Published in final edited form as:

Clin Obstet Gynecol. 2016 December ; 59(4): 743–755. doi:10.1097/GRF.0000000000000232.

Current Management of the Axilla

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Abstract

Despite advances in estimating prognosis and predicting response to adjuvant systemic therapy, the status of the axillary lymph nodes remains a critical component in initial surgical planning and in determining therapeutic strategies for patients with breast cancer. Buoyed by evidence from multi-institutional randomized clinical trials, the last two decades have witnessed remarkable and practice-changing advances in our approach to the axilla. This review concentrates on the current best practice in axillary management for both node-negative and node-positive patients with particular focus on the evolving management of the axilla in the era of neoadjuvant systemic therapy.

Keywords

axilla; sentinel lymph node biopsy; neoadjuvant therapy

Introduction and Historical Perspective

In the 19th Century, Halsted described the importance of the removal of the axillary contents in reducing rates of local recurrence in women with breast cancer. This radical approach to local-regional control persisted through the first half of the 20th Century. In the 1940s one of the first challenges to this approach substituted radiotherapy for surgery for treatment of the axilla. This recognition, that it appears unnecessary to carry out an axillary lymph node dissection when the axilla is not involved with disease, is a fundamental tenet of the more recent, pivotal clinical trials that have shaped the current, tailored approach to axillary management in breast cancer patients. Firm evidence for the prognostic significance of axillary nodal metastases was provided in 1970 from the Mayo Clinic. Axillary nodal involvement was identified as the main determinant in survival, with five-year survival rates of 86% in node-negative patients compared to 50% in node-positive patients.

Since that time, the surgical management of the axilla has changed substantially. The adoption of sentinel lymph node biopsy (SLNB), first described in 1994, heralded a means of axillary staging with less morbidity. SLNB alone is now the standard staging procedure

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Disclosures: The authors have no conflicts of interest to disclose. This manuscript was funded in part by NIH/NCI Cancer Center Support Grant No. P30 CA008748

among all clinically node-negative (cN0) breast cancer patients. The last decade has increasingly seen SLNB as the sole axillary surgical procedure among select patients with low-volume axillary metastases based on the results of the visionary ACOSOG Z0011 trial (1). This article will focus primarily on the current standard of care in management of the axilla in two broad patient groups: those that are clinically node negative and those that are clinically node positive at presentation as well as a discussion of axillary management in a number of specific patient groups.

Axillary management in clinically node-negative patients with invasive breast cancer

Advances in breast cancer screening have seen a reduction in the number of patients who present with axillary nodal involvement. Contemporary statistics demonstrate that one-third of breast cancer patients have axillary lymph node metastases and less than one-third of these will have clinically palpable axillary lymph nodes. The accuracy and safety of SLNB in breast cancer patients who are clinically node negative has been validated through a wide range of studies, including eight randomized trials that have been subject to a meta-analysis (2). In clinically node-negative patients who have a negative SLNB, these trials all have demonstrated low rates (1.2%) of axillary recurrence in patients with a negative SLNB who had no further surgery.

The largest study to compare survival and regional control between SLNB alone to axillary lymph node dissection (ALND) in clinically node-negative patients was the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial (3). Patients were assigned to SLNB plus ALND or to SLNB alone with ALND only if the sentinel node(s) were positive. The 2010 report of final outcomes data, with a median follow-up of 8 years, concluded that both overall and disease-free survival did not substantially differ between the two groups. Less than 1% of both the SLNB followed by ALND group and the SLNB-only group experienced an axillary recurrence as a first disease relapse event.

Management of patients with micrometastases (N1mi) or isolated tumor cells N0 [1+]

The 7th edition of the American Joint Committee on Cancer (AJCC) Staging Manual classifies smaller nodal metastases, detected either by routine hematoxylin and eosin (H&E) or immunohistochemistry (IHC) as:

- pN0 (i+): Malignant cells in regional lymph node(s) 0.2 mm (H&E or IHC).
- pN0(mi+): Positive pCR but no regional lymph node metastases detected by histology.
- pN1mi: Micrometastases (>0.2 mm and/or more than 200 cells, but none >2.0 mm)

