response; TNCF, theprubican-doxorubicin + vinorelbine + cyclophosphamide + 5-fluoruracil

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Table 9. Planned or ongoing studies.

Trial Name or investigator	Description	Reference
Korean Radiation Oncology Group (KROG) 08-06. Investigator: Yoonsun Chung	Phase 3 multi-institutional randomized trial started in 2008 to investigate the role of internal mammary lymph node irradiation in patients with breast cancer. Node positive patients (N=748) after BCS or mastectomy are randomly assigned to RT ± IM nodes.	Mentioned in Chang 2013 (210)
Athena Breast Cancer Network	A single-arm prospective observational study planned within the University of California Athena Breast Health Network. PMRT will be omitted in selected patients after NACT (selected low-risk female patients, intermediate-risk group based on biology and clinical pathologic factors).	Mentioned in Fowble 2013, 2012 (34,35)
NCT02031042, Stockholm South General Hospital / Swedish Breast Cancer Group	Sentinel node biopsy before and/or after NACT in breast cancer. Currently recruiting	http://clinicaltrials.gov/show/NCT02031042
Alliance Co-operative Group A011202, [merger of American College of Surgeons Oncology Group (ACOSOG), Cancer and Leukemia Group B (CALGB), and North Central Cancer Treatment Group (NCCTG)]. NCT01901094	"A Randomized Phase III Trial Evaluating the Role of Axillary Lymph Node Dissection in Breast Cancer Patients (cT1-3 N1) Who Have Positive Sentinel Lymph Node Disease After Neoadjuvant Chemotherapy". The study seeks to define the standard of care for axillary management in patients with residual N+ disease after NACT. The trial will include cT1-3N1 patients treated with NACT. Patients with positive SLN (ypN+) will be randomly assigned to completion ALND or axillary radiation. All patients will receive radiation to the breast or chest wall (depending on the type of breast surgery) and to the undissected supraclavicular and level III axillary nodes. Currently recruiting.	http://clinicaltrials.gov/show/NCT01901094 http://www.allianceforclinicaltrialsinoncology.org/
The NSABP (National Surgical Adjuvant Breast and Bowel Project) B51/RTOG (Radiotherapy Oncology Group) 1304 (NCT01872975)	Clinically N1 before NACT and then ypN0 in dissected axillary nodes (SLNB or ALND) at time of surgery. After mastectomy, patients are randomly assigned to no RT vs chest wall and regional nodal RT, and after lumpectomy, random assignment is to breast RT alone vs breast and regional lymph node RT. The trial started in 2013, with estimated final data collection for primary outcome, and study completion in 2028. Currently recruiting.	http://clinicaltrials.gov/show/NCT01872975 http://www.nsabp.pitt.edu/B-51.asp
NSABP-RTOG 9353	See NSABP B51 above as it appears to be the same study	(34,211)
SUPREMO (Selected Use of Postoperative Radiotherapy after Mastectomy), BIG-2-04, EORTC 22051	Started 2006-2009 in various countries. Target accrual 3700. Comparison of chest wall RT or no chest wall RT in patients with 1-3 involved LN or N- with grade 3 histology and/or lymphovascular invasion, mastectomy. The primary endpoint will be OS at 5 y, powered to detect a 4% difference in OS; follow-up planned at least 10 y. Will also be cardiac and quality of life substudies, and tissue microarrays to identify molecular signature of radiosensitivity and relapse.	Kunkler, 2009 (212) http://clinicaltrials.gov/show/NCT00966888

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Evidence-Based Series #1-19: Section 3

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

Locoregional Therapy of Locally Advanced Breast Cancer (LABC): Development Methods, Recommendations Development and External Review Process

Muriel Brackstone, Glenn G Fletcher, Ian Dayes, Yolanda Madarnas, Sandip SenGupta, Shailendra Verma, and Members of the Breast Cancer Disease Site Group[5]

Report Date: September 29, 2014

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (56). 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 care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC produces evidence-based and evidence-informed guidelines, known as Evidence-Based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (56,213). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

This EBS is comprised of the following sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its

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

interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.

- *Section 2: Evidentiary Base.* Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: Development Methods, Recommendations Development, and External Review Process.* Summarizes the EBS development process, the recommendations development process and the results of the formal external review of the draft version of the EBS.

FORMATION OF GUIDELINE DEVELOPMENT/WORKING GROUP

The Breast Cancer DSG asked the PEBC to develop a guideline on locoregional therapy in locally advanced breast cancer (LABC). In consultation with the DSG, a Working Group was identified from the DSG membership. This Working Group consisted of one surgeon, two medical oncologists, one radiation oncologist, one pathologist, and one health research methodologist. The Working Group and DSG also formed LABC guideline development group. This group would take responsibility for providing feedback on the guideline as it was being developed and acted as Expert Panel for the document at Internal Review, reviewing the document and requiring changes as necessary before approving it.

RESEARCH QUESTIONS

The Working Group developed the following research questions:

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

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

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

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

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

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

GUIDELINE REVIEW

Almost all PEBC document projects begin with a search for existing guidelines that may be suitable for adaptation. The PEBC defines adaptation, in accordance with the ADAPTE Collaboration, as "the use and/or modification of (a) guideline(s) produced in one cultural and organizational setting for application in a different context" (214). This includes a wide spectrum of potential activities from the simple endorsement, with little or no change, of an existing guideline, to the use of the evidence base of an existing guideline with *de novo* recommendations development.

For this document, an Internet search of Canadian and international health organizations, as well as MEDLINE and EMBASE was conducted to identify existing clinical practice guidelines, systematic reviews, and health technology assessments relevant to our guideline questions. Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the AGREE II instrument.

EVIDENTIARY BASE DEVELOPMENT

Using the research questions described previously, a search for RCTs, meta-analyses, and existing systematic reviews was conducted using the MEDLINE and EMBASE databases (1996 to December 2013) and the Cochrane Library, as described in Section 2 of this EBS.

INITIAL RECOMMENDATIONS

Using the evidentiary base in Section 2, the Working Group developed a set of initial recommendations. These initial recommendations were developed through a consideration of the aggregate evidence quality and the potential for bias in the evidence and the likely benefits and harms of BCS vs mastectomy, radiotherapy (RT) use or extent, and of SLNB vs axillary lymph node dissection (ALND). The Working Group considered the values they used in weighing benefits compared with harms, and then made a considered judgment. This process is described in detail for each topic area.

Topic Area 1. Breast Conserving Surgery vs Mastectomy After NACT

Key Evidence for Benefits and Harms

BCS is considered to have generally better cosmetic effects and, for some female patients, may have less impact on body image, self-esteem, and sexuality than complete breast removal by mastectomy. With BCS there is usually no need for additional reconstructive surgery and the operation may be less complex. In some cases of BCS there may be positive margins requiring re-excision. The risks of recurrence and breast cancer mortality may be higher with BCS than mastectomy. There were no RCTs found to prove or disprove this. In cases of recurrence after BCS, further surgery may be needed and some patients would rather reduce this possibility by having mastectomy as initial treatment.

Aggregate Evidence Quality and Potential for Bias

No RCTs on this topic were found in the literature review. Recommendations are based on current practice and use of BCS plus RT in early breast cancer (which overlaps with the definition of LABC).

Values of the Working Group

The survival rate is unlikely to be worse with mastectomy, but there is insufficient evidence to determine whether it is equivalent or better than BCS. The Working Group valued long-term recurrence and survival outcomes (which are either equivalent or better with mastectomy) more highly than psychosexual issues or short-term adverse effects (which are better with BCS). Some patients may have a strong preference for BCS, especially if the risk of recurrence is very low.

Considered Judgment

It is recommended that modified radical mastectomy continue to be the standard of care in LABC. BCS plus RT may be considered for some patients with non-inflammatory LABC on a case-by-case basis when the full tumour bed can be resected (disease can be resected completely), especially when there is strong patient preference for breast conservation.

Topic Area 2a. Radiotherapy aafter Mastectomy

Key Evidence for Benefits and Harms

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis found that recurrence rates after RT were lower in patients with node-negative cancer compared to patients who did not receive RT. Recurrence rates with RT were also lower in patients with positive nodes both overall and in all subgroups analyzed. RT improved survival rates in patients with positive nodes. The 2005 meta-analysis found RT resulted in lower survival in patients with node-negative cancer who had mastectomy plus axillary clearance. The latest 2014 analysis subdivided patients with node-negative cancer by type of axillary dissection (sampling or clearance). In the clearance group RT had no effect on recurrence rates but a detrimental effect on survival rates, whereas in the axillary sampling group RT resulted in less recurrence and no effect on the mortality rate. The detrimental effects of RT on survival are thought to be due to cardiovascular/pulmonary adverse effects. These are greatly reduced when RT is administered with modern 3D planning and techniques, compared with those used in the older studies (which started approximately 30-50 years ago).

Although the relative recurrence and breast-cancer specific survival benefits are still expected to exist, the absolute benefit may be very small for those at very low risk of recurrence due to optimal systemic therapy or other patient characteristics. In these cases, the benefit needs to be weighed against the risk of adverse effects of RT. Most of the included studies analyzed long-term follow-up and therefore were not concerned with early effects.

Lymphedema is more likely when surgery includes ALND or/and when RT includes the nodal areas. Comparing groups with RT to without RT, the BC study (112,113) found 9% vs 3% arm edema, the DBCG 82b&c trials (114) found lymphedema rates of 14% vs 3% (NS) by objective assessment and 43% vs 17% (p=0.02) by subjective assessment, and the South Sweden study (115) found 6.8% vs 3.9% lymphedema. The DBCG 82b&c trials also reported a significant decrease in shoulder mobility (objective assessment 45% vs 15% slight and 5% vs 0% moderate/severe, p=0.004; symptomatic 17% vs 2%, p=0.001). Decreased strength (14% vs

2%), arm weakness (28% vs 19%), and paresthesia/hypesthesia (21% vs 7%, NS) were also reported.

