Chapter 10
Surgical Management of the Axilla in Node-Negative and Node-Positive Disease at Diagnosis

Joanna S. Lee, Priscilla F. McAuliffe, and Ronald R. Johnson

Introduction

Accurate nodal staging is important in breast cancer treatment because nodal involvement is a major prognostic predictor for breast cancer outcome. Nodal disease status widely determines the extent of systemic therapy, surgical treatment, radiation therapy, and reconstructive surgery. Historically, axillary lymph node dissection (ALND) was used to stage the axilla in all patients with breast cancer. However, axillary management has now evolved to utilize sentinel lymph node biopsy (SLNB), a less extensive surgery that still allows accurate staging of the axilla. The safety of SLNB alone in clinically node negative (cN0) patients with presumed low axillary disease burden is well established in the upfront surgery setting. The success of less extensive surgical intervention in the axilla is likely a factor of improved systemic and radiation therapy options, which also contribute to local disease control and improved overall oncologic outcomes.

In patients presenting with cN0 axilla, who are then found to have limited pathologic sentinel lymph node involvement, three clinical trials demonstrate that ALND is not necessary for all patients undergoing upfront surgery. The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial was a practice-changing study that demonstrated no significant differences in locoregional recurrence (LRR), disease-free survival (DFS), and overall survival (OS) in patients with cN0 breast cancer with confirmed metastases in 1 or 2 sentinel lymph nodes (SLN), who were treated with breast conservation therapy (BCT) and whole breast radiation (WBRT), without ALND [1]. The International Breast Cancer Study Group (IBCSG) 23-01 trial demonstrated that ALND may be safely omitted in cN0 patients with limited

J. S. Lee · P. F. McAuliffe · R. R. Johnson (✉)
Breast Surgical Oncology, University of Pittsburgh, Pittsburgh, PA, USA
e-mail: leejs7@upmc.edu; mcauliffepf@upmc.edu; johnrr@upmc.edu

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SLN involvement, showing no difference in 5-year DFS, but more surgery related toxicities, like lymphedema and neuropathy, in the ALND group [2]. The European Organization for Research and Treatment of Cancer (EORTC) 10981-22023 AMAROS trial also showed that, in patients with cT1-T2 N0 primary breast cancers treated with upfront surgery, radiation therapy is non-inferior to ALND. It is compelling that the patients in the axillary radiation group without ALND had significantly less lymphedema [3].

Axillary management following neoadjuvant chemotherapy (NAC) is also evolving. Use of NAC in early-stage breast cancer has increased over time with the goal to downstage the extent of surgery in both the breast and axilla. Depending on tumor biology, achieving pathologic complete response (pCR) following NAC is an important prognostic factor, especially for triple negative breast cancer (TNBC) and HER2 positive (HER2+) breast cancer. Although there is no overall survival difference between administration of chemotherapy in the neoadjuvant versus the adjuvant setting, a survival benefit has been demonstrated in the subset of patients with residual invasive disease following NAC who receive additional adjuvant chemotherapy.

Axillary management following neoadjuvant endocrine therapy (NET) is not well-known and there is paucity of information on this topic. Per the American Society of Breast Surgeons practice guidelines for the use of NST, NET produces the best response rates in postmenopausal women with clinical stage 2–3 breast cancer with strongly hormone receptor positive (HR+) breast cancer. Significant tumor downstaging using NET usually requires 4–6 months of continuous therapy, but pCR is rarely observed. Because pCR is rarely observed following NET, the clinical utility in axillary management is unknown. There is no established role for NET in premenopausal women currently. This chapter will review available literature regarding the optimal surgical management of axilla following NAC and will also briefly discuss surgical axillary management following NET. A different chapter in this book will go into more depth regarding the role of NET.

