Axillary Management in Breast Cancer Patients: A Comprehensive Review of the Key Trials

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Abstract:

Optimal regional management in breast cancer patients has yet to be established. In patients who are clinically node negative, but sentinel lymph node biopsy (SLNB) positive, the treatment paradigm has shifted towards the de-escalation of further axillary management. In patients with two or less positive sentinel nodes, the standard of practice has shifted away from complete axillary lymph node dissection (ALND) as a result of the ACOSOG Z0011 trial.

The role of regional nodal irradiation (RNI) to the axilla and supraclavicular regions has also been investigated in the setting of positive SLNB in trials such as MA20 and EORTC 22922. Having shown evidence of benefit in locoregional control, efforts are now focused on comparing ALND with RNI in patients with limited nodal disease. Results of early trials such as AMAROS suggest non-inferiority of radiotherapy.

In patients with node positive or locally advanced disease, neoadjuvant chemotherapy (NAC) is often used to downsize or downstage the disease. The accuracy SLNB following NAC has been investigated, with discordant results reported from a number of trials.

Current trials in progress seek to validate the non-inferiority of RNI compared to ALND in patients with limited nodal disease, or in some trials, the complete omission of further axillary management.

There is a global paradigm shift towards de-escalation of axillary management based on recent evidence suggesting lack of benefit from overaggressive treatment. This review aims to summarize the seminal trials addressing regional management in breast cancer to illustrate this fact.

Introduction:

The management of the axilla in breast cancer remains a controversial topic. It is important to distinguish between the patient that is clinically node positive and the patient who is clinically node negative but has a positive sentinel node biopsy. It is well established that a sentinel lymph node biopsy (SLNB) is standard initial workup in breast cancer patients who are clinically node negative and do not have high risk features. The absence of cancer cells in the SLNB confirms that no further surgical management of the axilla is warranted. Completion axillary dissection (ALND) is also no longer standard practice for up to 2 positive sentinel nodes based on data from ACOSOG Z0011 and the AMAROS studies\textsuperscript{1,2}. The AMAROS study confirms improved outcomes with radiation over axillary dissection but it is still common practice to complete the axillary dissection if more than 2 nodes are positive despite the absence of data to support this historic practice.

The focus of medicine in the 21st century is appropriately moving toward person-centered care and improved quality of life. This has led to a move away from the extremely morbid surgeries initially implemented in the 1800’s. In recent decades there has been increased recognition of
the role of axillary surgery as a staging and prognostic tool rather than a therapeutic intervention. This review aims to summarize the seminal trials conducted and in progress concerning axillary management in patients with breast cancer, and provide an opinion regarding current practice recommendations.

Caution needs to be exercised when interpreting studies as to the exact definitions of clinical and pathological nodal status. It is important to recognize that the interpretation of clinical versus pathologic nodal status has changed. Strict application of current TNM rules suggest that a sentinel node biopsy without resection of the primary tumor constitutes clinical node staging and that pathological nodal staging requires primary tumor resection. Previously, clinically node positive was defined as palpable axillary nodes.

**Surgery**

ALND has largely been abandoned in the clinically node negative patients due to significant morbidity, namely lymphedema of the arm and hand, restricted shoulder mobility, and even weakness and parasthesiae\(^3\). Petrek et al. reported a 49% incidence of lymphedema in patients who underwent mastectomy and ALND at 20 years\(^4\). The following studies describe surgical axillary management options for patients with nodal status divided into the following categories: node negative, micrometastatic (<2mm lesion), and macrometastatic (>2 mm lesion) (Table 1).

**Node negative disease**

A number of studies earlier in the decade have provided evidence that ALND does not confer any survival benefit in patients without axillary node metastases.

**NSABP-B32 (2010)**

The NSABP-B32 is a landmark trial that compared 3986 women with negative SLNBs that were randomized to ALND (group 1) versus no further axillary treatment (group 2). The majority of patients in both arms received adjuvant systemic treatment. Radiotherapy was delivered to 82% of patients of the entire study cohort. The study primary endpoint was overall survival (OS). In a 10-year update, it was reported that there is no significant difference in OS, disease free survival (DFS), or local recurrence between the two trial arms. Kaplan-Meier estimates for 8-year OS was reported as 91.8% and 90.3% for groups 1 and 2 respectively. Similarly, 8-year DFS for groups 1 and 2 were 82.4% and 81.5% respectively. The regional nodal recurrence was greater in group 2, with 14 events compared to 8 in group 1, although the results did not achieve statistical significance (\(p = 0.22\))\(^5\).

This trial shaped practice guidelines and provided evidence that ALND in the context of a negative SLNB did not confer any significant added benefit in terms of both OS and DFS. SLNB alone was established as a viable standard in surgical management of patients without nodal metastases.

**Micrometastatic disease**
In the setting of lymph nodes with micrometastatic disease, axillary management is not as well established. Micrometastatic disease is a clinical prognostic factor. From the results of the MIRROR study, micrometastatic disease is shown to decrease 5-year DFS in women with early breast cancer in comparison to node negative patients\textsuperscript{6}. Two trials address the surgical management of microscopic axillary lymph node disease.