The ECOG EST3181 study (116) found 7.5% severe adverse effects in the RT patients (2.7% skin/mucosa, 2% hematologic, 0.7% infections/respiratory/hepatic/other) vs 3% without RT. The BMFT 03 German study (18) found that 25% of RT patients had acute skin reactions, and 28% had long-term skin alterations (1-2 years after RT). Radiation pneumonitis has been reported in approximately 1-4% of patients (33,115,117), although this increased to 23% (p=0.008) when RT and anthracycline chemotherapy were both used. Note that the higher rates were in older trials (enrolment 1978-85) and the more recent MA.20 trial reported grade ≥2 pneumonitis of 1.3% with RT vs 0.2% without RT (p=0.01). There is also a very low risk of rib fracture or brachial plexopathy (18,115). In some of the older RT regimens there was a significant excess of contralateral breast cancer and non-cancer mortality, primarily from heart disease and lung cancer (15). The Stockholm study reported higher risk of second primary tumours (12% vs 5%, p=0.01), especially lung cancers after 10 years (3.7% vs 0.3%) (19). Other than lymphedema and early (often transient) effects on the skin, careful treatment planning is likely to reduce (but not eliminate) the other risks.

Aggregate Evidence Quality and Potential for Bias

The conclusion is based on individual patient meta-analysis of all studies; therefore, it is considered to be of highest quality. Data are limited for the T3N0 subgroup as it was not analyzed separately from T1-2N0 (considered as early breast cancer). RT improves survival rates for all N+ subgroups studies, but there were no studies including taxanes or other newer chemotherapies.

Values of the Working Group

The Working Group valued minimizing recurrence and mortality rates over other adverse effects. There may be subgroups for which the benefit is small due to their low risk of recurrence, and in these patients treatment needs to be decided on an individual basis.

Considered Judgment

Radiotherapy following mastectomy is recommended for patients with LABC.

Topic Area 2b. Locoregional vs Breast/Chest Wall

Key Evidence for Benefits and Harms

A meta-analysis of three trials (25) concluded that regional RT to internal mammary (IM) and medial supraclavicular (MS) nodes improves DFS, OS, DMFS rates in Stage I-III breast cancer. Adverse effects of RT are as described for Question 2a, although lymphedema may be more severe when locoregional radiation is used. The need for three-dimensional treatment planning is likely greater; in its absence adverse effects on cardiovascular and pulmonary systems may outweigh benefits for lower-risk patients.

Aggregate Evidence Quality and Potential for Bias

Three studies have been conducted; however, two of these have been only been reported in abstract form. These studies included different sets of nodes (IM, MS, or all locoregional nodes) and different subgroups of patients. Although the conclusion is that

locoregional radiation is needed, it is not possible to specify exactly which nodes need to be included.

Values of the Working Group

The Working Group valued minimizing recurrence and mortality rates over other adverse effects. There may be subgroups for which the benefit is small due to their low risk of recurrence; in these patients treatment needs to be decided on an individual basis.

Considered Judgment

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

Topic Area 2c. RT After Pathologically Complete Response

Key Evidence for Benefits and Harms

Harms of RT are as indicated in 2a and 2b. The potential benefit would be reduced recurrence and mortality rates.

Aggregate Evidence Quality and Potential for Bias

No prospective randomized studies were found in the literature review that randomized patients after pathologically complete response (pCR). Therefore, there is no justification to change the current standard of care, which is to administer RT.

Values of the Working Group

The Working Group valued minimizing recurrence and mortality rates over other adverse effects.

Considered Judgment

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

Topic Area 3. SLNB or ALND for Staging Wwhen NACT is Used

Key Evidence for Benefits and Harms

ALND is more invasive surgery than SLNB and there is higher risk of surgical complications and of lymphedema occurring or being more severe. Some people have allergies to the blue dye used in SLNB. ALND results in more complete removal of lymph nodes and therefore there are fewer nodes left that could contain residual cancer. There is no evidence as to whether this has clinical impact on treatment or survival.

Aggregate Evidence Quality and Potential for Bias

Studies found that SLNB is technically feasible, but did not compare ALND to SLNB for determining the most appropriate treatment or for long-term outcomes.

Values of the Working Group

The Working Group valued long-term survival more highly than increased risks of lymphedema or other surgical complications.

Considered Judgment

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

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

Topic Area 4. Treatment in Patients Who Do Not Respond to NACT

Key Evidence for Benefits and Harms

There is no evidence for relative benefit or harm in the literature review because relevant RCTs were not found.

Aggregate Evidence Quality and Potential for Bias

Anthracycline-taxane is standard therapy, but sometimes anthracycline is administered first. In these cases, the taxane portion should also be administered as shown in the NSABP B-27 trial and according to current practice. There is little other RCT evidence on which to base recommendations and only suggestions for possible approaches are provided.

Values of the Working Group

The Working Group values saving the patient's life; therefore, further treatment is recommended. Some treatments may have adverse effects.

Considered Judgment

It is recommended that patients receiving neoadjuvant anthracycline-based therapy whose tumours do not respond or where there is disease progression be expedited to the taxane portion of the anthracycline-taxane regimen.

For patients who fail to respond or who progress on first-line NACT there are several therapeutic options to consider, including second-line chemotherapy, hormonal therapy (if appropriate), RT, or immediate surgery (if technically feasible). Treatment should be individualized considering tumour characteristics, patient factors and preferences, and risk of adverse effects. Management of patients who do not respond to initial neoadjuvant therapy should be individualized through discussion at a multidisciplinary case conference.

It is recommended that clinical trials be designed for patients with LABC who fail to respond to NACT in a prospective, randomized fashion so that more definitive treatment recommendations can be obtained.

INTERNAL REVIEW

Almost all PEBC documents undergo internal review. This review is conducted by the Expert Panel and the Report Approval Panel. The Working Group was responsible for incorporating the feedback and required changes of both of these panels, and both panels had to approve the document before it could be sent to External Review.

Expert Panel Review and Approval

The Breast DSG acted as the Expert Panel for this document. The members of this group were required to submit conflict of interest declarations before reviewing the document. These declarations are described following the Internal/External Review sections. The document had to be approved by formal vote. To be approved, 75% of the DSG membership needed to vote or abstain; of those who voted, 75% had to approve the document. At the time of the voting, the DSG members could suggest changes to the document, and possibly make their approval conditional on those changes. In those cases, the Working Group was responsible for considering the changes, and if those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted for approval again.

The document was circulated by email to the DSG members on May 7, 2014 and all members responded by May 28, 2014. There were 18 votes and one abstention. Of the votes, there were eight approvals and nine additional approvals with some suggestions for consideration. One person did not approve unless changes were made. Approval was 94%; therefore, the guideline was considered to be approved by the DSG.

The Working Group considered all the feedback and made some changes to Section 1 as a result. Almost all the comments were related to the definition of LABC, and whether Stage IIB should be excluded or commented on separately. Although one reviewer preferred that Stage IIB be removed from the definition of LABC, the Working Group decided that it was not feasible or desirable to redo the evidence summary because most studies contained a heterogeneous patient group and extremely few dealt specifically with Stage III cancers. As suggested by one reviewer, we incorporated the footnote describing the rationale and limitations of the LABC definition into part of the text of Target Population (see page 1-2 of Section 1) because this is essential to the document and addresses some of the other comments. There was concern that Recommendation 1 stated modified radical mastectomy is the standard of care for LABC (i.e., for all patients with LABC), and that this did not really apply to patients with Stage IIB breast cancer. Although the Working Group did not feel it appropriate to list all situations in which BCS may be considered, Recommendation 1 was modified to clarify that mastectomy does not apply to everyone, and the judgment of the surgeon (as well as patient preference) is required.

Recommendation 1 as Circulated to the DSG:

- It is recommended that modified radical mastectomy continue to be the standard of care in locally advanced breast cancer (LABC).

- Breast-conserving surgery (BCS) plus RT may be considered for some patients with non-inflammatory LABC on a case-by-case basis when the full tumour bed can be resected (disease can be resected completely), especially when there is strong patient preference for breast conservation.

Revised Recommendation 1 as a Result of Comments:

- For most patients with LABC, modified radical mastectomy should be considered to be the standard of care.

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

A qualifying statement was also revised to clarify that evidence is weak for BCS in LABC overall, but that there are exceptions.

As a result of two comments, we included a qualifying statement for Recommendation 1 indicating that there is continuing evolution in the type of surgery offered (e.g., skin-sparing mastectomy with immediate reconstruction), but these are beyond the scope of this guideline. One comment on Question 4 suggested some patient groups (e.g., ER+, lobular histology) do not respond as well to chemotherapy. Although commented on in Section 2 of this EBS, the Working Group believes that Recommendation 4-2 (consider second-line chemotherapy, hormonal therapy if appropriate, RT, or immediate surgery) is sufficient. A separate guideline on lobular cancer may be useful, but is not feasible to assess in the current guideline.

Report Approval Panel Review and Approval

The purpose of the Report Approval Panel (RAP) review is to ensure the methodological rigour and quality of PEBC documents. The RAP consists of nine clinicians with broad experience in clinical research and guideline development, and the Director of the PEBC. For each document, three RAP members review the document: the Director and two others. RAP members must not have had any involvement in the development of the guideline before Internal Review. All three RAP members must approve the document, although they may do so conditionally. If there is a conditional approval, the Working Group is responsible for ensuring the necessary changes are made; with the Assistant Director of Quality and Methods, PEBC, making a final determination that the RAP's concerns have been addressed.

In May–July 2014 the RAP reviewed this document. The RAP approved the document on July 29, 2014.

Key issues raised by the Report Approval Panel included the following:

1. The health benefits are well described throughout. Section 3 describes the possible risks/side effects of the various treatments and procedures and I would suggest the main/salient negative aspects of each question be integrated in Section 2.

2. The qualifying statements and key evidence are too long and narrative; this detracts from the explicitness one comes to expect from recommendations. I would encourage the authors to limit themselves to statements and incorporate some of the text into Section 2. The deliberations by the guidelines group (p 69) are very good and the reader should be referred should be referred there.