Initial guidelines recommended a completion ALND when these were found. However, studies have shown that with modern adjuvant therapy regimens, additional surgical treatment of the axilla confers no advantage to overall or disease-free survival for these

patients. Upon central pathology review of nodal specimens from initially SLNB negative patients in the NSABP B-32 trial, ITCs were identified in 11%, and a further 4% of specimens contained micrometastases. The absolute reduction in overall survival in patients with ITCs or micrometastases was only 1.2%. Crucially, women with these smaller volume nodal metastases who underwent an SLNB plus ALND did not have any survival advantage over patients undergoing SLNB alone. The prospective, observational ACOSOG Z0010 study identified a similar rate of occult sentinel node metastases, in 10.5% of patients (4). In both the Z0010 study and the NSABP B-32 trials, decisions regarding adjuvant systemic therapy were taken independently of results of the sentinel node IHC analysis. This supports current practice whereby decisions regarding adjuvant systemic therapy reflect consideration of biological or molecular factors associated with the primary tumor rather than solely on the basis of occult sentinel nodal metastases. Five-year overall survival in the Z0010 study exceeded 95% with no difference in overall or disease-free survival between patients with negative sentinel nodes compared to those with immunohistochemistry-positive occult metastases. The findings of these two studies were corroborated by the International Breast Cancer Study Group (IBCSG) 23-01 trial in which clinically node-negative patients with an SLNB containing micrometastases were randomized to completion ALND or no further axillary surgery (5). The majority of patients underwent breast-conserving surgery (91%), and received adjuvant systemic treatment (96%). Additional involved axillary nodes were found in 13% of patients who had a completion ALND. However, 5-year disease-free survival did not significantly differ in the SLNB-alone (87.8%) vs. the ALND (84.4%) group. In patients who did not undergo ALND, the rate of disease recurrence in the undissected axilla was less than 1%. Taken in conjunction, the findings of these trials confirm that completion ALND is not required for patients in whom occult sentinel lymph node metastases (<2.0 mm) are identified.

Management of patients with macrometastases (N1)

Lymph node macrometastases are tumor deposits of more than 2.0 mm in size. Patients with sentinel lymph node macrometastases have traditionally been treated by completion ALND or axillary radiotherapy, but the harbinger of change to this approach was the ACOSOG Z0011 trial (1) which recruited patients between 1999 and 2004. Eligibility criteria included patients with clinically T1 to T2, node-negative breast cancer who were selected to undergo breast-conserving surgery and SLNB. All patients had a positive SLNB by routine H&E staining, and were randomized to completion ALND or no ALND and no further axillary-specific radiotherapy. Any patient with 3 or more positive sentinel nodes was excluded. Accrual to the study and event rates were both lower than expected, resulting in the early closure of the trial. All patients received whole-breast irradiation and almost all received adjuvant systemic therapy (58% chemotherapy, 46% hormonal therapy). 41% of the study patients had small volume metastases (micrometastases or ITCs). In the cohort who did undergo a completion ALND, additional positive axillary nodes were found in 27% of cases. Subsequent discussion and critique of the trial has focused on the design of the radiotherapy fields. The trial authors did acknowledge that the tangential field whole-breast irradiation used in both groups resulted in a portion of the axilla receiving radiotherapy in patients on both arms of the study. To discount variation in radiation as a confounder for the final outcome results, further analysis has shown that there was no significant difference between

treatment arms in the use of protocol-prohibited nodal fields (6). At follow-up (median 6 years), there were no differences between the SLNB followed by completion ALND- and SLNB-only groups in the rates of axillary (0.5% vs. 0.9%), breast (3.6% vs. 1.9%), or overall locoregional recurrence (4.1% vs. 2.8%).

The ACOSOG Z0011 trial has had a major impact on contemporary breast surgical oncology practice. As reflected in the most recent National Comprehensive Cancer Network (NCCN) guidelines, it is accepted that in patients with tumors 5 cm or less who have no clinically suspicious axillary lymph nodes, and who are undergoing breast-conserving surgery, and subsequent whole-breast irradiation and systemic therapy, omitting completion ALND in the setting of two or fewer metastatic lymph nodes on SLNB does not increase the risk of axillary recurrence. The 10-year follow up results of the Z0011 trial were presented at the 2016 ASCO meeting and confirmed the very low rate of axillary recurrence of <2% in both groups, negating any concerns that a spate of late axillary recurrences may be seen with the SLNB-only group. In patients undergoing a mastectomy who have a positive SLNB with macrometastases, no such strategy to omit further axillary treatment exists.