**IBCSG 23-01 (2013)**
This European study investigated 934 patients who had T2 or less invasive breast cancer, with at least one sentinel lymph node containing micrometastatic disease. Patients were randomized to receive ALND versus no ALND with the primary study endpoint being DFS. Adjuvant radiotherapy was given to 97.4% of patients who underwent lumpectomy. Radiotherapy was delivered by tangents, intra-operative partial breast irradiation (PBI), or a combination. The majority of patients in each study arm received tangential radiotherapy (70%). Overall 96% of all patients received adjuvant systemic therapy. Omission of ALND was determined to be non-inferior in regards to 5 year DFS, which was 84.4% for the ALND cohort compared to 87.8% in the non-ALND cohort (\(p= 0.0042\)). Similarly, 5-year OS was 97.6% for ALND compared to 97.5% without ALND. Multivariate analysis showed that only tumor size and grade were significant predictors of DFS, whereas ALND had no significant effect\textsuperscript{7}.

The ALND group reported greater adverse outcomes including grade 3+ lymphedema and grade 3 neuropathy.

This study provides evidence that ALND does not confer survival benefit in patients with micrometastatic lymph node disease, but instead increases morbidity. It should also be noted that patients who received PBI did not receive any radiation dose to the axilla.

**AATRM 048 (2013)**
This Spanish study looked at 233 patients who had invasive breast cancer with tumor sizes less than 3.5cm and micrometastatic lymph node disease. The trial randomized patients to either no further surgery or ALND after lumpectomy and sentinel biopsy. All patients received adjuvant systemic therapy and whole breast irradiation. Care was taken to ensure that only breast tissue, and not the axilla, was irradiated by tangential fields. High tangents or a third field were not allowed by trial protocol. The primary endpoint was DFS. At a mean follow-up of 5-years, a total of 4 trial patients experienced disease recurrence (1.8%), with 3 in the non-ALND cohort and one in the ALND cohort. The difference however, was not statistically significant (\(p = 0.33\))\textsuperscript{8}.

Although a smaller trial, this study presents similar results as IBCSG 23-01, suggesting that avoiding ALND in patients with micrometastatic lymph node disease was non-inferior to ALND.

**Node positive disease**

Until recently ALND after positive SNB was the standard of care. In the past decade there have been several studies confirming that ALND may be overtreatment for many of these patients.
ACOSOG Z0011 (2011)
A total of 856 patients were randomized to ALND vs no ALND following breast conserving surgery (BCS), SLNB, and adjuvant whole breast irradiation (WBI). WBI was delivered by tangential radiation fields and specified no third field nodal irradiation. All patients had T1 or T2 disease, were clinically node negative, but had up to 2 lymph nodes with metastatic disease on SLNB. Nearly all patients received adjuvant systemic therapy (96.5%). The primary endpoint was OS. At a median follow-up of 6.3 years, both trial arms did not result in statistical difference between OS and DFS. The 5-year OS was 92.5% in the SLNB arm and 91.8% in the ALND group (HR = 0.79). Similarly, the 5-year DFS was 83.9% and 82.2% in the two arms respectively (HR = 0.82). The loco-regional recurrence rate was 5.3% in SLNB at 10 years, compared to 6.2% in the ALND arm (p=0.36).²

This has been the most influential study in changing practice to omit ALND in breast cancer patients with macroscopic lymph node metastases. Given similar survival rates, the ACOSOG Z0011 study results have begun to steer management guidelines away from complete ALND in patients with 2 or less macroscopically positive lymph nodes on SLNB.

Radiation fields were not standardized in the SLNB arm, and this has somewhat muddied the interpretation. The study clearly showed no benefit to surgery, however the argument has been postulated that radiation to the lower axilla may have compensated. It has been suggested that there was a bias toward tangents resulting in greater coverage of the lower axilla. Jagi et al reconstructed the radiation fields from the Z0011 study and showed that there was no substantial difference in tangent fields between the two arms, although, more than half of patients in each analyzed arm received high tangents. Additionally however, they found that nearly 20% of analyzed patients received a third nodal field (especially those with a greater number of positive nodes), which was trial protocol violation⁹,¹⁰

To reassess the validity of the Z0011 results, two trials are currently in the accrual process. The SENOMAC trial is a non-inferiority trial comparing ALND versus no ALND following surgery with the primary endpoint being DFS at 5 years. It differs from Z0011 in that it includes patients with T3 disease as well as those who have been treated with mastectomy. The investigators also require electronic reporting of regional nodal volumes¹¹. The other, is the SERC trial.

SERC (2014, accruing)
This French randomized control trial is a non-inferiority trial that is currently accruing. It compares ALND versus no ALND in clinically node negative breast cancer patients with tumors up to 5 cm and positive SLNB results. Unlike the Z0011, there is no upper limit to the number of positive sentinel nodes. Patients with indications for neoadjuvant systemic therapy however are excluded. Patients will have undergone lumpectomy and SLNB prior to randomization. The accrual target is 3000 patients. The primary endpoint is DFS, with secondary endpoints being axillary recurrence rate and OS. Radiotherapy will be delivered by tangential fields to the breast or chest wall as indicated. Patients with macrometastatic lymph node disease (N1+) will receive nodal irradiation to the supraclavicular and/or level 3 axilla in accordance to each center’s
guideline. Radiotherapy treatment of micrometastatic lymph node disease, as well as internal mammary chain irradiation, are left to the discretion of each institution.