Benefit of NAC

Depending on tumor phenotype, NAC can effectively downstage the extent of surgery both in the breast and in the axilla. Even for patients with relatively smaller cN0 cancers at diagnosis, NAC may foster breast conservation by improving the tumor to breast size ratio. NAC also allows for in vivo assessment of tumor response. Furthermore, earlier data have shown that NAC receipt can result in downstaging of nodal involvement in patients presenting with cN+ disease which may consequently lead to less extensive axillary surgery. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial compared preoperative and postoperative doxorubicin and cyclophosphamide for operable breast cancer. This study showed that, regardless of the presenting clinical nodal status or tumor size, NAC resulted in

significant reduction in nodal positivity, 59% with NAC vs. 43% with adjuvant therapy, $p < 0.001$ [4]. Following this study, NSABP B-27 reported an even greater reduction in nodal involvement following NAC with the addition of preoperative docetaxel to the regimen described in B-18—50.8% for NAC versus 58.2% for adjuvant therapy, $p < 0.001$ [5]. Long-term updates of NSABP B-18 and B-27 also confirmed that the addition of docetaxel to NAC with doxorubicin and cyclophosphamide significantly increased the rate of pCR and that those patients who achieved pCR had superior DFS and OS [6]. A study from the University of Texas MD Anderson Cancer Center (MDACC) also showed significant reduction in nodal disease after NAC compared with up-front surgery group, particularly in patients with T2–T3 primary tumor (T1: 12.7% vs. 19%, $p = 0.2$; T2: 20.5% vs. 36.5%, $p < 0.0001$; and T3: 30.4% vs. 51.4%, $p = 0.04$) [7].

An additional benefit of NAC is the assessment of end-chemotherapy response, which could open the door for additional adjuvant systemic therapy options for the appropriate patients. Several recent studies showed a survival benefit with additional adjuvant chemotherapy for those patients who do not achieve pCR following NAC. The CREATE-X UNIM Clinical Trial showed that the addition of adjuvant capecitabine prolonged DFS and OS among patients with HER2-negative (HER2−) breast cancer who had residual invasive disease following standard NAC regimens containing anthracycline, taxane, or both [8]. The study demonstrated improved DFS and OS in the capecitabine group (DFS: 74.1% vs. 67.6%, $p = 0.01$; OS: 89.2% vs. 83.6%, $p = 0.01$). The KATHERINE trial showed a 50% reduction in risk of recurrence of invasive breast cancer or death with adjuvant trastuzumab emtansine (T-DM1) compared to with adjuvant trastuzumab alone (HR 0.50, $p < 0.001$) in patients with HER2+ breast cancer who had residual disease following standard NAC containing taxane, with or without anthracycline and trastuzumab [9].

Benefit of NET

Endocrine therapy in adjuvant setting is a widely accepted, important component of breast cancer treatment for the luminal subtype, hormone receptor positive (HR+), HER2− breast cancer as per NCCN guidelines. Similar to NAC, the use of endocrine therapy in neoadjuvant setting can potentially downstage the extent of disease and provide in vivo information about the cancer's responsiveness to endocrine therapy. ACOSOG Z1031 is a randomized phase II NET trial comparing response rates between letrozole, anastrozole, and exemestane that reported overall clinical response rate of 69% with no differences between the three different aromatase inhibitors. This study showed that NET increases BCT rate as 51.5% of the patients who were not BCT candidates at initial surgical consultation were able to successfully undergo BCT following NET [10].

In regard to the axilla, there is scarce data in literature looking at the role of NET on the downstaging of axillary surgical management. A study from Memorial

Sloan Kettering Cancer Center (MSKCC) reports the nodal pCR rate was 11% following NET. The nodal downstaging rates with NET and NAC were not significantly different (11% with NET vs. 18% with NAC, $p = 0.37$). Patients who achieved nodal pCR with NET were older, $p = 0.004$ and had greater progesterone expression, $p = 0.031$ [11]. A recent NCDB analysis looking at 4580 patients undergoing NET showed that the overall axillary pCR was 14.5%. The patients who achieved a pCR were more likely to have smaller axillary disease burden ($p = 0.008$), have a higher grade ($p = 0.003$), and have a ductal histology ($p = 0.04$) [12]. Another NCDB analysis looking at 4495 patients who received NET, raises an interesting question of the oncologic significance of residual nodal disease after NET, whether this has the same prognostic implications as residual disease following NAC. This analysis reports very low rates of pCR overall, 1.4% pCR in the breast and 1.2% pCR in both breast and axilla. Regardless of the low rates of pCR, there was no significant different in OS between patients who achieved axillary pCR and those who had residual small volume axillary disease, isolated tumor cells (ITCs), or micrometastases. Additionally, survival outcomes for the patients following NET were more similar to patients undergoing upfront surgery than those who received NAC [13].