3. Some of the wording used in Section 2 to indicate study selection criteria is unclear.

4. Consider adding references to identify specific clinical practice guidelines at the start of the Results section.

5. For Question 1 it is stated that guidelines were not endorsed in full as they do not address the question based on RCT evidence. Some readers may find it confusing they are still cited in Section 1. It would be helpful to explain the process the group used.

6. Recommendations 2a and 2b have bullets outside the recommendation box. Are these part of the recommendations?

7. 2b includes evidence from three RCTs that do not currently meet the inclusion criteria. This needs to be clear.

8. It is unclear how many references were retained for each of the questions.

9. Consider rewording the questions to more clearly indicate at what point a decision is being made.

10. The volume of material and level of detail is so great the message is sometimes lost.

The Working Group made the following changes in response to the RAP review:

1. Additional discussion of adverse effects has been added to Section 2.

2. Key evidence and qualifying statements were edited to include only the most important details. The reader is referred to Section 2 for more details. Statements on adverse effects were retained as this is mandated in the PEBC guideline process.

3. The description of study selection criteria was reworded to be clearer to the reader.

4. Guidelines are already listed in Appendix C. Citations have been added to the text.

5. A sentence was added in the overall results portion to indicate that "endorsement" of another guideline before the systematic review is a very narrowly defined process which would replace the PEBC preparing a guideline. A decision to not endorse a guideline overall does not preclude endorsing portions during the recommendation process.

6. These were meant to supplement the recommendation but not be part of it. These points have been incorporated into the qualifying statements.

7. Both Section 1 and 2 have been revised to ensure it is clear that these studies are in a broad group of patients with Stage I-III cancer, and not specifically LABC, and do not meet the inclusion criteria of approximately ≥50% LABC in either the full study or reported subgroup analysis.

8. This is now stated more explicitly overall and for each question.

9. The questions have been reworded as suggested.

10. See response 2. Some portions of Section 2 were also deleted or shortened.

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following approval of the document at Internal Review, the draft document with recommendations modified as noted under Internal Review was circulated to external review participants for review and feedback

Methods

Targeted Peer Review: During the guideline development process, ten targeted peer reviewers from across Canada considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Several weeks before completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Seven reviewers agreed (two surgical oncologists, three radiation oncologists, two medical oncologists) and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on August 15, 2014. Follow-up reminders were sent at two and three weeks. The Working Group reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Medical oncologists, surgical oncologists, surgeons (including general surgeons and plastic surgeons), radiation oncologists, pathologists, and advanced practice nurses in the PEBC database who had indicated breast cancer as an area of interest were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. The notification email was sent on August 19, 204. The consultation period ended on September 16, 2014. The Working Group reviewed the results of the survey.

Results

Results of the Targeted Peer Review are given in Tables 10 and 11, while results of the Professional Consultation are reported in Tables 12 and 13. Concerns or suggestions for improvement along with the response of the authors are listed for both the targeted peer review and professional consultation. For professional consultation 28 responses were received: 10 medical oncologists, 4 pathologists, 6 radiation oncologists, 5 surgeons, and 3 surgical oncologists. Several indicated it is an excellent guideline.

Table 10. Responses to nine items on the targeted peer reviewer questionnaire.

Targeted Peer Review Question	Reviewer Ratings (N=7)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				4	3
2. Rate the guideline presentation.			1	4	2
3. Rate the guideline recommendations.			1	3	3
4. Rate the completeness of reporting.			1	3	3
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			2	3	2
7. Rate the overall quality of the guideline report.			1	4	2
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
8. I would make use of this guideline in my professional decisions.			1	2	4
9. I would recommend this guideline for use in practice.			1	2	4

6. What are the barriers or enablers to the implementation of this guideline report?

Barriers may be lack of knowledge of the guideline by surgeons and oncologists (especially those in community hospitals), disagreement with recommendations, and resistance to the use of neoadjuvant therapy in operable LABC patients. The data may be overwhelming for some readers. There appears to be no dedicated plan for implementation other than publication.

Enablers include that the guideline addresses common questions in need of guidance and increased awareness possible if referred to in multidisciplinary tumour boards. Recommendations are consistent with clinical practices in most centres.

Summary of Written Comments
The main points contained in the written comments and the guideline authors' responses are provided in Table 11.

Table 11. Targeted peer review comments and Working Group responses.

Comment	Authors' Response
Add area of practice in the author list.	Added
In the results section (especially Question 2a) it is easy to get lost in the detail but this speaks to the volume of data available. A shorter text may help.	This has been edited and some material on other systematic reviews deleted. Tables have been relocated to the end of the results section for better readability.
This is a fantatsic collection of data. It might be helpful to consider use hyperlinks to allow a reader to specifically review the evidence base for one recommendation at a time.	Hyperlinks have been added
Rec 1: Be careful of terminology. Surgical wide excision of the remaining tumor in the original tumor bed [appropriate] vs any tissue previously involved [not appropriate]) Resection of all the tissue previously involved is not necessary.	This is a difference in interpretation. We mean that all tumour must be removed. A sentence was added to clarify that after response to NACT this would be a smaller tumour of tissue excised.
Rec 1: Mention importance of prechemotherapy clip placement in pts considering BCS in a qualifying statement (in addition to preamble). Also consider stating that clip placement within the lumpectomy cavity at the time of surgery for pts undergoing BCS, especially if the pt is having oncoplastic sugery is also important to radiation oncologists.	Added a sentence to the quallifying statements. We are not aware of data on whether this helps with radiation accuracy and it was not part of the review.
Rec 1: It should be "mastectomy" instead of "modified radical mastectomy" as this refers to lymph node surgery as well which is already addressed in in question 3.	This has been changed.
Rec 2a: Revise qualifying statement bullet 4 … improvements in recurrence and disease-specific survival rates have not necessarily translated into advantages **in OS in low risk groups (RT vs no RT risk < 10%).**	Wording has been revised
Rec 2a It could be clearer in the discussion/qualifying statement that many N0 patients included in the EBCTCG analysis do not have LABC and thus drawing conclusion from the analysis for LABC patients would be erroneous.	It is stated clearly that the node-negative group consists of patients with primarily early cancer ant therefore there is limited data for T3N0.
Rec 2a. It is unfortunate that the literature search was done prior to the recent EBCTCG publication; much of the uncertainty in the qualifying statement/discussion with respect to the survival benefit of PMRT in node positive patients could have been eliminated based on the most recent report.	The authors had looked at the EBCTCG 2014 publication(16) and determined it would not affect the recommendations. However the data has been added and integrated better into the document.
Rec 2b: With respect to PMRT for T3N0, the traditional indication for PMRT was disease >5cm (i.e T3); in fact, the last Canadian national guideline published in CMAJ recommended PMRT. Perhaps this point should be discussed and acknowledged.	True pathological T3N0 is rare, as many patients with cT3N0 disease are later found to have involved nodes. There is insufficient evidence to not use PMRT
Rec 2b: First sentence of qualifying statement bullet 3 is unclear, suggest "In light of incomplete data, any recommendations regarding the role of regional radiation **to specific nodal groups (e.g., IMC, MS, apical axilla, full axilla)** in LABC are significantly limited."	Wording has been revised
Rec. 2c can be incorporated into Rec. 2a.	As this was a separate question to be

	answered, it is prefered that the recommendation also be separate.
Rec 3: SLNB after NACT: Do you want to add (as per ACOSOG Z1071 and SENTINA) that more than 2 sentinel nodes and dual tracer use decrease the FN rate?	This was inadvertently omited during editing and has been added back. While preferred, it is not always possible to identify more than 1 sentinel node.
Rec 3.1: Key Evidence; The FN rate in ACOSOG Z1071 was greater than 12% when 2+ SN were removed (more than 14% if 1+SN were harvested). This is not reflected by the statement that says that the FN are not dissimilar than for early breast ca.	A sentence was lost during revisions and the last sentence (… are not dissimilar) should not refer to the Z1071 trial. This has been reworded.
Rec 3.1: Qualifying Statement 2 is quite confusing: "If no RT is given, ALND is recommended". The patients that would not be selected for RT will probably have lower risk cancer. Post neoadjuvant, if a SNBx is negative for a patient that presented with a 6cm tumor of the breast that is treated with mastectomy, there is little evidence that RNI would be of any benefit. I would recommend removing this statement, It adds little to the recommendation anyways.	RT is recommended for all LABC patients (see Rec 2a) based on very strong evidence. If this recommendation cannot be followed, then we recommend ALND. It needs to be stressed these are LABC patients receiving neoadjuvant chemotherapy and therefore not generally lower risk. Trials are ongoing.
Rec 3.1: Qualifying statement 3: Remove completely. This is not supported by any data and does not add to the strength of the recommendation.	Agreed
Rec 3.2: Another benefit of SNBx after NACT is that there will be a decrease in the number of ALND 2nd to axillary pCR (as per B-27/Mammounas). If the SNBx is done prior to NACT, all patients with node + disease will have ALND since repeat SNBx after NACT is not accurate.	B27 SNL was a substudy that was NOT randomized therefore cannot comment on reduction in ALND and SLN negative rates after. As discussed, there is insufficient evidence to make a recommendation regarding timing of SLNB
Rec 4.1: Is there any specific data that supports only the early move from anthracycline to taxane? The use of taxane followed by anthracycine is also very common and increasing in use. If the panel recommends not giving an ineffective regimen, I suggest changing the recommendation to : in the presence of an anthracycline-taxane based regimen …. be expedited to the next agent – or something similar	Agree and have reworded the recommendation.
Rec 4.3: I am not certain that it is appropriate for this recommendation to be present in an evidence based guideline. Certainly, everybody would love to see a RCT in patients resistant to NACT. But number of events would be so small – and subtype of patients different - that this is very unlikely to happen. **I suggest removing it.**	The recommendation has been removed and the need for trials mentioned under "Future Research"
Rec 4-2: in cases of patients that fail to respond or progress on first line NACT, the consideration for alternatives such as second line chemo, radiation, surgery etc. is very vague other than to discuss in multidisciplinary conferences. This could be made more clear and be more helpful for decision making	There was insufficient evidence to recommend particular strategies and this is most appropriately decided on a case-by-case basis in multidisciplinary conference.
How do we define stable and progressive disease? After how many cycles without response should we switch to another agent?	Definitions used in the studies are in Table 7 however there is no uniform definition in the oncology community. Studies tended