Preliminary results for the first 1000 patients were presented at the 2017 San Antonio Breast Cancer Symposium. The only observation was the correlation between chemotherapy timing and non-sentinel lymph node detection rate.

The significance of this study is that patients with a greater number of positive lymph nodes were allowed.

**Radiation**

Adjuvant breast irradiation is recommended following BCS to decrease the risk of local recurrence. The whole breast is commonly irradiated (WBI). In the setting of a mastectomy, the chest wall may be irradiated if there are high risk features. Both treatments are usually administered using tangential fields. The following studies address regional radiotherapy (Table 2).

**Regional Nodal Irradiation**

Regional lymph nodes of the breast include the axilla (Levels I-III), supraclavicular fossa (SCN), and the internal mammary nodal (IMN) chain. Metastases usually occur to the axillary nodes first, however direct extension to SCN and IMN has been reported.

Adjuvant radiotherapy using tangential fields does include axillary nodes and may adequately treat level I lymph nodes. Current evidence suggests there is benefit in treating regional nodes in patients with higher risk breast cancers, but there is still controversy as to the extent of nodal irradiation to confer this benefit.

**MA 20 (2015)**

This Canadian study randomized 1832 women with node positive or high-risk node negative breast cancer to receive WBI alone or WBI plus RNI, including axillary, SCN, and IMN nodal regions. High risk node negative features included tumors that were T3 or greater, 2 cm or greater with fewer than 10 nodes removed, G3 or greater, LVI positive, or ER-. All women received breast conserving surgery and adjuvant systemic treatment. SLNB positive patients underwent ALND to levels I and II. WBI was delivered by tangents within the control arm, in which the superior field edge was defined at the sternal angle to include all breast tissue. In the experimental arm, the tangents were either widened to include the IMN, or a separate field used altogether. A dedicated anterior field was used to treat the SCN and level 3 axilla in this same arm. For patients with higher risk disease, defined as less than 10 nodes removed or more than 3 positive axillary nodes, the lateral aspect of this field was extended to include axillary levels 1 and 2 as well as the addition of a non-divergent posterior field.

The primary endpoint was OS. At a median of 9.5 years of follow-up, the investigators concluded no significant difference in OS between the two groups, with a rate of 82.8% and
81.8% in the experimental and control arms respectively. Interestingly however, the DFS was observed to be 82% in the experimental group and 77% in the control group (HR 0.69, p = 0.05). This represents a 24% relative increase in DFS in the treatment group with the addition of RNI.

Results of this large multi-centre trial present convincing evidence that, there is a significant reduction in both locoregional and distant disease recurrence in node positive or high risk node negative patients, albeit without apparent survival advantage.

EORTC 22922 (2015)
This study investigated 4004 patients with stage 1-3 invasive breast cancer with risk of IMN metastasis. Tumors were central, medial, or in the case of lateral tumors, required macroscopic axillary lymph node involvement. All patients underwent breast surgery, SLNB, adjuvant radiotherapy with WBI or to the chest wall, and received subsequent ALND in the case of a positive SLNB. Patients were then randomized to no RNI versus RNI, which included SCN or IMN regional irradiation. Less than 10% of patients in each arm received axillary radiation dose as a result of tangential fields. Nearly all patients received adjuvant systemic therapy.

The primary endpoint was OS. At a median follow-up of 10.9 years, the investigators found that OS was 82.3% in the treatment group and 80.7% in the non-treatment group, although the difference was not significant (HR 0.87, p= 0.06). The DFS at 10.9 years was 72.1% and 69.1% in the same respective groups, and found to be significant (HR 0.89, p = 0.04). Additionally, there was significant difference between arms in regard to distant DFS (HR 0.86, p = 0.02) and breast cancer mortality (HR 0.82, p = 0.02).

Like the MA20 trial, the results of this study showed a small but significant benefit in DFS, distant DFS, and breast-cancer specific deaths in patients who received RNI to the SCN and IMN. There was a trend towards increased OS in the RNI group when analyzing the total cohort.

POSNOC (2014, accruing)
This British trial is currently accruing patients to investigate whether omitting adjuvant axillary management is non-inferior to ALND or axillary radiotherapy in patients with ≤ T2 disease and 1 to 2 macrometastatic lymph nodes. The accrual target is 1900 patients who have undergone BCS or mastectomy, adjuvant WBI or chest wall radiotherapy, and adjuvant systemic therapy. They will then be randomized to no further treatment (experimental), or adjuvant ALND or axillary RNI (control). The primary study endpoint will be axillary recurrence.

In essence, POSNOC is another study that strives to build upon and generalize the findings of the ACOSOG Z0011 trial. The study authors emphasize that the POSNOC study differs in that patients with mastectomies are included. This study excludes patients with micrometastatic lymph node disease only. Radiotherapy is standardized, and patients are treated with either axillary surgery or radiotherapy.
BOOG 2013-07 (2014, accruing)
This Dutch trial is a non-inferiority RCT, currently in accrual phase, which compares completion axillary treatment versus no further axillary treatment following mastectomy and SLNB. Patients have ≤T2 disease with up to 3 positive nodes on SLNB (including micrometastatic disease). Some patients will undergo chest wall irradiation based on institutional guidelines. Further completion axillary treatment can be either ALND or RNI. In the case of RNI, this can be axilla alone or include SCN depending on centre. Nodal target regions will be contoured for evaluation during trial analysis.