Feasibility of SLNB After NAC

Because nodal status is a key prognostic predictive factor for breast cancer, accurate assessment of the extent of axillary disease following NAC is very important. For those patients who have excellent response to NAC, less invasive axillary surgery can minimize surgical morbidity.

Historically, there were concerns that SLNB may inaccurately represent the axilla following NAC, due to altered lymphatic drainage, secondary to treatment-related tissue changes, including fibrosis [14, 15]. Due to these concerns, some investigators performed SLNB prior to initiation of NAC [16]. The potential benefit of performing SLNB before NAC is that the knowledge of pathologic nodal status before NAC could help streamline the need for adjuvant radiotherapy and facilitate the planning for reconstructive surgery in appropriate patients. However, a potential drawback of performing SLNB before NAC is the loss of the ability to downstage microscopic axillary disease. Combined data from the NSABP B-18 and B-27 trials demonstrate that the pathologic response post-NAC is more important than pre-NAC stage in terms of predicting oncologic outcomes. Specifically, the lack of nodal pCR is the strongest predictor of 10-year LRR, HR 4.5, $p < 0.001$. These findings suggest that the decision to proceed with SLNB pre-NAC should only be considered for unique situations with multidisciplinary consensus [17].

Clinically Node-Negative Patients

Despite initial concerns about the accuracy of SLNB following NAC, recent studies demonstrate similar SLN identification rates and also similar false negative rates (FNR) as those seen in the upfront surgery setting for cN0 patients after NAC. Results from NSABP B-27 concluded that SLNB is applicable following NAC with an 84.8% identification rate and an FNR of 10.7%. The study reports a non-significant trend toward improved identification rate among surgeons who performed a higher number of sentinel node procedures [15]. The GANEA 1 study was designed to look at the detection rate, the FNR, and the accuracy of SLNB following NAC. In the cN0 group, the SLN identification rate was 95% with an FNR of 9%, confirming the feasibility of SLNB after NAC. However, for the cN+ group, a significantly lower identification rate of 82% was reported ($p = 0.08$) [18]. The GANEA 2 study goes on to elaborate that among the patients in the cN0 group treated with SLNB alone, only one axillary relapse occurred during the follow-up period from 2010 to 2014, confirming that negative SLNB after NAC allows for safe omission of ALND in patients with no initial nodal involvement prior to NAC [19]. A study from MDACC reported similar SLN identification rates for up-front surgery compared to NAC: 98.7% and 97.4%, respectively. The FNR was 4.1% for up-front surgery and 5.8% for NAC; $p = 0.4$ [7]. The Netherlands Cancer Registry study also showed comparable SLN identification rates: 98% for up-front surgery versus 95% for NAC [20].

Although studies show comparable SLN identification rates and FNR, another concern that is raised is the long-term consequences of possibly leaving lymph nodes with potentially chemotherapy-resistant disease. Unfortunately, literature on this particular topic is scarce. A MDACC study showed a low regional recurrence of 1.2% in patients with a negative SLNB after NAC who underwent SLNB alone without ALND, with a median follow up of 47 months [7]. Similarly, the University of California at Los Angeles also reported low axillary recurrence of 0.7%, at a median follow up of 52 months [21].

Clinically Node-Positive Patients

Patients who are cN+ can achieve nodal pCR after NAC in up to 20–70%, based on their tumor biology. The highest rate of nodal pCR is seen in TNBC and HER2− breast cancer patients [22]. Three large, multicenter, prospective trials demonstrated the feasibility of SLNB in patients with cN+ disease at diagnosis following NAC (Table 10.1).