	to switch if progressive disease was noted after 2-4 cycles but this needs to be decided individually.
The document's position on T3N0(IIB) disease is not clear (and it is possible that it is impossible to be clear regarding this group). The document makes a qualifying statement that the decision regarding the use of PMRT should be individualized but is confusing with regards to recommendation for CW alone vs CW and nodal radiation. The final sentence in the final bullet in the qualifying statements for Recommendation 2b suggests that the full axilla should be radiated in patients with anything less than ALND. Does the group feel that SLNB is not adequate in this group?	Added a statement that cancers clinically T3N0 are often (>50% of the time) found to have pathologically involved nodes, and therefore should be considered T3Nx unless there is SLNB prior to NACT, or full ALND. In the later case, they may be treated as for T2N0.
The quoted risk of pneumonitis (4%) seems high; maybe a range would be important here. Grade 2+ pneumonitis in MA 20 abstract was 1.3% vs 0.2%. I don't think may radiation oncologists quote patients a 4% risk of clinical pneumonitis.	This has been changed to cite the MA.20 study in Section 1, and to distinguish MA.20 from the older trials in Section 2.
The molecular subgroup analysis could be expanded as LABC is very diverse.	Results are mostly preliminary or from retrospective analyses and therefore not discussed in detail. We have this section to acknowledge molecular subroups may be crucial but data is currently insufficient; it is expected this will become more important in the future.
Adverse effects could be discussed more.	We chose to discuss only those considered major enough that they may affect the balance of whether or not to give treatment. Original publications may be consulted for further effects.
There has been a tendency recently to include other guidelines to justify CCO guidelines, and am unsure what level of evidence this is.	We consider it appropriate to include other guidelines on related issues that were not directly addressed (for example, analytical or surgical techniques, or treatment in other stages of cancer). When on the same topic, recommendations of other guidelines are often cited for comparison purposes, though in the absence of RCT evidence they may have more prominence.

Professional Consultation: Twenty-eight responses were received. Key results of the feedback survey are summarized in Table 12.

Table 12. Responses to four items on the professional consultation survey.

General Questions: Overall Guideline Assessment	Number of Responses (%)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0 (0%)	0 (0%)	2 (7%)	12(43%)	14 (50%)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	0 (0%)	1 (4%)	4 (14%)	3 (11%)	20 (71%)
3. I would recommend this guideline for use in practice.	0 (0%)	0 (0%)	4 (14%)	3 (11%)	21 (75%)

4. What are the barriers or enablers to the implementation of this guideline report?

The enablers mentioned included the clear and concise recommendations consistent with current practice and recognizing deficiencies in the evidence.

Potential barriers to implementation may include:

- Difficulty in dissemination of recommendations: some clinicians may not read or implement it.
- Resistance to change
- Non-uniformity of practice patterns, regional practices, lack of interdisciplinary team and rounds at some centres.
- Difficult with referral to radiation oncology, availability of medical oncologists, breast cancer surgeons and radiation oncologists who are experienced and comfortable treating LABC.
- Surgeons may need education regarding benefits of neoadjuvant therapy, timing of surgery, and early referral of patients.
- Many physicians practice outside the "fall back" recommendations of this document, which affects discussions of patients. Current practice in many centres has already moved beyond this document.
- There are qualifiers for a few of the guidelines that would negate the application of the guideline to a sub-population of patients.
- Pathology issues: need consistent classification of tumours, standardization of SLN analysis (section thickness, use of immunoperoxidase for micrometastases and ITCs), availability of breast pathologists, resources to read prognostic markers in a timely fashion.

Summary of Written Comments

The main points contained in the written comments and the guideline authors' responses are provided in Table 13

Table 13. Professional consultation comments and Working Group responses.

Comment	Authors' Response
In general, timing is not addressed, and should be. Clips should be placed in breast tumour if it will not delay treatment. SLN may be considered pre-chemotherapy if it will not delay chemotherapy greater than 1 or 2 wks. Radiation should begin after surgery, surgery should occur within 6-8 weeks of chemo etc. etc.	This was not addressed in the studies that were within the scope of the literature search and was not specifically part of the research question or search strategy. Principles of timely treatment delivery, analogous to that used in most clinically trials, should be followed, but the evidence on this area was not reviewed.
It may be helpful to give some more recommendations or comments regarding systemic therapy, for example, the role of adjuvant chemotherapy in patients with LABC already treated with neoadjuvant chemotherapy.	Chemotherapy use, as well as treatment of metastatic or recurrent cancer, was outside the scope and trials were not included in the literature search. The PEBC/CCO Guideline 1-21 may be looked at for use of chemotherapy in early breast cancer.
Introduction. The statement "in vivo chemosensitivity...regimen change" is nice in theory, but has no practical application currently.	The word "may" has been added. This is a potential use that may become more important (e.g., KATHARINE trial)
Q1: I would discuss breast size to tumor size ratio here - a patient may have large breasts and taking out a 5-6cm tumor would not significantly alter her cosmesis. Qualifying statements - do you want a clearer statement that you do NOT need to remove the same amount of tissue with a lumpectomy post chemo as the original tumor size? There is a risk of recurrence even after mastectomy and rads (i.e. don't imply only risk of recurrence after BCS) "patients may wish to eliminate this possibility by having mastectomy as initial treatment"	While the entire tumour bed needs to be resected, the volume will be smaller after neoadjuvant therapy (if there is a response) and therefore less tissue will need to be removed. A sentence has been added to be more explicit about this. Changed "eliminate" to "reduce"
Q1. In the NSABP B-18 study, despite a significant increase in BCS with neoadjuvant chemotherapy, there was no effect on either DFS or OS, thereby suggesting that post-neoadjuvant breast conservation, if surgically possible, is a reasonable and safe approach.	This is not a prospective RCT of BCS vs mastectomy and the authors note subgroup numbers were very low. It is suggestive but not sufficient evidence and additional trials are required.
Q2a. For the locoregional (radiation and surgery), the issue of reconstruction/ implants has not been addressed. This affects the feasibility and timing of radiation	This was not part of the scope of the guideline. A separate guideline on reconstruction is being prepared by the PEBC and the Surgical Oncology Program of CCO [17-10: Clinical practice guideline for breast cancer reconstruction surgery (BCRS) (immediate and delayed) across Ontario: Patient

	indications and appropriate surgical options]
Q2b. Helpful to outline indications for radiating the axilla (if any) and related evidence.	The exact nodes to irradiate were not addressed by the RCTs in the literature review, though we had stated that RT is generally recommended. The NCCN guideline is cited in this regard.
Q2b: Define "lower risk" for considering locoregional rads post mastectomy	Sometimes 10% is used (see EGCTCG meta-analyses); however this is a value judgement and requires discussion between the patient and physician. SLN proven N0 prior to chemotherapy is of lower risk than N+. The data available does not support excluding any subgroup.
Q3. The recommendation of ALND as standard of care in clinically node negative patients is inconsistent with available data. If sentinel node biopsy is good enough for patients receiving upfront surgery then it is difficult to understand why it would not be acceptable for women responding to neoadjuvant systemic therapy. The argument of the potential for positive nodes in the axilla does not have much merit. In ACOSOG Z0011 ~25% of women in ALND arm had additional positive nodes, but their removal was not associated with any effect on DFS or OS.	The available evidence such as Z0011 is for early breast cancer. The implications of FN in LABC are less clear and this is stated in the document. Patients who received NACT may not receive adjuvant chemotherapy.
Q3-2. If you do SLNB before chemo you lose the benefit of the chemo "cleaning out" or converting a group of patients from node positive to node negative	See previous response. We are recommending ALND if there positive nodes initially (i.e., no change in treatment due to nodal effect of NACT).
Q4. The recommendation "fail to respond or disease progression... expedite to taxane portion" is not specific. A stable patient (i.e. not responding in breast but not progressing either) after two cycles of FEC I would continue with the third cycle before switching. A patient 'stable' on hormones I would continue, a patient progressing on hormones I would switch etc.	This has been reworded, but the intent is that if a second agent is part of the regimen then it should be administered. The oncologist will need to use judgment about when this occurs, and we have not specified.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the authors and the Report Approval Panel of the PEBC. Updates of the report will be conducted in accordance with the PEBC Document Assessment and Review Protocol.

CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest Policy, the guideline authors, Breast DSG members, and internal and external reviewers were asked to disclose potential conflicts of interest. Of the Working Group, one author (MB) received a database grant from Roche Pharmaceuticals, is principle investigator of a trial on neoadjuvant chemotherapy and radiation, and published an opinion on surgical considerations in LABC patients receiving neoadjuvant chemotherapy; one author (ID) indicated the guideline could potentially increase the number of referrals for PMRT.

For the Expert Panel, 14 members declared they had no conflicts of interest, and 5 declared potential conflicts. PB and DM declared grants or other research support from pharmaceutical companies. DM also declared involvement as a principal investigator for clinical trials on a related topic. RG declared a travel grant from Roche to attend a conference. SD and MC declared managerial responsibility for a department that received funding from Roche for meetings. SD, MC, and DM published editorials/opinions on topics of this guideline.

The RAP declared no conflicts. Four targeted peer reviewers declared no conflicts. Of the others reviewers, JB received consulting fees from Roche, research grants/support from RNA Diagnostics, was principle investigator of related trials, and has co-authored a meeting report on neoadjuvant care in LABC; CS received research grants/support from Hoffman La Roche, was chair 2012-14 of the LABC Canadian National Consensus, and published commentary/opinions on LABC treatment and knowledge translation; and AA received a grant from Hoffman La Roche for LABC clinic, and published an opinion on surgical considerations in LABC patients receiving neoadjuvant chemotherapy.