Sentinel lymph node biopsy: technical considerations

The lowest false-negative and non-identification rates have been reported with the use of blue dye and a radiocolloid (technetium-99m) in combination. The use of blue dye alone obviates the need for any additional equipment or procedures, albeit there is a risk of serious allergic reactions in 1–2% of cases. Proponents of a single modality approach have reported high success rates with each technique in isolation. A subareolar injection of either tracer has become the favored technique. Superficial (subareolar, periareolar, deep dermal, and intradermal) and deep (peri- or intra-tumoral) injections of radiocolloid and blue dye are both effective for identification of axillary sentinel nodes. Based on data from a recent meta-analysis, the use of a deep injection technique is associated with a higher rate of identification of extra-axillary sentinel nodes (7).

Axillary Radiotherapy

Radiotherapy has been validated as an effective primary therapeutic modality for treating the axilla in clinically node-negative patients. AMAROS was a non-inferiority trial designed to determine if axillary radiotherapy resulted in comparable survival outcomes to ALND in patients with a positive SLNB (8). Eligibility criteria included clinically node-negative patients with a unifocal primary tumor up to 3 cm, increased to 5 cm in the final two years of enrollment. Patients were randomized prior to SLNB to either ALND (a standard level I and II clearance) or axillary radiotherapy consisting of 50Gy to axillary levels I to III and medial supraclavicular fossa if the SLNB was positive. The majority (82%) of the 1425 patients with a positive SLNB underwent breast-conserving surgery. In both arms, 60% of the sentinel node metastases were macrometastases. As in the Z0011 trial, the number of axillary recurrence events was lower than anticipated. Post-treatment lymphedema rates were lower in the axillary radiotherapy group, although no clinically relevant difference was noted in patient-reported arm symptoms between the two groups. Five-year axillary recurrence rates (0.4% ALND vs. 1.2% axillary radiotherapy), disease-free survival (87% ALND vs. 83% axillary radiotherapy), and overall survival (93% ALND vs. 93% axillary

radiotherapy) were comparable between the two groups. In light of the findings from the ACOSOG Z011 trial, it must be acknowledged that 77% of patients in the AMAROS trial had only one positive SLN and only 5% had 3 or more positive nodes. These patients with low-volume disease many may not have required additional axillary specific treatment. Therefore, caution must be taken in extrapolating the findings to patients at higher risk of locoregional failure when considering axillary radiotherapy as an alternative to ALND in SLNB positive patients.

The efficacy of nodal irradiation acted as the premise for the recently reported NCIC Clinical Trials Group MA.20 trial (9). In women with early-stage breast cancer treated with breast-conserving surgery, investigators compared whole-breast irradiation plus regional nodal irradiation with whole-breast irradiation alone. The cohort were deemed higher risk of local-regional recurrence on the basis of positive axillary lymph nodes (majority with 1–3 nodes involved) or negative axillary nodes (10%), but with high-risk features, such as large tumor size or lymphovascular invasion (LVI). This trial was not studying nodal irradiation as a substitute for ALND, as patients with a positive SLNB did undergo ALND. The additional regional nodal irradiation targeted the ipsilateral internal mammary lymph nodes, and the supraclavicular and axillary lymph nodes. Most patients received adjuvant chemotherapy (91%) and/or endocrine therapy (76%). Ten-year overall and breast-cancer–specific survival rates were equivocal. The nodal irradiation group had a marginally lower rate of isolated locoregional recurrence (4.8% vs. 7.8%). The absolute regional recurrence rate at 10 years was 2.5% in the group that did not undergo nodal irradiation. Regional nodal irradiation was generally well tolerated but did confer greater risks of lymphedema.

The challenge remains to accurately identify which patients will benefit from comprehensive nodal irradiation after ALND. Traditional clinic-pathological factors such as 4 positive nodes, extracapsular nodal extension, or substantial LVI may influence these decisions, but genomic profiling will likely serve as a more robust predictor of locoregional failure. Support for this hypothesis comes from analysis of loco regional recurrence in node negative, estrogen receptor positive patients recruited to the NSABP B-14 and NSABP B-20 trials whose tumors were characterized by the 21-Gene Recurrence Score Assay. The findings suggested that the efficacy of radiation therapy may not be uniform across the 3 recurrence score categories but that radiation may indeed be more effective with a higher recurrence score (10).