The ACOSOG Z1071 evaluated the FNR of SLNB after NAC in cN+ patients with overall reported FNR of 12.6%. Further subset analysis showed that the use of

Table 10.1 Trials demonstrating feasibility of SLNB in cN+ patients following NAC

Studies	Total patients	Pre-NAC biopsy	SLN identification rate (%)	Overall FNR (%)
ACOSOG Z1071 [23]	637	Yes	92.7	12.6
SENTINA [26]	592	No	87.8	14.2
SN FNAC [27]	153	Yes	87.6	13.4

dual-tracer technique reduced the FNR to 10.8% ($p = 0.05$). Additionally, removal of three or more SLN further improved FNR to 9.1% ($p = 0.007$) [23]. Lastly, the use of immunohistochemistry (IHC) further reduced the FNR to 8.7% [24]. It is interesting to note that a follow-up study on Z1071 showed that post-NAC ultrasound (US) alone was not predictive of pathologic nodal response after NAC. When the US demonstrates normal lymph node morphology, 56.3% of these patients still had residual disease on final surgical pathology. On the other hand, 28.2% of patients with persistently suspicious nodal morphology on US demonstrated nodal pCR on final surgical pathology [25].

The SENTinel NeoAdjuvant (SENTINA) trial was a 4-arm, multicenter trial from Europe. Unlike in ACOSOG Z1071, pathologic confirmation of metastases in clinically suspicious nodes with percutaneous biopsy pre-NAC was not mandatory in this study. One of the arms looked at patients who converted from cN+ to cN− status following NAC. Overall FNR was 14.2%. Dual-tracer technique reduced the FNR to 8.6%, $p = 0.15$ and removal of three or more SLN further improved FNR to 7.3%, $p = 0.008$. The use of IHC was not discussed in this study [26].

Sentinel Node Biopsy Following Neoadjuvant Chemotherapy (SN-FNAC) trial was the last of the three prospective trials looking at SLNB for cN+ patients following NAC. This Canadian trial was closed early with the publications of the SENTINA and ACOSOG Z1071 trials. The overall FNR was 13.4%. As shown in ACOSOG Z1071, the use of IHC improved the FNR to 8.4%. This trial also demonstrated dual-tracer technique and the removal of two or more SLN were important [27]. The surgical techniques that are shown to improve FNR are organized and reviewed again later (Table 10.2).

Evaluation of Clipped Node

In the subset analysis of the ACOSOG Z1071 trial, FNR was reduced to 6.8% when the biopsy-proven metastatic lymph node was clipped and removed at the time of surgery [28]. With this finding, MDACC proposed the procedure called targeted axillary dissection (TAD), where the clipped lymph node is localized with ^{125}I radioactive seed to ensure removal at the time-planned SLNB. In this study, the FNR for

Table 10.2 Modifications on the technique to improve FNR

Studies	IHC (%)	Single tracer (%)	Dual tracer (%)	1 SLN (%)	2 SLN (%)	≥3 SLN (%)
ACOSOG Z1071 [23, 24]	8.7	20.3	10.8	Not reported	21.1	9.1
SENTINA [26]	Not reported	16	8.6	24.3	18.5	7.3
SN FNAC [27]	8.4	16	5.2	18.2	≥2 SLN removed 4.9	Not reported

SLNB alone was 10.1% and the FNR for the clipped lymph node alone was 4.2%. When TAD is utilized, the FNR was reduced to 2% [29, 30]. A similar study from the University of Pittsburgh also demonstrated that SLNB combined with directed removal of the clipped axillary lymph node with a ^{125}I radioactive seed, termed directed-SLNB, accurately reflected the axillary nodal status following NAC, as those patients who had residual nodal disease all had disease seen in the clipped node [31]. These studies demonstrated that the clipped lymph node was not an SLN in 9–27% of the cases indicating that SLNB alone may potentially miss the previously known biopsy-proven positive lymph node [28–31]. The National Comprehensive Cancer Network (NCCN) guidelines endorse the use of SLNB for patients with cN+ disease who convert to cN0 following NAC. The NCCN guidelines also state that the FNR with SLNB following NAC can be improved by marking biopsied lymph nodes to document their removal, using dual tracer, and removing >2 SLN [32].