The potential conflicts declared did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC Conflict of Interest Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi@mcmaster.ca

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Appendix A. Members of the Cancer Care Ontario Breast Cancer Disease Site Group.

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Maureen Trudeau, Cochair	Medical Oncologist, Sunnybrook Health Sciences, Toronto, Ontario
Philippe Bedard	Medical Oncologist, Princess Margaret Hospital, Toronto, Ontario
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Mark Clemons	Medical Oncologist, The Ottawa Hospital Cancer Centre, Ottawa, Ontario
Ian Dayes*	Radiation Oncologist, Juravinski Cancer Centre, Hamilton Health Sciences, Hamilton, Ontario
Susan Dent	Medical Oncologist, The Ottawa Hospital Cancer Centre, Ottawa, Ontario
Bindi Dhesy-Thind	Medical Oncologist, Juravinski Cancer Centre, Hamilton Health Sciences, Hamilton, Ontario
Leela Elavathil	Pathologist, Hamilton Health Sciences, Hamilton, Ontario
Orit Freedman	Medical Oncologist, Durham Regional Cancer Centre, Lakeridge Health, Oshawa, Ontario
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Mihaela Mates	Medical Oncologist, Cancer Centre of Southeastern Ontario, Kingston General Hospital, Kingston, Ontario
David McCready	Surgical Oncologist, Princess Margaret Hospital, Toronto, Ontario
Bob Myers	Medical Oncologist, Credit Valley Hospital, Mississauga, Ontario
Francisco Perera	Radiation Oncologist, London Health Sciences Centre, London, Ontario
John Semple	Surgeon (post-cancer breast reconstruction), Women's College Hospital, Toronto, Ontario
Sandip SenGupta*	Pathologist, Kingston General Hospital, Kingston, Ontario
Ted Vandenberg	Medical Oncologist, London Health Sciences Centre, London, Ontario
Shailendra Verma	Medical Oncologist, The Ottawa Hospital Cancer Centre, Ottawa, Ontario
Cindy Walker-Dilks* (until June 2011)	Health Research Methodologist, Program in Evidence-Based Care, McMaster University
Glenn Fletcher*	Health Research Methodologist, Program in Evidence-Based Care, McMaster University

***Members of the Working Group**

Appendix B. Search strategy.

1-19 LABC. SEARCH HISTORY

EMBASE 1996 to 2011 Week 50, Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2011, Ovid MEDLINE(R) Daily Update November 16, 2011, Ovid MEDLINE(R) In-Process & Other NonIndexed Citations December 16, 2011

Search One (Main Search)
(exp Breast Neoplasms/ or exp breast tumor/ or exp breast cancer/ or breast cancer.mp. or breast neoplasm:.mp. or ((cancer: or neoplasm: or tumo?r: or carcinom:) and (breast or mammar:)).mp)
and
(((LABC or (local: adj advanc:) or ((inflammatory or non-inflammatory or non-inflammatory or high-risk or (high: adj risk) or (rapid: adj progress:) or premetastatic or pre-metastatic or large operable) adj3 breast) or (((stage adj3 (2b or IIb or 3: or III:)) or stage 2 or Stage II or T1N2 or T1N3 or T2N1 or T2N2 or T2N3 or T3: or T4: or pT3: or pT4: or pN2 or pN3) adj3 breast)).ti,ab. or (((stage adj3 (2b or IIb or 3: or III:)) or stage 2 or Stage II or T1N2 or T1N3 or T2N1 or T2N2 or T2N3 or T3: or T4: or pT3: or pT4: or pN2 or pN3).ti,ab. and (breast or mammar: or mastect:).ti.)) ***Or***
(((preoperative or initial or upfront or neoadjuvant or neo-adjuvant or induction or primary) adj2 (chemo: or system: or therapy)).mp. or exp neoadjuvant therapy/))

Supplementary Search
(exp Breast Neoplasms/ or Breast/ or ((cancer: or carcinoma: or neoplasm: or tumo:r:).tw and (breast or mammar:).tw)) and (high adj risk).tw and (randomized controlled trial.pt or exp Mastectomy/ or (conserv: or excis: or mastectomy or lumpectomy or tumo?rectomy or quadrantectomy).mp or (non-respon: or nonrespon:).tw or treatment failure.mp. or exp Treatment Failure/ or fail:.tw or (lack adj3 respon:).tw or (second adj line).tw or progress:.tw or salvage.tw or inoperable.tw)

eliminate notes, letters, comments, editorials, reviews (except systematic review/guideline); eliminate those in previous searches

RCT 7312
Systemic review/guidelines: 1175
Radiotherapy 2557
LABC 3749
Neoadjuvant 4833
Other 257

Supplementary Searches for Radiotherapy

eliminate notes, letters, comments, editorials, reviews (except systematic review/guideline); eliminate those in previous searches

Radiotherapy and Clinical Trials: 2819
(exp Breast Neoplasms/ or exp breast tumor/ or exp breast cancer/ or breast cancer.mp. or breast neoplasm:.mp. or ((cancer: or neoplasm: or tumo?r: or carcinom:) and (breast or mammar:)).mp)
and
(exp Radiotherapy Planning, Computer-Assisted/ or exp Radiotherapy, Computer-Assisted/ or exp Radiotherapy/ or (RT or radiation treatment or RT or irradiation treatment or irRT).mp)
and
((clinical trial or randomized controlled trial).pt. or exp clinical trial/ or random allocation.mp. or random allocation/ or random:.tw. or double-blind method.mp. or double-blind method/ or single-blind method.mp. or single-blind method/ or placebos/ or placebo:.tw)

Radiotherapy and Systematic Reviews or Guidelines: 541
(exp Breast Neoplasms/ or exp breast tumor/ or exp breast cancer/ or breast cancer.mp. or breast neoplasm:.mp. or ((cancer: or neoplasm: or tumo?r: or carcinom:) and (breast or mammar:)).mp)
and
(exp Radiotherapy Planning, Computer-Assisted/ or exp Radiotherapy, Computer-Assisted/ or exp Radiotherapy/ or (RT or radiation treatment or RT or irradiation treatment or irRT).mp)
and
(meta-analysis.mp. or meta-analysis/ or meta-analysis.pt. or (meta-analy: or metaanaly: or meta analy:).tw. or (systematic review or systematic overview).mp. or (cochrane or MEDLINE or embase or cancerlit).ti. or (hand search or hand-search or manual search).ti. or practice guideline$.mp. or Practice Guideline/ or practice guideline.pt. or practice parameter:.tw)

OTHER SEARCHES

Ovid MEDLINE(R) <1996 to October Week 3 2010>, Ovid MEDLINE(R) Daily Update <October 29, 2010>, Ovid MEDLINE(R) In-Process & Other Nonindexed Citations <October 29, 2010>

(Breast Neoplasms/ or ((cancer: or neoplasm: or tumo?r: or carcinom:).tw and (breast or mammo: or mammar:).tw)) and ((LABC or (local: adj advanc:) or (inflamm: or non-inflamm: or noninflamm:) or (Stage III: or stage 3:) or (T2b or Stage IIB or T3: or T4:)).tw)

limit to English, eliminate notes, letters, comments, editorials, reviews (except systematic review/guideline)

19 (K) MEDLINE(R) <1996 to March Week 1 2010>: not relevant, not updated: 1557 results
(exp Breast Neoplasms/) and (Neoadjuvant Therapy/ or Neoplasm Staging/) and (axilla/ or axilla:.tw or lymph node excision/ or sentinel lymph node biopsy/ or (SLN or SLNB or SLND or sentinel).tw)

23 (O): MEDLINE 1996 to June 21, 2011; EMBASE to 2011 Week 24: not relevant, not updated: 154
(exp breast neoplasms/ or exp breast cancer/ or breast.mp) and axillary staging.mp

Original Searches 6498 (specific searches, includes K and O not to be updated, in endnote Sept 2011)

D: general search: 3827 additional citations not in endnote

Appendix C. Existing guidelines on locoregional treatment of LABC.

Guideline	Q1	Q2	Q3	Q4
PMRT				
Alberta Provincial Breast Tumour Team, 2012 (59). Adjuvant RT for invasive breast cancer.		•		
Belkacémia et al, 2011 (60). Radiotherapy for invasive breast cancer: Guidelines for clinical practice from the French expert review board of Nice/Saint-Paul de Vence.		•		
Expert Panel on Radiation Oncology–Breast, 2012 (26). American College of Radiology ACR Appropriateness Criteria: Postmastectomy Radiotherapy		•		
Expert Panel on Radiation Oncology-Breast, 2011 (11). American College of Radiology ACR Appropriateness Criteria: Locally Advanced Breast Cancer.	•	•		
Sautter-Bihl et al, 2008 (61). DEGRO practical guidelines for RT of breast cancer II. Postmastectomy RT, irradiation of regional lymphatics, and treatment of locally advanced disease.		•		
Truong et al, 2004 (62). Clinical practice guidelines for the care and treatment of breast cancer: 16. Locoregional post-mastectomy RT. Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer, Health Canada		•		
Kurtz, 2002 (63). EUSOMA Guidelines. The curative role of RT in the treatment of operable cancer.		•		
Recht et al, 2001 (64). Postmastectomy RT: clinical practice guidelines of the American Society of Clinical Oncology (ASCO). See also Recht and Edge, 2003 (65). Evidence-based indications for postmastectomy irradiation.		•		
General Management				
Gradishar et al, 2013 (12). NCCN Breast Cancer Clinical Practice Guidelines in Oncology: Breast cancer.		•	•	•
Aebi et al, 2011 (66). Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.		•		
Dawood et al, 2011 (14). International Expert Panel on Inflammatory Breast Cancer: Consensus Statement for Standardized Diagnosis and Treatment	•	•		
Kaufmann, 2010 (67). Locoregional Treatment of Primary Breast Cancer: Consensus Recommendations from an International Expert Panel.		•		
Cardoso et al, 2010 (68). Scientific Support of the College of Oncology: Update of the National Guidelines on Breast Cancer. Belgian Healthcare Knowledge Centre		•		
Campbell et al, 2009 (69). Management of Early Breast Cancer. New Zealand Guidelines Group		•		
NICE, 2009 (70). Early and Locally Advanced Breast Cancer: Diagnosis and Treatment.	•	•		
Shenkier et al, 2004 (55). Clinical practice guidelines for the care and treatment of breast cancer: 15. Treatment for women with Stage III or locally advanced breast cancer. Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer, Health Canada		•		•
Schwartz, 2004 (13). Proceedings of the Consensus Conference on Neoadjuvant Chemotherapy in Carcinoma of the Breast, April 26–28, 2003, Philadelphia, Pennsylvania	•	•	•	•

Appendix D. AGREE II scores for clinical practice guidelines from the SAGE Inventory of Cancer Guidelines.