Invasive Breast Cancer, Clinically Node Positive

In identification of patients who are clinically node positive, the AJCC definition of clinically detected is “detected by imaging studies or by clinical examination.” Increasingly, axillary ultrasound (US) combined with US-guided lymph node biopsy (core biopsy or FNA) is used as to assess axillary lymph nodes at time of presentation. Establishing axillary nodal positivity preoperatively will select patients with axillary metastases who can proceed to ALND immediately without SLNB or, increasingly, commence neoadjuvant systemic treatment with a view to axillary downstaging. The sensitivity of axillary US for identifying involved axillary nodes is 50%, with a false-negative rate of 25% (11). Nonetheless, a judicious use of, as well as interpretation of, US-guided axillary staging is required when

deciding on the surgical management of the axilla. As established by the ACOSOG Z0011 trial, further treatment is not required in certain patients with one or two positive axillary nodes, and the mere presence of abnormal nodes on imaging in clinically node-negative patients is not a reliable indicator of the need for ALND (12).

Neoadjuvant Chemotherapy

Initially introduced for locally advanced breast cancer, the indications for neoadjuvant chemotherapy have expanded, motivated by a steady rise in pathological complete response (pCR) rates. In essence, neoadjuvant chemotherapy should be considered in any patient for whom adjuvant chemotherapy is indicated. The NCCN advocates axillary US in patients selected for neoadjuvant chemotherapy both for clinically node-positive patients to allow confirmatory biopsy as well as for clinically node-negative patients whereby any suspicious nodes should be sampled by FNA or core biopsy.

The NSABP B-18 trial was one of the first randomized trials to compare preoperative and postoperative chemotherapy and closed to accrual in 1993. The rate of finding positive axillary nodes at time of surgery was 57% in the group who received adjuvant systemic therapy compared to 41% in the neoadjuvant cohort, providing evidence that neoadjuvant chemotherapy downstages involved axillary lymph nodes in a considerable proportion of patients. Present-day neoadjuvant regimens can expect almost half of patients to convert from biopsy-confirmed node positive to pathological node negative (ypN0) (Table 1). In those studies that have provided details of axillary response in terms of molecular subtypes, a clear differential in response rates is evident, with the highest pCR rates in patients with HER2 amplified primary tumors treated with neoadjuvant chemotherapy and anti-HER2 therapy.

The NSABP B-27 trial provided early data examining the practicality of performing SLNB following neoadjuvant chemotherapy. An attempt was made at SLNB in 18% of patients and was successful in 85% of these, with a false-negative rate of 11%. This trial accrued between 1995 and 2000, relatively early in the SLNB era, and while most patients were clinically node negative, the findings have been replicated in contemporary studies where the focus has been to examine the feasibility and accuracy of SLNB post neoadjuvant therapy in patients who were node positive at presentation,

To date, three major trials have assessed the applicability of SLNB in patients who are node positive at presentation and revert to clinically node negative following neoadjuvant therapy. The eligibility criteria and findings of these trials are summarized in Table 2.

The ACOSOG Z1071 trial enrolled women with biopsy-proven clinical stage T0–T4, N1 or N2 breast cancer (13). The primary focus was to determine the false-negative rate of SLNB in originally node-positive patients following neoadjuvant chemotherapy. The majority of patients had mobile lymphadenopathy at presentation, i.e., clinical stage N1, and, following neoadjuvant treatment, over 80% of these had no residual palpable axillary nodes. The study protocol stipulated that at least two sentinel nodes be removed, after which a completion ALND was performed. While 93% of patients had at least one sentinel node identified, only

79% met the criteria for removal of two sentinel nodes followed by a completion ALND. The false-negative rate in cN1 patients who had at least two sentinel nodes removed was 12.6%. A reduction in the false-negative rate was evident as the number of sentinel nodes removed increased: 31%, one node; 21%, two nodes; dropping to a clinically acceptable 9% only when three or more nodes were removed. The false-negative rate was also lower (11%) when both blue dye and radiocolloid were used for mapping.

The SENTINA (Sentinel Neoadjuvant) trial enrolled both clinically node-negative and node-positive patients prior to neoadjuvant chemotherapy (14). The study encompassed four arms, one of which examined initially clinically node-positive patients who reverted to clinically node negative after neoadjuvant treatment, and is therefore comparable to the Z1071 trial. These patients received a post neoadjuvant SLNB followed by completion ALND. Unlike the Z1071 trial, biopsy of clinically or radiologically suspicious axillary nodes was recommended but not mandatory. The most common modality for lymph node mapping was the use of radiocolloid alone. The overall sentinel node detection rate was 80%, with a false-negative rate of 14%. Just like in ACOSOG Z1071, the false-negative rate varied according to the number of sentinel nodes removed: 24%, one node; 18%, two nodes; and less than 8% when three or more nodes were removed.