With these trials showing feasibility and low FNR of SLNB following NAC, the trend in clinical practice is clearly changing. A recent survey of the American Society of Breast Surgeons showed that 85% of the practitioners now offer SLNB to their patients following NAC, compared to 45% before these trials. The majority of the practitioners consider the following components of the surgical technique to be important: dual-tracer technique (86%), clipping the lymph node to ensure removal (82%), and removal of >2 SLN (70%) [33]. A National Cancer Database (NCDB) review done by Dana Farber Cancer Center also shows that the recent trend reveals a significant increase in the use of SLNB for cN+ patients following NAC, increased from 31.8% in 2012 to 49% in 2015 ($p < 0.001$). In this study, factors associated with SLNB following NAC were age < 45 at diagnosis, treatment facility, clinical N1 vs. N2 status, HER2+ and TNBC subtype, and choice of breast conservation therapy versus mastectomy. In this study, ALND was omitted in 36.9% of patients with isolated tumor cells (ITCs), 23.6% with micrometastatic disease, and 13% with macrometastatic disease [34]. The GANEA 3 study is a prospective multicenter diagnostic study currently ongoing to further assess the benefit of targeting the initially involved, clipped node.

Role of Radiation Therapy

Nodal basin radiation after SLNB is an accepted, non-inferior alternative to ALND among patients with limited nodal disease burden (1 or 2 positive nodes) undergoing up-front surgery [1, 3]. However, the indications for radiation therapy following NAC is not as standardized as in up-front surgery setting. The traditional approach is that the decision for radiation therapy would be made based on the pre-NAC stage. A large NCDB review looked at the role of post-mastectomy radiation therapy (PMRT) in patients with cN+ disease with nodal pCR following NAC. There was no statistical OS with PMRT. However on the subset analyses, PMRT was associated with a significant improvement in OS for patients with clinical stage IIIB/IIIC disease, or residual invasive disease in the breast following NAC ($p < 0.05$) [35]. A multicenter study from South Korea also showed that there was no statistical difference in OS with PMRT for patients who achieved nodal pCR following NAC [36].

Future Directions

Although overall clinical practice is heading toward downstaging axillary surgery following NAC to minimize surgical morbidity, there are still no published prospective data evaluating the long-term oncologic safety of omitting ALND. There are several clinical trials ongoing to further investigate this further (Table 10.3).

Table 10.3 Ongoing clinical trials

Studies	Country	Primary outcome	Accrual period (start date – primary completion date – completion date)	Estimated enrollment	Accrual
Alliance A011202 [37]	USA (NCT01901094)	Invasive breast cancer-recurrence free interval (IBC-RFI)	2/2014–1/2024 – -not reported	1660	Recruiting
ATNEC [38]	United Kingdom (NCT04109079)	DFS Patient reported lymphedema	12/2020–2/2030–2/2030	1900	Recruiting
TAXIS [39]	Switzerland (NCT03513614)	DFS	8/2018–3/2029–12/2043	1500	Recruiting
NSABP B-51 / RTOG 1304 [40]	USA (NCT01872975)	IBC-RFI	8/2013–7/2023–8/2028	1636	Recruiting
NEONOD 2 [41]	Italy (NCT04019678)	DFS	6/2019–6/2022–6/2027	850	Recruiting

The Alliance A011202 trial (NCT01901094) is looking at cN+ patients whose sentinel nodes remain persistently positive following NAC. The participants are then randomized to ALND or no further axillary surgery. All patients receive regional nodal irradiation. The primary end point of this study is ipsilateral locoregional invasive cancer recurrence with secondary endpoints looking at OS, lymphedema rate, adequacy of radiation fields, and residual cancer burden [37]. There are two similar European trials ongoing. First is the British ATNEC trial (NCT04109079), a prospective multicenter randomized trial looking at patients with 1–2 positive nodes following NAC with randomization to ALND vs. radiation therapy [38]. Second is the Swiss TAXIS trial (NCT03513614), a prospective multicenter randomized trial looking at ALND vs. excision of clinically suspicious clipped nodes and radiation therapy to the axilla [39]. The primary endpoint is DFS at 5 years for both of these European trials.