The accrual target is 878 patients. The primary endpoint is axillary recurrence rate at 5 and 10 years. Secondary endpoints include quality of life, OS, locoregional recurrence (LRR), and distant DFS.

Similar to POSNOC, this trial aims to evaluate the omission of completion axillary treatment. This study does allow patients with up to 3 positive lymph nodes rather than 2, and includes patients with microscopic lymph node metastases.

RNI versus ALND
A number of studies compared RNI with ALND in its efficacy of managing the axilla.

AMAROS (2014)
The AMAROS trial investigated 4806 patients with T1-T2, clinically node negative invasive breast cancer with positive SLNB. This was a non-inferiority trial comparing RNI to the ALND standard. Patients were randomized to receive ALND versus RNI to all levels of the axilla and medial SCN. All patients underwent breast conserving surgery followed by WBI, or mastectomy with or without chest wall irradiation. Radiotherapy quality assurance was performed prior to the initiation of the study. In the ALND arm, axillary RNI was allowed in patients with 4 or more positive nodes on SLNB according to institutional protocols. Systemic therapy was administered at the discretion of the treating clinicians, and 90% patients in each trial arm received systemic therapy.

The primary endpoint was LRR, with secondary endpoints of DFS, OS, and rate of adverse events such as lymphedema. At a median follow-up of 6.1 years, the 5-year LRR rate was 0.43% in the ALND group compared to 1.19% in the RNI group. The non-inferiority test was however underpowered given the low incidence of events. Similarly, there was no significant difference in DFS or OS between the two arms. It should be noted that a small number of patients in each arm received both ALND and RNI (5.6% and 1.7% in the ALND and RNI arms respectively).

Conversely, there was a statistically significant increased incidence in lymphedema at each the 1 (p < 0.0001), 3 (p = 0.003), and 5 (p < 0.0001) year marks in the ALND group in comparison to the RNI group. Measuring arm circumference at these same time points derived a similar conclusion at 3 and 5 years.
This phase 3 trial provides evidence that RNI is a viable alternative to ALND in early breast cancer patients, although the primary endpoint was underpowered given the paucity of locoregional recurrence in the study. Patients experienced similar rates of DFS and OS, with the added benefit of a lower lymphedema risk within 5 years of treatment for patients receiving RNI.

Edinburgh Trials (2016)
The Edinburgh breast unit pooled the outcomes of their two previously conducted RCTs. Patients with invasive breast cancer under 5cm in size were randomized to ALND versus SLNB plus RNI in the case of positive lymph nodes (up to N1 disease). Patients underwent mastectomy in the first trial and lumpectomy with WBI in the second. In the pooled analysis, 301 women with node positive disease were included. All patients received adjuvant systemic therapy with chemotherapy or endocrine therapy. RNI was given to the internal mammary chain, shoulder fields, and SCN in the mastectomy trial. In the lumpectomy trial, RNI was delivered by a direct anterior field covering the axilla and SCN with a posterior axillary boost.

The composite outcomes were OS, breast cancer-specific survival (BCSS), time to LRR, and time to distance metastasis. There was no observed difference in OS between ANLD and RNI (HR 0.98, p = 0.876), BCSS (HR 1.07, p = 0.688), or time to distant metastasis (HR 1.03, p=0.847) at a median follow up of 19 years. There was however a significant difference in LRR. Patients treated with RNI were more than twice as likely to recur as those who underwent ALND with an HR of 2.64 (p=0.05).

Results from this trial suggest that although ALND appears superior to RNI in regards to halving LRR, this did not translate into any clinically meaningful survival advantages20.

Chemotherapy
Systemic therapy is the mainstay in treatment of patients with advanced disease. Chemotherapy may be used in the neoadjuvant setting for patients with locally advanced breast cancer (LABC). NAC may reduce axillary tumor burden allowing the avoidance of morbid axillary treatment21. There is also a potential role for in vivo prognostication based on nodal response to chemotherapy. Some evidence suggests that in patients with nodal complete pathological response (pCR) following NAC, further axillary management may not be beneficial22,23. The NSABP-B18 showed similar OS and DFS in comparing adjuvant chemotherapy (AC) and neoadjuvant chemotherapy (NAC) in patients with stage I to IIB disease24. The following studies address chemotherapy in regional management (Table 3).

SLNB post Neoadjuvant Chemotherapy
One of the main concerns regarding SLNB post NAC is the risk of false negative results. There lies a theoretical risk of residual axillary disease burden if there is heterogeneous response in sentinel and non-sentinel nodes, or if lymphatic drainage is altered by scarring from systemic therapy. This is particularly concerning in patients with clinically node positive disease prior to NAC. A number of prospective trials address this question.
NSABP B27 (2005)
The NSABP B27 trial was a three-arm study that investigated the efficacy of NAC using doxorubicin and cyclophosphamide in comparison with other arms that added docetaxel in the NAC and AC settings. It was determined that there was no significant difference in 9 year OS or DFS\textsuperscript{24}.

A retrospective analysis of the B27 protocol looked at the feasibility of SLNB post NAC. Study authors found that the SLN identification rate (IR) was 84.8%. Moreover, the false negative (FN) rate was 10.7% (95% CI, 5.6-15.8%), which was comparable to pre-NAC SLNB FN rates that ranged from 7-14%. It was observed that increasing tumor size trended towards a higher FN rate (p = 0.33)\textsuperscript{25}.