Assessment was performed by SAGE and is reproduced from the Guidelines Resource Centre at www.cancerview.ca

Alberta Health Services. Adjuvant RT for invasive breast cancer (59)

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
Scope and Purpose:	Stakeholder Involvement:	Rigour:	Clarity Presentation:	Applicability:	Editorial Independence:
86.1%	27.8%	36.5%	86.1%	20.8%	50.0%

Health Canada. Locoregional post-mastectomy RT (62)

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
Scope and Purpose:	Stakeholder Involvement:	Rigour:	Clarity Presentation:	Applicability:	Editorial Independence:
68.1%	57.3%	74.4%	80.2%	27.8%	77.1%

Health Canada. Treatment for women with Stage III or locally advanced breast cancer (55)

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
Scope and Purpose:	Stakeholder Involvement:	Rigour:	Clarity Presentation:	Applicability:	Editorial Independence:
62.5%	37.5%	54.2%	82.3%	12.5%	64.6%

American College of Radiology (ACR). Postmastectomy Radiotherapy (26) [assessment was on the 2008 version]

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
Scope and	Stakeholder	Rigour:	Clarity	Applicability:	Editorial

Purpose: 63.9%	Involvement: 55.6%	45.8%	Presentation: 66.7%	22.9%	Independence: 25.0%

American College of Radiology (ACR). Locally Advanced Breast Cancer (11) [assessment was on the 2007 version]

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
Scope and Purpose: 58.3%	Stakeholder Involvement: 50.0%	Rigour: 46.9%	Clarity Presentation: 69.4%	Applicability: 22.9%	Editorial Independence: 25.0%

NICE: Early and Locally Advanced Breast Cancer: Diagnosis and Treatment (70)

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
Scope and Purpose:	Stakeholder Involvement:	Rigour:	Clarity Presentation:	Applicability:	Editorial Independence:
83.3%	88.9%	85.4%	91.7%	70.8%	87.5%

French expert review board of Nice/Saint-Paul de Vence. Radiotherapy for invasive breast cancer (60)

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
Scope and Purpose:	Stakeholder Involvement:	Rigour:	Clarity Presentation:	Applicability:	Editorial Independence:
52.8%	36.1%	59.4%	69.4%	18.8%	29.2%

Locoregional treatment of primary breast cancer: consensus recommendations from an International Expert Panel (67)

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
Scope and Purpose:	Stakeholder Involvement:	Rigour:	Clarity Presentation:	Applicability:	Editorial Independence:
72.2%	38.9%	41.7%	88.9%	20.8%	62.5%

ESMO clinical practice guidelines for diagnosis, treatment and follow-up (66) [assessment of 2010 version]

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
Scope and Purpose:	Stakeholder Involvement:	Rigour:	Clarity Presentation:	Applicability:	Editorial Independence:
25.0%	11.1%	17.7%	69.4%	16.7%	37.5%

Scientific support of the College of Oncology: update of the national guidelines on breast cancer. Belgian Healthcare Knowledge Centre (68)

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
Scope and Purpose:	Stakeholder Involvement:	Rigour:	Clarity Presentation:	Applicability:	Editorial Independence:
86.1%	36.1%	74.0%	91.7%	27.1%	29.2%

Management of Early Breast Cancer. New Zealand Guidelines Group (69)

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
Scope and Purpose:	Stakeholder Involvement:	Rigour:	Clarity Presentation:	Applicability:	Editorial Independence:
94.4%	77.8%	67.7%	91.7%	54.2%	79.2%

The following guidelines are not rated, but have the following comment. *This guideline does not meet the minimum inclusion thresholds and does not have an AGREE II assessment*. As of June 2011, the AGREE II assessment of SAGE records will only be applicable to guidelines produced by new development groups and previous high performers. The high-performing development groups have historically produced guidelines with a minimum score of 50% on the Rigour of Development AGREE domain.

- NCCN guidelines, which would include Breast Cancer (12)
- International Expert Panel on Inflammatory Breast Cancer: Consensus Statement for Standardized Diagnosis and Treatment (14)

Appendix E. Systematic reviews and meta-analyses (also see table of guidelines).

Author, year	Type of review	Topic	Patient characteristics	Results or comments
Delaney, 2011 (215)	Systematic review, to April 2009	Breast Cancer	PMRT in LABC Axillary management	• For PMRT: evaluated EBCTCG, Whelan, Gebski, DBCG, Stockholm, South Sweden. Recommended for high risk (LN+ , particularly >3 nodes, positive margins, larger tumour >5 cm); consider when less nodes involved • Internal mammary chain irradiation remains of uncertain benefit • Insufficient evidence to recommend for or against irradiation of supraclavicular fossa nodes; might be considered reasonable to include if at high risk of involvement (e.g., ≥3 node involved in axillary surgery)
Rowell, 2009 (83)	Systematic review, to March 2008	Chest wall PMRT, node-negative	Node-negative, only trials with axillary clearance	• Based primarily on EBCTCG 2005, Gebski, Whelan, plus 4 RCTs (Stockholm, DBCG 82b&c, Finnish) • PMRT for node-negative breast cancer requires re-evaluation. PMRT should be considered for those with 2 or more risk factors
Rutqvist, 2003 (216)	Systematic overview, published to 2001	Radiation effects in breast cancer	29 trials + 6 meta-analyses + 5 retrospective studies. BCS or mastectomy	• Strong evidence for a substantial reduction in locoregional recurrence rate following PMRT to chest wall and regional nodal areas. • Strong evidence that PMRT increases DFS and breast cancer specific survival; conflicting data on overall survival • Strong evidence PMRT decreases non-breast cancer specific survival, is attributed mainly to cardiovascular disease. The heart is the most important organ at risk during RT for breast cancer. Minimizing radiation doses to the heart muscle and the coronary arteries is necessary for avoiding later effects of ischemic cardiovascular disease. These adverse effects were particularly prominent in early treatment studies that used older RT methods. • Strong evidence PMRT in addition to surgery and systemic therapy in mainly pts with node-positive cancer decreases local recurrence rate and improves survival
EBCTCG, 2011 (20)	Individual patient data meta-analysis	Radiotherapy (RT) after BCS	BCS	• Fifth cycle analysis of BCS + RT (does not include mastectomy). Not of direct relevance to this project.
McGale, 2006 (21); cited in Plastaras, 2006 (22)	Individual patient data meta-analysis	RT after mastectomy	BCS, mastectomy	• Fourth cycle update of surgery ± RT by the EBCTCG, conference abstract only plus report of presentation; minor revision of data compared with EBCTCG, 2005 (15)
EBCTCG, 2005 (15)	Individual patient data meta-analysis	RT after BCS or mastectomy		• Fourth cycle update of surgery ± RT. • Reported data separately for BCS or mastectomy • Mastectomy data divided into node negative or node positive

Author, year	Type of review	Topic	Patient characteristics	Results or comments
				• For PMRT + axillary clearance, reported subgroup analyses
EBCTCG, 2000 (23)	Individual patient data meta-analysis	RT after BCS or mastectomy		• Third cycle update of surgery ± RT. Less pts and shorter follow-up compared with fourth cycle. Improvement in recurrence but not long-term survival
EBCTCG, 1995 (10)	Individual patient data meta-analysis	RT after BCS or mastectomy		• Second cycle update of surgery ± RT. Earlier results, less pts and shorter follow-up compared with third cycle.
Cuzick, 1994 (217)	Meta-analysis	Surgery (mastectomy) ± RT		• Included 7941 female pts from 8 trials. Lower rates of death from breast cancer but increased cardiac deaths with RT, need to use techniques that minimize cardiac dose
Gebski, 2006 (78)	Systematic review / meta-analysis	PMRT studies in EBCTCG 2000	Radiation dose and coverage	• Analyzed studies covered in EBCTCG by subgroups according to whether PMRT was optimal dose and coverage or not
Whelan, 2000 (17)	Systematic review / meta-analysis	Studies in EBCTCG 1995 on systemic therapy + PMRT	Stage I to III; 2 RCTs limited to Stage III	• 18 RCTs, included studies in EBCTCG analysis on randomized PMRT in pts receiving (mostly adjuvant) systemic therapy, mostly N+
Vinod, 1999 (96)	Systematic review (1966-98)	IMC irradiation	6 RCTs, 9 retrospective series on early stage breast cancer	• Some retrospective data suggested IMC irradiation improved survival in mediocentral and axillary node-positive tumours, but was not supported by RCTs. Two RCTs on high-risk operable breast cancer of which one found survival advantage of PMRT but couldn't delineate contribution of IMC
Chen, 2008 (95)	Systematic review in title but no search details	IMC irradiation		• Approximately 1/5 of IM SLN are pathological, although most centres do not perform IM node biopsies because of concerns about morbidity and lack of established survival benefit. Although locoregional tumour control improves survival, IM node RT was used in 24/25 PMRT studies in the EBCTCG meta-analysis (15); therefore, the contribution of IM node treatment itself is unclear. IM node RT has been shown to cause cardiotoxicity. Trials are still ongoing; until results are available lymphoscintigraphy may help guide decisions of systemic and locoregional treatment, although potential benefits of treatment must be balanced against the risk of added morbidity.