The SN-FNAC trial recruited patients from ten academic centers in the U.S. and Canada, required biopsy-proven axillary nodal disease for inclusion, and closed to accrual in 2012 upon publication of the Z1071 trial with a total of 145 eligible patients (15). The findings replicated those of the Z1071 trial, with lowest false-negative rates obtained when dual tracer mapping with both blue dye and radiocolloid was used and when 3 or more sentinel lymph nodes were removed.

For SLNB after neoadjuvant chemotherapy to be considered a safe and viable strategy in the treatment of clinically node-positive patients who revert to clinically node negative with neoadjuvant chemotherapy, based on these trials, the current best advice is to employ dual modality mapping with both blue dye and radiocolloid and to attempt to identify three sentinel nodes. This may seem challenging given that in the NSABP B-32 and other large prospective trials of SLNB, the median number of identified sentinel nodes was two, but with the use of dual mapping, identification of 3 or more sentinel lymph nodes is possible in at least 86% of patients (16).

Recent attention has focused on the feasibility of US-guided placement of a clip to mark biopsy-confirmed metastatic axillary node(s) prior to the commencement of neoadjuvant therapy. A variety of localization techniques have been utilized to guide the surgeon in selectively removing these clip-containing lymph nodes at the time of axillary surgery. Retrieval of this marked node at the time of surgery after neoadjuvant therapy ensures removal of the biopsy-positive node at the time of surgery and therefore is best placed to confirm the presence or absence of a treatment response. In the largest reported series to date, the false-negative rate was reduced to 4% with retrieval of the clipped node, and overall, in the cohort, the clipped node was not the sentinel node in 23% of cases (17). In the patients in the Z1071 trial in whom the biopsied node was clipped prior to treatment, a similarly low false-negative rate of 7% was identified. Further study is required to assess the

utility of this strategy as a means of reducing the false-negative rate of axillary assessment after neoadjuvant chemotherapy.

Persistent clinically positive axilla

Even with improvements in pCR rates, many patients with positive axillary adenopathy at presentation will have residual axillary disease following neoadjuvant chemotherapy. Residual nodal disease outside of the sentinel node(s) was found in 39% of patients in the Z1071 trial and in 42% of pre-treatment clinically node-positive patients who reverted to clinically node negative following chemotherapy in the SENTINA trial. At present, outside the remit of a clinical trial, the standard surgical approach to patients with residual axillary disease is completion ALND.

The prognostic implications of clinically node-positive patients who received neoadjuvant chemotherapy and who remain pathologically node positive have been demonstrated in an updated analysis of NSABP B-18 and B-27 neoadjuvant trials. High rates of locoregional recurrence were observed following ALND: 15–22% after breast-conservation, and 17–22% after mastectomy. This high locoregional failure rate suggests that these patients may benefit from adjuvant regional nodal radiotherapy in addition to any planned whole-breast or post mastectomy chest-wall radiotherapy. The targeted nodal areas are those of the non-dissected axilla and supraclavicular nodes. While reductions in rates of locoregional recurrence have been validated in a number of clinical trials, the results also reveal that the addition of regional nodal radiotherapy to planned whole-breast or chest-wall radiotherapy increases the morbidity associated with ALND with rates of lymphedema of up to 28%.

Whether axillary radiotherapy will provide comparable regional control to ALND in patients who remain node positive after neoadjuvant chemotherapy is currently the focus for the Alliance for Clinical Trials in Oncology A11202 study. This randomized trial is evaluating the role of completion ALND in patients with clinical T1–T3 N1 M0 breast cancer who have a positive SLNB following neoadjuvant therapy. SLNB positive patients are randomized to either completion ALND followed by nodal irradiation (un-dissected axilla, supraclavicular nodes, and internal mammary nodes) or to no further axillary surgery followed by radiotherapy to the full axilla, supraclavicular nodes, and internal mammary nodes. The primary outcome is breast cancer recurrence-free survival.