The results of this analysis proposed the first piece of evidence that SLNB post NAC may be a feasible option for restaging in lieu of ALND.

SENTINA (2013)
This multicenter prospective cohort study investigated 1737 patients with breast cancer who underwent NAC. Patients were divided into 4 arms. Arms A and B included patients who were clinically node negative and underwent SLNB prior to NAC. Arm A patients were those who were found to be SLNB negative and received no further axillary treatment. Patients in arm B were SLNB positive and underwent secondary SLNB and ALND following NAC.

The C and D arms consisted of patients who were clinically node positive by palpation or ultrasound. They received NAC upfront, and nodal status was evaluated clinically thereafter. Patients in arm C were those who were clinically node negative and underwent subsequent SLNB and ALND. Patients in arm D remained clinically node positive and received ALND.

The primary endpoint of the SENTINA study was the FN rate of the SLNB in cohort C patients, with secondary endpoints being the surgical identification rate (IR) in arms B and C as well as the FN rate in arm B. Study authors found that the FN rate was 14.2% in this cohort, and up to 20% when only one of either radiotracer or dye was used. The IR was 80%. The removal of 3 or more lymph nodes however significantly decreased the FN rate to under 10%.

In cohort B, the FN rate was 51.6% and IR was 60.8% when the second SLNB was performed in previously SLNB positive patients.

The study results suggest that performing a SLNB following NAC in patients with previous nodal disease, whether SLNB or clinically positive, results in unacceptably high FN and IR rates. A recent meta-analysis by Pesek et al. calculated a pre-chemotherapy SLNB FN rate of 7.0\textsuperscript{26}. Hypotheses include alteration of lymphatic drainage after systemic treatment. SLNB of 3 or more lymph nodes however appears to improve detection rates and accuracy\textsuperscript{27}. 
ACOSOG Z1071 (2013)
This study was designed to investigate the FN rate post NAC in patients who had initial clinically node positive disease. A total of 756 patients with T0-4 and N1-2 disease were enrolled in the trial. After NAC, all patients underwent SLNB first followed by ALND to determine FN rate.

Study authors found that in patients with initial cN1 disease, the FN rate was 12.6% when sampling up to 2 SLN. This is greater than the pre-specified 10% threshold. It was found that the FN rate decreased when 3 or more nodes were sampled compared to only 2 (9.1% vs 21.1%). The FN rate was significantly lower with dual tracer mapping at 10.8% compared to 20.3% with a single agent\textsuperscript{28}.

The conclusion of this study suggests that SLNB post-NAC in clinically node positive patients may result in a higher rate of FN results, and that they should be interpreted with caution. It however also provides evidence that sampling 3 or more SLNs can decrease that rate within acceptable limits. These results reflect those observed in the SENTINA trial.

A post-hoc analysis of the locoregional management post NAC in the trial population revealed significant variability to radiotherapy usage and techniques. Patients who remained node positive or had residual tumor post-NAC received axillary radiotherapy more frequently, and the difference was found to be statistically significant (p = 0.002). Study authors called for a need for greater uniformity and guidelines for radiotherapy in the NAC setting\textsuperscript{29}.

SN FNAC (2015)
This multicenter prospective study investigated 153 patients with clinically node positive breast cancer who received NAC. Clinical T4 and N3 patients were excluded. Post NAC, all patients underwent SLNB and subsequent ALND. Any lymph node metastasis determined pathologically, including micrometastatic disease, was considered positive. All biopsy results were analyzed by immunohistochemistry (IHC).

Because the trial design was similar to the ACOSOG Z1071, it was closed to accrual early, having reached 51% of its target.

An interim analysis was performed which yielded similar results to the Z1071 trial. The overall FN rate of SLNB post-NAC was 8.4% in all patients. The FN rate with the removal of one SLN was 18.2%, whereas it was 4.9% with two or more nodes. Similarly, the use of dual tracers decreased the overall FN rate from 16% to 5.2%. The IR was 87.6% for all patients.

Unlike the Z1071, SN FNAC supports that SLNB post NAC boasts an acceptable FN rate under 10% in initial clinically node positive patients. Key differences that this study purports are the inclusion of patients with micrometastatic disease on pathology and the mandatory utility of IHC in the SLNB analysis process. Study authors call for further investigation prior to determining guidelines for SLNB in the neoadjuvant setting\textsuperscript{30}.
Further node specific management following NAC is an area of controversy. In a post hoc analysis of the NSABP B18 and B27 trials, patients with pCR following NAC were found to have a lower LRR rate, questioning the need for adjuvant nodal management in this patient subset\textsuperscript{31}. A few trials are currently in the accrual phase further investigating this question.

**NSABP B51 (accruing)**
Looking beyond the reliability of SLNB in the NAC setting, the NSABP B51 trial investigates the omission of adjuvant RNI in clinically node positive patients who demonstrate a pathological complete response (CR) at ALND post NAC. The study aims to enroll 1636 patients over 5 years with definitive analysis at 7.5 years. Patients are eligible if they have T1-3 tumors and N1 disease with pathological CR post NAC. Patients will be randomized to receive axillary RNI versus no further axillary treatment. Mastectomy patients receiving RNI will also receive chest wall radiation. All lumpectomy patients will receive WBI. All patients will receive the appropriate systemic therapy as clinically indicated. The primary study endpoint is invasive breast cancer recurrence free interval (IBC-RFI)\textsuperscript{32,33}.