NSABP B-51/Radiation Therapy Oncology Group (RTOG) 1304 trial (NCT01872975) is a study looking at the benefit of regional nodal irradiation in cN+ patients who achieve nodal pCR following NAC. Patients with clinical T1-T3, biopsy-proven N1 disease undergo the scheduled axillary staging, SLNB vs. SLNB with ALND vs. ALND, following NAC. Patients who achieve nodal pCR will then be randomized to no regional nodal irradiation vs. regional nodal irradiation. The only field that is affected by this trial is the regional nodal basin. For patients undergoing breast conservation, everyone will receive the planned whole breast radiation and boost. For patients undergoing mastectomy, no chest wall radiation will be administered in patients who are randomized to no regional nodal irradiation. The primary endpoint is to assess recurrence-free interval, with secondary endpoints looking at OS, cosmetic outcome, toxicity, molecular predictors of recurrence, etc. [40].

The Italian NEONOD 2 trial (NCT04019678) is a multicenter non-inferiority trial designed to assess whether or not completion ALND could be omitted safely for patients micrometastatic disease in the SLN following NAC. The primary endpoint is DFS [41].

The results of these ongoing trials will likely further develop optimal axillary management strategies following NAC, and perhaps be able to individualize each patient's axillary treatment, based on response to NAC. When making these important treatment decisions, it is important to keep the tumor biology information in mind, as there is clear data showing the failure to achieve pCR in patients with triple negative breast cancer is associated with worse prognosis, while it is not the case for hormone receptor-positive breast cancer [42].

Conclusion

Accurate axillary staging following NST is important for adjuvant treatment planning and decision making. In terms of surgical axillary management following NAC, literature has demonstrated that SLNB is able to accurately stage the axilla

following NAC for both cN0 and cN+ patients. For cN+ patients, there are modified techniques to minimize the FNR with SLNB as described before (using dual tracer, removal of >2 lymph nodes, and localizing the clipped lymph node if possible). Therefore, it is also important for the surgeons treating breast cancer to clearly understand and learn the important technical aspects of axillary staging following NAC for optimal oncologic outcome and to minimize surgical morbidity. At this time, while awaiting the results of the ongoing clinical trials, ALND remains the standard for patients with any residual axillary disease after NAC, regardless of the quantity of residual disease. In determining the optimal treatment plan for those patients who achieve nodal pCR with SLNB alone following NAC, there needs to be careful multidisciplinary evaluation of each patient's pre-NAC stage, tumor biology, response in the breast, age, and presence of other aggressive features like lymphovascular invasion, as the rate of regional recurrence in this subset of patients is unknown. The key question remains whether the pre-NAC stage vs. post-NAC stage determines the risk of LRR and the patient's overall oncologic outcome in the long run. Ongoing clinical trials as discussed before will address these difficult questions in the near future.

NET can be a safe and effective option for postmenopausal patients with strongly HR+, HER2− breast cancer. As mentioned before, NET allows for the opportunity to assess the endocrine responsiveness which may be important for overall oncologic prognosis. Given the low toxicity profile associated with NET, the use of endocrine therapy should be considered as a valuable treatment option in neoadjuvant setting for the correct patient population. It is well accepted that NET increases BCT rate with clinically significant partial response with tumor downstaging in the breast. However, the role of NET in surgical axillary management is limited as it rarely results in axillary pCR, hence not able to downstage axillary management. Further investigation is needed and dedicated randomized clinical trials are indicated to better utilize NET for axillary management in the future.

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