Abbreviations: BCS, breast-conserving surgery; IMC, internal mammary chain; PMRT, postmastectomy radiotherapy; RCT, randomized controlled trial; RT, radiotherapy;

Appendix F. Studies comparing mastectomy with versus without radiotherapy: List of trials included in published meta-analyses or current search.

Study Name and Details							Publications, Analysis, or Literature Search Where Study is Included					
Study Name, Reference †	**Start year**	**N**	**Stage, nodes †**	**Surgery †**	**Radio-therapy †**	**Systemic therapy**	**EBCTCG, 2000 (23)**	**EBCTCG, 2005 (15)**	**Gebski, 2006 (78) (RT quality)**	**Whelan, 2000 (17) (Chemo)**	**Chemo-therapy + optimal RT**	**Current search for 1-19**
Mastectomy with Axillary Sampling ± RT												
Wessex (Southampton, UK) Turnbull, 1978 (218)	1973	151	Early breast cancer	SM	BW, AF, IMC	None	Yes	Yes	Optimal			
Edinburgh 1 Stewart, 1994 (219)	1974	348	Stage I-II, LN- or LN not assessed	SM +AX sampling (≥1 nodes) and group without AX	BW, AF	None	Yes	Yes	Optimal			
Nottingham Morgan , 1992 (220)	1985	76	Stage I- II, grade III, N+	SM + AX sampling (3 nodes)	BW, AF	26 pts Starting end of 1987: CMF (pre) or TAM (post)	Yes	Yes	Optimal			Update (221), excluded (not LABC)
CRC, UK; in EBCTCG, 2000 (23) [unpublished]	1986	64			various	None	Yes	Yes	[Not evaluated]			
Mastectomy with Axillary Clearance ± RT												
NSABP B-03 Fisher, 1968, 1970 (222,223)	1961	748	N+ or N-; confined to breast ± axilla and tumour movable in relation to the chest wall	RM (Halsted), axillary contents	AF, IMC	None	Yes	Yes	Excluded			
Berlin-Buch ABC; in EBTCG, 2000 (23)	1962	255			BW, AF, IMC	None	Yes	Yes	[Not included]			
Oslo X-ray Host, 1977 (224,225)	1964	544	345 Stage I, 201 Stage II	Halstead RM	BW, AF, IMC	Ovarian irradiation	Yes	Yes	Inadequate (25-41 Gy); 200 kV			
Oslo Co-60 Host, 1977 (224)	1964 (1967)	541	Stage I-II	Halstead RM	AF, IMC	Ovarian irradiation	Yes	Yes	Inappropriate target volume			
Heidelberg XRT Friedl, 1984 (226)	1969	143		RM	AF, IMC	None	Yes	Yes	Inappropriate target volume			

Study Name and Details							Publications, Analysis, or Literature Search Where Study is Included					
Study Name, Reference †	**Start year**	**N**	**Stage, nodes †**	**Surgery †**	**Radio-therapy †**	**Systemic therapy**	**EBCTCG, 2000 (23)**	**EBCTCG, 2005 (15)**	**Gebski, 2006 (78) (RT quality)**	**Whelan, 2000 (17) (Chemo)**	**Chemo-therapy + optimal RT**	**Current search for 1-19**
Stockholm A Rutqvist, 1993 (227); Arriagada, 1995, 2010 (165,166); Gyenes,1998 (167)	1971	960	≈60% N0, 57% T1, 31% T2	MRM	BW, AF, IMC	None	Yes	Yes	optimal			Cardiac results (167)
SASIB Groote, cited in (23,78)	1971	377		RM	BW, AF, IMC	None	Yes	Yes	Optimal			
Mayo Clinic (Mayo 76-56-32) Ahmann, 1978 (228)	1973 (1974)	241	Stage II-III	RM (MRM), complete ax removal	BW, AF, IMC	PAM or CFP	Yes	Yes	Optimal	Yes	Yes	
INT Milan 1 EBCTCG, 2000 (23)	1973	56		RM	AF, IMC	None	Yes	Yes	Inappropriate target volume			
DFCI Boston (N1-3; N4+) Griem, 1987(119); Shapiro (118)	1974	206	Stage II-III	RM (MRM)	BW, AF	AC vs CMF vs MF	Yes	Yes	Optimal	Yes	Yes	Cardiac substudy (118)
Piedmont OA Muss, 1991 (229)	1976	158 N=? for sub-group	Stage II, N+ Subgroup <3 positive nodes or <3 cm	RM (RM/MRM), 10+ nodes removed	(BW) AF, IMC AF, IMC	PAM vs CMF	Yes	Yes	Inappropriate target volume for subgroup (only overall results reported)	Yes		
SECSG 1 Velez-Garcia, 1992 (230)	1976	270	Stage II-III, N2-3 only (≥4 nodes)	TM (RM/MRM), complete dissection ≥10 nodes removed	BW, AF, IMC	CMF	Yes	Yes	optimal	Yes	Yes	
Glasgow N1, N2+ subgroups McArdle,1986 , 2010 (163,164)	1976	219	Stage II, N+, 34% >3 positive nodes	SM + AX clearance to level of AX vein	BW, AF, IMC	CMF	Yes	Yes	Inadequate (37.8 Gy)	Yes		Yes

Study Name and Details							Publications, Analysis, or Literature Search Where Study is Included					
Study Name, Reference †	**Start year**	**N**	**Stage, nodes †**	**Surgery †**	**Radio-therapy †**	**Systemic therapy**	**EBCTCG, 2000 (23)**	**EBCTCG, 2005 (15)**	**Gebski, 2006 (78) (RT quality)**	**Whelan, 2000 (17) (Chemo)**	**Chemo-therapy + optimal RT**	**Current search for 1-19**
MD Anderson 7730B Buzdar, 1984 (154)	1977	97	Operable, 61% Stage II; 24% Stage III, 15% Stage IV; N+ (31% N1, 69% N2+)	29% RM, 54% MRM, 14% ext. SM	BW, AF, IMC, S	FAC ± BCG	Yes	Yes	Optimal		Yes	
South Swedish BCG Tennvall-Nittby, 1993 (231); Ryden , 1992 (232); Killander, 2007, 2009 (115,121); Gustavsson, 1999 (162)	1978	762	Mostly Stage II (allowed Stage I with size 20 mm)	MRM, dissection to AX vein	BW, AF, IMC	Premenopausal: cyclophos-phamide Postmenopausal: TAM	Yes	Yes	Inadequate (BW=38 Gy)	Yes		Yes
Toronto-Edmonton From EBCTCG, 2000 (23) (unpublished)	1978	50	Not specified	RM (M)	AF, IMC (BW, AF)*	Ovarian irradiation + CMFP ± BCG	Yes	Yes	Optimal?, not evaluated	Yes	Yes	
BCCA Vancouver Ragaz, 1997, 1999, 2005 (112,113,233)	1979	318	Stage I-II, N+	MRM, level I + II ALND, median 11 nodes reviewed	BW, AF, IMC	CMF ER+: ovarian irradiation + CMFP	Yes	Yes	Optimal	Yes	Yes	Yes
Dusseldorf U. Faber, 1979 (234)	1977	88	T1a, T2a, T3a; ≥4 positive nodes	MRM (Patey type)	BW, AF, IMC	LMF	Yes	Yes	Optimal	Yes	Yes	
Coimbra Gervasio , 1998 (152) [abstract]	1980	112	Stage II	MRM	BW, AF, IMC	AC	Yes, no data	Yes	Inadequate (BW=36 Gy)	Yes		
Metaxas Athens Papaioannou, 1983 (120)	1978	105	LABC; T3-4a, some T4b; Stage IIB-III; most Stage III	TM including pectoralis fascia; complete AD (levels I-III)	BW, AF, IMC	Oncovin +AC +MF+ Nolvadex (antiestrogen); oophorectomy if premenopausal or within 1 y after menopause	Yes	Yes	Optimal	Yes	Yes	
Helsinki Blomqvist, 1992 (117)	1981	99	N+ Stage II (T1-2, N1)	RM (MRM), AX evacuation	BW, AF, IMC	CAFt + TAM	Yes	Yes	Optimal	Yes	Yes	
NSABC Israel Hayat, 1990 (235)	1981	112	Stage II	RM (MRM)	BW, AF, IMC	CMF	Yes	Yes	Optimal	Yes	Yes	

Study Name and Details							Publications, Analysis, or Literature Search Where Study is Included					
Study Name, Reference †	**Start year**	**N**	**Stage, nodes †**	**Surgery †**	**Radio-therapy †**	**Systemic therapy**	**EBCTCG, 2000 (23)**	**EBCTCG, 2005 (15)**	**Gebski, 2006 (78) (RT quality)**	**Whelan, 2000 (17) (Chemo)**	**Chemo-therapy + optimal RT**	**Current search for 1-19**
Danish BCG 82b Overgaard, 1997 (156) Premenopausal; N0, N1, N2 subgroups	1982	1801	Stage II-III;	SM +ax (level 1 & part of level 2; median 7 nodes)	BW, AF, IMC	CMF	Yes	Yes	Optimal	Yes	Yes	Yes
Danish BCG 82c Overgaard, 1999 (157) Postmenopausal; N0, N1, N2 subgroups	1982	1375	Stage II-III	SM +ax (level 1 & part of level 2; median 7 nodes)	BW, AF, IMC	Tamoxifen	Yes	Yes	Optimal	Yes	Yes	Yes
Danish BCG 82b &c combined (85,114,159-161)							Yes	Yes	Optimal	Yes	Yes	Yes
ECOG EST3181 Olson, 1997 (116)	1982	312	LABC, Stage III	RM or MRM, ≥8 LN removed (median 17)	BW, AF, IMC	CAF +H + TAM	Yes	Yes	Optimal	Yes	Yes	Yes
BMFT 03 Germany GBSG 03 Germany Schmoor, 2000 (18)	1984	199	Stage II-III: N+ (≈60% N1, 40% N2+), T1a-T3 (≈30% T1, 70% T2)	MRM (Patey), en bloc AD, >6 nodes removed	BW, AF, IMC	CMF	Yes	Yes	Optimal	Yes	Yes	Yes
Mastectomy Only (no axillary surgery) ± RT												
Kings/Cambridge (Cancer Research Campaign) Murray, 1976 (236); Baum, 1980 (237); Elston 1982 (238)	1970	2268	Stage I or II (T1-2, N0-1)	SM	BW, AF, IMC	None	Yes	Yes	Inadequate (28.5-46 Gy)			
NSABP B-04 Fisher, 1980 (239); Fisher, 1985 (240)	1971	717	N-	TM/SM	BW, AF, IMC	None	Yes	Yes	Optimal			
Scottish D From EBCTCG, 2000 (23)	1978	93		SM	BW, AF, IMC	± TAM	Yes	Yes	Optimal		Yes	