**ALLIANCE A011202 (accruing)**
The A011202 trial seeks to define management standards for patients with node positive disease after NAC. This study includes T1-3 breast cancer patients treated with NAC and subsequent positive SLNB with up to N1 disease. They will then be randomized to receive ALND or axillary nodal irradiation following standard primary tumor treatment, including radiotherapy to the breast or chest wall. Both groups will also receive radiotherapy to the SCN and IMN. Patients in the ALND arm will receive radiotherapy to any axillary levels that are not treated by surgery. The target accrual is 2918 patients. The primary outcome is IBC-RFI\textsuperscript{22,34}.

**Summary and Conclusion**

There has been a general trend towards de-escalation of invasive axillary management in the past decade. Given the mounting evidence against the necessity of ALND in many patient populations, there is an opportunity to spare the risk of morbidity associated with the procedure.

Axillary management in SLNB negative patients is well established. The results of the NSABP B32 trial confidently reports no additional survival benefit of subsequent ALND, but instead increased arm-related morbidity\textsuperscript{5}. In patients with micro-metastatic axillary disease, the results of the IBCSG 23-01 and the AATRM048 studies suggest that there is no DFS or OS advantage in completing ALND in addition to SLNB\textsuperscript{7,8}. It should be noted that nearly all patients in these trials received adjuvant systemic therapy, potentially contributing to the control of any metastatic disease present.

The greatest controversy still lies in patients with pathologically positive lymph nodes. In patients with up to 2 macroscopically positive lymph nodes, the Z0011 trial presents convincing evidence that performing no further axillary surgery is non-inferior to ALND, with equivocal OS
and DFS at 5 years, as well as LRR at 10 years. However, the trial had its weaknesses. Radiotherapy quality was inconsistent, with certain patients receiving RNI against trial protocol as WBI with high tangents, potentially treating the lower axilla\(^2\).

The role of RNI has been investigated in managing patients with node positive disease. Both the MA 20 and EORTC 22922 sought to determine the additional benefit of RNI in patients with node positive or high-risk node-negative disease whom have undergone ALND. Both trials purport similar outcomes of increased DFS and LRR advantage with the use of RNI compared to no further axillary treatment. Interestingly, no significant OS difference was observed in either study, suggesting that there is no translational mortality advantage in locoregional control. It is likely that adjuvant systemic therapy played a large role in patient OS\(^{15,16}\).

Part of the de-escalation paradigm focuses on the use of non-surgical options to manage the axilla. The AMAROS and Edinburgh trials compared RNI versus ALND in the management of the SLNB positive axilla. The AMAROS trial concluded that there was no significant difference in DFS or LRR between the two arms\(^1\). Interestingly however, the Edinburgh trials reported a significant difference in LRR, with patients undergoing RNI twice as likely to recur than their ALND counterparts\(^{20}\). Nevertheless, both studies concluded that there was no significant difference in OS between the two modalities.

The feasibility of SLNB in the NAC setting was initially investigated in retrospective analysis of the NSABP B27 trial, which deemed it a viable option given its acceptable FN rates\(^{25}\). The SENTINA, ACOSOG Z1071, and SN FNAC trials set out to confirm these findings\(^{27,28,30}\). Trial results were variable, but several factors were determined to optimize SLNB in the NAC setting to minimize FN rates. These include the removal of greater than 2 lymph nodes, use of dual tracers, and the use of immunohistochemistry (IHC) in pathological analysis.

Surgical clip placement to mark nodal disease was also has been found to decrease the FN rate. Caudle et al. performed a prospective study and found that using a surgical clip on biopsy positive nodes pre-NAC reduced the FN rate to 2% in the NAC setting with targeted clipped-node removal compared to 10.1% with SLNB\(^{35}\). A recent meta-analysis of 19 studies purported a collective FN rate of 13%, with an IR of 91% in patients with clinically node positive disease undergoing NAC. It concluded that SLNB in the setting of NAC was feasible and did not have a detrimental survival impact\(^{36}\).

Several studies that seek to provide guideline changing evidence for axillary management are ongoing. The SENOMAC and SERC trials aim to strengthen the findings of the Z0011 by investigating the effect of omitting ALND in SLNB positive patients. Both studies however, have broader inclusion criteria in order to provide more generalizable results\(^{11,12}\).

POSNOC and BOOG 2013-07 studies aim provide further insight into the utility of any additional axillary management, whether RNI or ALND, in the setting of N1 disease. Study authors aim to standardize radiotherapy delivery, and expand inclusion criteria to mastectomy patients\(^{17,18}\).
The NSABP-B51 and ALLIANCE A011202 trials will address axillary management in the NAC setting. The B51 trial will investigate adjuvant RNI versus no axillary treatment in patients with pathological CR post NAC\textsuperscript{32}. Similarly, the A011202 will investigate axillary treatment versus no treatment but utilizing RNI or ALND in patients who are persistently node positive post NAC\textsuperscript{34}. The primary endpoint of both trials is IBC-RFI.

The MA39 trial is a non-inferiority trial that compares RNI versus no RNI in node positive patients with biomarker low risk disease. Patients are included if they are ER positive and receiving endocrine therapy for 5 years, have an Oncotype Dx score < 18, and limited macroscopic nodal disease (1-3 positive nodes if ALND, 1-2 if lumpectomy plus SLNB, and 1 if mastectomy plus SLNB). The primary endpoint is IBC-RFI, with secondary endpoints that include DFS, BCSS, OS, and toxicity\textsuperscript{37}.

Studies have emerged that address the utility of even SLNB itself. The SOUND trial is an Italian trial investigating the omission of SLNB in patients with cT1N0 disease undergoing lumpectomy. It began accrual in 2012, with the primary endpoint being distant DFS. Patients were randomized to SLNB versus no SLNB cohorts\textsuperscript{38}. Similarly, the German INSEMA trial is a two-phase trial that investigates the omission of SLNB in patients with ≤ cT2N0 disease in its first phase. The second phase is analogous to the Z0011 trial and randomizes patients with ≤ 3 positive sentinel nodes from the first phase to undergo ALND versus no ALND. The primary endpoint is DFS\textsuperscript{39}.

There has been a surge of interest in axillary de-escalation in the recent decade in the management of node positive breast cancer. The 2016 Kyoto Breast Cancer Consensus Conference update shows that 74% of experts were prepared to forego ALND in patients with limited macrometastatic disease, following the results of the Z0011 trial. Another 80% were comfortable performing SLNB in the NAC setting in initial pN0 patients or patients who achieved pathological CR\textsuperscript{40}. With the amounting evidence, it seems that more clinicians are accepting and implementing the idea of de-escalating axillary management on a global basis. Results from current and future studies should provide further clarity to the matter.

**Recommendations**

In our center, the current guidelines for locoregional management are as follows for patients with invasive breast cancer and positive SLNB (clinical negative nodes):

- Those with T1-T2 disease and 1-2 nodes positive following SLNB receive radiotherapy to the breast or chest wall as well as levels 1-3 axilla and SCN. The IMN are included at the discretion of the treating physician.

- Those with 3 nodes positive on SLNB will undergo further ALND. If the patient has had an extensive ALND revealing limited disease, radiotherapy may be delivered to the breast or chest wall and the SCN.
Patients with clinical T3 or N1 and greater disease are considered to have locally advanced breast cancer (LABC). Most patients will receive NAC followed by management of the primary tumor with lumpectomy or mastectomy. In regards to the axilla:

- Patients with palpable nodes or nodes seen on imaging (ycN1+) will undergo ultrasound guided biopsy of the lymph nodes followed by subsequent ALND if positive.
- Patients without nodes that are palpable or visible on imaging (ycN0) will undergo SLNB with at least 3 sentinel nodes biopsied. Some surgeons however will still perform ALND in these patients. They will then receive regional radiotherapy as detailed above.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Clinical Question</th>
<th>Primary Endpoint</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B32</td>
<td>1999-2004</td>
<td>SLNB vs. ALND in node negative patients</td>
<td>OS at 10 years</td>
<td>No significant difference in OS and DFS</td>
</tr>
<tr>
<td>IBCSG 23-01</td>
<td>2001-2010</td>
<td>SLNB vs. ALND in patients with micrometastatic nodal disease. Non-inferiority trial</td>
<td>DFS at 5 years</td>
<td>Non-inferiority of SLNB alone in terms of DFS. Similar OS rates.</td>
</tr>
<tr>
<td>AARTM 048</td>
<td>2001-2008</td>
<td>SLNB vs. ALND in patients with micrometastatic nodal disease</td>
<td>DFS at 5 years</td>
<td>No significant difference in DFS</td>
</tr>
<tr>
<td>ACOSOG Z0011</td>
<td>1999-2004</td>
<td>SLNB vs. ALND in patients with up to 2 macroscopic lymph node metastases</td>
<td>OS at 5 years</td>
<td>No significant difference in OS or DFS</td>
</tr>
</tbody>
</table>

Table 1: Landmark Trials in the Surgical Management of the Axilla. SLNB = sentinel lymph node biopsy, ALND = axillary lymph node dissection, OS = overall survival, DFS = disease free survival
<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Clinical Question</th>
<th>Primary Endpoint</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA 20(^{15})</td>
<td>2000-2007</td>
<td>WBI vs. WBI plus RNI in node positive or high risk node negative patients</td>
<td>OS at 10 years</td>
<td>No difference in OS, but higher risk of locoregional/distant recurrence in non-RNI group</td>
</tr>
<tr>
<td>EORTC 22922(^{16})</td>
<td>1996-2004</td>
<td>WBI vs. WBI plus SCN and IMN RNI in node positive or high risk node negative patients</td>
<td>OS at 10 years</td>
<td>Small but significant improvement in DFS with RNI. Trend towards improved OS with RNI.</td>
</tr>
<tr>
<td>AMAROS(^{1})</td>
<td>2001-2010</td>
<td>ALND vs. RNI in patients with positive nodal disease. Non-inferiority trial</td>
<td>LRR at 5 years</td>
<td>RNI was non-inferior to ALND in terms of LRR, OS, and DFS</td>
</tr>
<tr>
<td>Edinburgh Trials(^{20})</td>
<td>1980-1995</td>
<td>ALND vs. RNI in patients with node positive disease</td>
<td>OS, BCSS, time to LRR, and distant recurrence</td>
<td>LRR was more than twice as high in RNI patients compared to ALND (HR 2.64).</td>
</tr>
</tbody>
</table>