Study Name and Details							Publications, Analysis, or Literature Search Where Study is Included					
Study Name, Reference †	**Start year**	**N**	**Stage, nodes †**	**Surgery †**	**Radio-therapy †**	**Systemic therapy**	**EBCTCG, 2000 (23)**	**EBCTCG, 2005 (15)**	**Gebski, 2006 (78) (RT quality)**	**Whelan, 2000 (17) (Chemo)**	**Chemo-therapy + optimal RT**	**Current search for 1-19**
85Z Tokyo CIH PS From EBTCG, 2005 (15)	1985				AF, IMC	CMF	No	Yes	[not included]			
88U Tokyo CIH CZ From EBTCG, 2005 (15)	1988				AF, IMC	CMF	No	Yes	[not included]			
Other Studies (not in EBCTCG meta-analyses) which compare mastectomy ± RT												
Finnish Klefstrom, 1987 (84)	1976	79	Stage III; 55-71% N+; mean 6.3 cm	MRM, axillary fat including nodes removed	BW, AF, IMC	VAC (levamisole to all groups in early years)	No	No	Optimal	Yes	Yes	
Manchester Q Easson, 1968 (241)	1948	720	Stage I-II, small portion Stage III	RM (Halsted)	BW, AF (apex only)		No	No	Optimal (? 35-40 Gy)			
Manchester P Easson, 1968 (241)	1953	741	Stage I-II, small portion Stage III	RM (Halsted)	AF, IMC		No	No	Inadequate (32-42 AF) Inappropriate target volume			
Tianjin Medical University Shi, 2003 (79)	1985	162	Stage I-IIIA		AF and/or IMC		No	No	[not included]			Yes

Inadequate Dosage (<40 Gy)	IMC not irradiated	Breast Wall not irradiated	Other deficiencies as indicated

† Most references are as cited in Gebski (78) or the EBCTCG (15,23) analyses. If the original data source was unavailable or did not indicate, then details such as the stage, type of surgery, and extent of RT are from Gebski, EBCTCG, or Whelan (17). As a result, some data fields are blank when these details were not reported in the reviews/meta-analyses.
*Type of RT unclear: EBCTCG 1995 and 2000 reports as BW and AF but EBCTCG 2005 reports as AF and IMC, appears trial is not published

Abbreviations
AC, doxorubicin (Adriamycin®) + cyclophosphamide; AD, axillary dissection; AF, axilla and supraclavicular fossa; ALND, axillary lymph node dissection; AX, axillary lymph nodes; BCG, Bacillus Calmette-Guérin; BW, breast/chest wall; CAF, cyclophosphamide + doxorubicin (Adriamycin®) + 5-fluorouracil; CAFt, cyclophosphamide + doxorubicin + futrafur; CFP, cyclophosphamide + 5-fluorouracil + prednisone; CMF, cyclophosphamide + methotrexate + fluorouracil; CMFP, CMF+ prednisone;
H, halotestin (fluoxymesterone); IM nodes, internal mammary nodes; IMC, internal mammary chain; LMF, Chlorambucil + methotrexate + fluorouracil; LN, lymph node;
M, mastectomy (type not specified); MF, methotrexate + fluorouracil; MRM, modified radical mastectomy (includes level I and II dissection); PAM (L-PAM), melphalan (phenylalanine mustard); RM, radical mastectomy (breast, chest wall muscles, and level I-III ALND); S, boost to scar; SM or TM, simple or total mastectomy (no ALND); TAM, tamoxifen; VAC, vincristine + doxorubicin + cyclophosphamide

Appendix G. Literature reviews evaluated by AMSTAR.

Review	A prior design	Duplicate selection/ extraction	Comprehensive literature search	Used grey literature	List of excluded studies	Characteristics of included studies	Assessed quality of studies	Used quality appropriately	Pooled or combined results appropriately	Publication bias assessed	Conflict of interest, funding sources*
EBCTCG (10,15,20-23,217) †	Yes	? (verification with RCT authors)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Used published + nonpublished data	No RCTs, None or ? overall
Delaney, 2011 (215)	Yes	No	Yes	Yes	No	No	No	N/A	N/A	No	Potential conflicts stated for authors
Rowell, 2009 (83)	Yes	No	MEDLINE, EMBASE, PROQUEST	Abstracts	Some	Yes	Some	Yes	Yes	No	No conflicts
Rutqvist, 2003 (216)	?	No	MEDLINE only	No	No	Yes	Some	?	No performed	No	Not stated
Gebski, 2006 (78)	Yes	Used 4 other reviews/ meta-analyses	Relied on other publications plus search 2002-2004	If in EBCTCG	Not applicable	Yes	Not stated	Yes (though dose cut-off seems arbitrary)	Yes	Indirectly as relied on EBCTCG	Not stated
Whelan, 2000 (17)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	?	Not stated
Vinod, 1999 (96)	Yes	Not stated	In MEDLINE only	No	No	Some (in text only)	No	NA	Not performed	No	Not stated
Chen, 2008 (95)	Not stated	Not stated	No (no details)	No	No	Yes	Some	NA	Not performed	No	No conflicts
Fowble, 2012 (35)	Yes	No	MEDLINE and Cochrane	Abstracts	No	Yes	?	NA	Not performed	No	No conflicts
Houssami, 2012 (135)	Yes	Yes	Yes, MEDLINE only	No	No	Yes	No	NA	Yes	No	No conflicts
Charehbili, 2014 (150)	Yes	Yes	PubMed only	No	No	Yes	Some	NA	Not performed	No	No conflicts
Dent, 2013 (147)	Yes	Yes (for included studies)	Yes (PubMed, BIOSIS)	Yes (abstract books)	No	Yes	Some	NA	Not performed	No	Potential conflicts stated

Note: Choices for each question were: Yes; No; ? (cannot answer); NA (not applicable).
* Conflict of interest: none of the reviews commented on conflicts within individual RCTs, some of the reviews indicated a statement about conflicts of interest for the review authors (other than EBCTCG which included a statement in some of the EBCTCG publications)
† Individual patient meta-analysis as in the EBCTCG analyses is considered the strongest evidence (73) and provides the most reliable and least biased means of addressing questions that are not answered in individual RCTs (74). The Cochrane Collaboration has withdrawn several reviews on topics covered by the EBCTCG (75-77) because the EBCTCG reviews are based on individual patient data, are of the highest quality, and represent the best available evidence on the effects of these treatments on relapse, second cancer, and death.

Appendix H. Quality assessment of new RCTs.

(Studies not reported in previous guidelines or meta-analyses cited)

Study, Author	Design	Reported Allocation Sequence	Allocation Concealed	Blinding	Balanced Baseline Characteristics	Industry Funding	Statistical Power and Target Sample Size	ITT Analysis	Withdrawals Described	Reported Loss to Follow-up	Terminated Early
Shi, 2003 (79)	Prospective	Randomized	Chinese study with English abstract, cannot assess								
EORTC 22922/ 10925 (29-31,92,93)	Prospective	Randomized, stratified	No	No	Yes	No	The study size was calculated to provide 80% probability of detecting a 4% improvement from 75%-79% in 10-y OS	Yes	Yes	Yes	No
Hennequin, 2013 (28)	Prospective	Multicentre, centrally randomized, stratified	No	No	Yes	No	The primary outcome was 10-y OS. The expected benefit was 10% at 10 y (i.e., 50% with IM node RT vs 40% without IM node RT). With this hypothesis, with a type I error of 5% and a type II error of 10%, 1300 pts were needed	Yes	Yes	Yes	No
NCIC-CTG MA.20 Whelan, 2011 (32,33,94)	Prospective	Randomized, stratified	No	No	Yes	No	Designed to detect HR=0.73 for OS with 80% power and two-sided α=5%; requires minimum 312 deaths	?	No (abstract only)	No	(?) Interim analysis reported
Stemmer, 2003 (24)	Prospective	Nonrandomized	NA	NA	Yes	NA	NA	NA	NA	No	NA
GeparTrio von Minckwitz 2008, 2013 (53,108)	Prospective	Randomized	No	No	Yes	Yes	Because the sample size was originally calculated for a one-sided test, corresponding one-sided P values are also quoted for the primary endpoint.	Yes	Yes	?	No
GeparQuinto Huober, 2013 (109)	Prospective	Randomized, stratified	No	No	Yes	Yes	It was expected that the addition of everolimus increases the pCR rate by an odds ratio of 2.62%-12.1%. A two-sided continuity corrected Pearson χ^2 test with α=0.05 and β=0.20 was chosen. The number of	Yes	No	No	Recruitment dropped , accrual prematurely closed with 403 pts randomized; estimated

Study, Author	Design	Reported Allocation Sequence	Allocation Concealed	Blinding	Balanced Baseline Characteristics	Industry Funding	Statistical Power and Target Sample Size	ITT Analysis	Withdrawals Described	Reported Loss to Follow-up	Terminated Early
							evaluable pts was calculated to be 540				statistical power dropped from 80%-65%
Qi, 2010 (54)	Prospective	Randomized	No	No	Yes	Not stated	The sample size calculated with a type I error (two-sided test) of 0.05 and a study power of 90%, for a further objective to detect a 1.43 rate ratio in excellent response rate between arm A and B. The target enrolment was estimated to be 107 eligible pts with total information per arm.	?	No	No	No