Table 2: Regional Nodal Irradiation Trials in Node Positive Patients. *SCN = supraclavicular lymph node, IMN = internal mammary lymph node, HR = hazard ratio, WBI = whole breast irradiation, RNI = regional nodal irradiation, ALND = axillary lymph node dissection, OS = overall survival, DFS = disease free survival, BCSS = breast cancer specific survival, LRR = locoregional recurrence.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Clinical Question</th>
<th>Primary Endpoint</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>SENTINA 27</td>
<td>2009-2012</td>
<td>FN rate of SLNB post NAC in node positive patients</td>
<td>FN rate post NAC</td>
<td>FN rate of 14.2% and IR of 80.1%. Removal of 3+ LN lowered FN rate &lt; 10%</td>
</tr>
<tr>
<td>ALLIANCE Z1071 28</td>
<td>2009-2011</td>
<td>FN rate of SLNB post NAC in node positive patients</td>
<td>FN rate post NAC</td>
<td>FN rate of 12.6% in cN1 patients with 2 LN removed. Removal of 3+ LN and dual tracer use significantly decreased FN rate</td>
</tr>
<tr>
<td>SN FNAC 30</td>
<td>2009-2012</td>
<td>FN rate of SLNB post NAC in node positive patients</td>
<td>FN rate post NAC</td>
<td>FN rate of 8.4% and IR of 87.6%. Study included micrometastatic disease and mandatory IHC analysis</td>
</tr>
</tbody>
</table>

Table 3: Trials for Sentinel Node Biopsy After Neoadjuvant Chemotherapy. *FN = false negative, LN = lymph node, SLNB = sentinel lymph node biopsy, IR = identification rate, NAC = neoadjuvant chemotherapy, IHC = immunohistochemistry
<table>
<thead>
<tr>
<th>Trial</th>
<th>Start Year</th>
<th>Clinical Question</th>
<th>Primary Endpoint</th>
<th>Secondary Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>SERC</td>
<td>2014</td>
<td>ALND vs. no ALND in cN0 patients but ≥ 1 pathologically positive lymph node</td>
<td>DFS</td>
<td>Axillary recurrence rate, OS</td>
</tr>
<tr>
<td>SENOMAC</td>
<td>2015</td>
<td>ALND vs. no ALND in cN0 patients with ≤ 2 pathologically positive lymph nodes</td>
<td>BCSS</td>
<td>LRR, OS, DFS</td>
</tr>
<tr>
<td>INSEMA</td>
<td>2015</td>
<td>SLNB vs. no SLNB in patients with ≤ cT2N0 disease, and then ALND vs. no ALND in</td>
<td>DFS</td>
<td>OS, LRR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>patients with ≤ 3 positive sentinel nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOUND</td>
<td>2012</td>
<td>SLNB vs. no SLNB in patients with cT1N0 disease</td>
<td>Distant DFS</td>
<td>DFS, OS, QoL</td>
</tr>
<tr>
<td>BOOG 2013-07</td>
<td>2015</td>
<td>No axillary treatment vs. ALND or Axillary RNI in patients with up to 3 macroscopic</td>
<td>RRR</td>
<td>Distant DFS, QoL, OS, LRR</td>
</tr>
<tr>
<td>POSNOC</td>
<td>2014</td>
<td>No axillary treatment vs. ALND or Axillary RNI in patients with up to 2 macroscopic</td>
<td>RRR</td>
<td>Arm morbidity, QoL, LRR, survival,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lymph nodes metastasis</td>
<td></td>
<td>economic evaluation</td>
</tr>
<tr>
<td>NSABP B51</td>
<td>2013</td>
<td>RNI vs no treatment in patients with pCR post NAC</td>
<td>IBC-RFI</td>
<td>OS, DFS, LRRFI, DRFI, and secondary</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>primary cancer rates</td>
</tr>
<tr>
<td>ALLIANCE</td>
<td>2015</td>
<td>RNI vs. ALND in patients with persistent node positive disease post NAC</td>
<td>IBC-RFI</td>
<td>OS, LRR, lymphedema</td>
</tr>
<tr>
<td>MA 39</td>
<td>2018</td>
<td>RNI vs. no RNI in patients with biomarker low risk disease</td>
<td>IBC-RFI</td>
<td>DFS, BCSS, OS, LRRFI, DRFI, toxicity,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>arm mobility, QoL, and economic evaluation</td>
</tr>
</tbody>
</table>

Table 4: Current Trials in Progress. *ALND = axillary lymph node dissection, RNI = regional nodal irradiation, pCR = pathological complete response, NAC = neoadjuvant chemotherapy, IBC-RFI = invasive breast cancer relapse free interval, OS = overall survival, DFS = disease free survival, LRR = locoregional recurrence, BCSS = breast cancer specific survival, RRR = regional recurrence rate, QoL = Quality of Life, LRRFI = locoregional recurrence-free interval, DRFI = distant recurrence-free interval.
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34. NCT01901094: Comparison of Axillary Lymph Node Dissection With Axillary Radiation for Patients With Node-Positive Breast Cancer Treated With Chemotherapy. Available at: 〈https://clinicaltrials.gov/ct2/show/NCT01901094〉
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