Surgical Approach for Axillary Lymph Node Dissection

For classification of lymph node stations within the axilla, the description of three axillary levels defined by the pectoralis minor muscle prevails. Level I nodes are lateral to the lateral border of pectoralis minor, level II nodes lie behind the muscle, and level III nodes are medial to the medial border of pectoralis minor extending to Halstead's ligament. A standard ALND involves removal of the axillary nodes from level I and II. A level III lymphadenectomy should be performed if gross disease is encountered at level II. In patients undergoing mastectomy, the axillary dissection can proceed through the mastectomy incision. Increasing rates of both skin-sparing and nipple-sparing mastectomy may necessitate a separate axillary incision to facilitate adequate axillary access.

Adverse Outcomes Following Surgery

It is well recognized that axillary surgery can result in considerable shoulder and arm morbidity. Participants in the ALMANAC trial, a randomized trial of SLNB versus standard axillary treatment, reported high rates of reduced shoulder flexion and abduction at one month postoperatively, but the majority had returned to near baseline at one year (18). Symptoms of arm pain and numbness are more persistent, with almost one-third of patients reporting some degree at one year. These symptoms are severe in only a minority of cases. Lymphedema following ALND remains one of the most feared complications. Reported rates vary between 11% and 20% based on recent trial data from studies such as Z0011, NSABP B32, and ALMANAC. Injury to the long thoracic nerve injury presents with severe burning or stabbing shoulder pain that usually subsides, to be followed by evidence of weakness resulting in the classical angel wing deformity.

Management of the Axilla in Special Circumstances

Occult breast cancer presenting with axillary metastases

Occult primary breast cancer, where patients present with adenocarcinoma in axillary lymph nodes and have no evident primary breast lesion, accounts for up to 0.8% of all newly diagnosed breast cancers. Evaluation of a patient who presents with palpable axillary adenopathy involves clinical breast examination, mammography and ultrasound, and breast MRI. The involved node must be biopsied, ideally with a core biopsy that will facilitate a thorough pathological assessment with a range of immunohistochemistry stains to confirm that the tumor is of breast origin (including but not limited to estrogen receptor, progesterone receptor, HER2, cytokeratins 7 and 20, mammaglobin, and S100). Other malignancies such as lymphoma, lung cancer and melanoma can present with axillary adenopathy as well as a range of benign conditions. A complete staging work-up includes a diagnostic chest, abdominal, and pelvic CT, and bone scan or FDG PET/CT to rule out distant metastases. Bilateral breast MRI is now the standard approach to breast evaluation in this cohort and detects a primary breast cancer in approximately 75% of women with a normal breast clinical examination, mammogram, and ultrasound. Because of the low specificity of lesions detected by breast MRI, these lesions should be subject to MRI or US guided biopsy if a correlate is identifiable on a second look US. Accurate localization of the primary breast lesion may facilitate breast-conserving surgery in some of these patients. The surgical management of the axilla in this setting remains a complete ALND. Increasingly, neoadjuvant chemotherapy should be considered, particularly taking into consideration the receptor profile. Optimal management of the ipsilateral breast in patients for whom, even after MRI, no primary breast lesion has been identified, is controversial. Observed rates of locoregional failure in patients who receive ALND only without treatment to the ipsilateral breast are high implying the need for treatment of the ipsilateral breast. A small number of comparative, non-randomized trials, recently collated as a meta-analysis, have demonstrated similar rates of both locoregional recurrence and overall survival in patients treated with ALND and mastectomy to those treated with ALND and whole-breast radiotherapy (19). Therefore, whole-breast radiotherapy is a breast-conserving alternative to mastectomy in these patients.

Locally recurrent disease to axilla

Long-term follow-up of both node-negative and node-positive patients has shown that the rate for developing an isolated axillary recurrence rates is low. However, if it does occur, axillary recurrence can severely negatively affect a patient's quality of life. Overall survival rates from time of axillary recurrence of 60% at 5 years have been reported. Any patient who presents with recurrent axillary disease should undergo a full systemic staging work up with CT and bone scan or FDG PET/CT due to the risk of synchronous, clinically occult distant metastases.

Core biopsy of the axillary recurrence, to facilitate receptor status assessment, is required to examine for evidence of discordance when compared to the primary tumor, as this will inform decisions regarding additional systemic therapy. If deemed amenable to surgical resection, isolated mobile axillary recurrences should be excised and combined with a level III axillary dissection. Patients with inoperable axillary recurrence such as supraclavicular nodes may be considered for radiotherapy if not already administered as part of the primary treatment or systemic chemotherapy, or a combination of both. These non-operative approaches rarely produce long-lasting control of disease, but may help with palliation.

Ductal carcinoma in-situ (DCIS)

In patients with pure DCIS, there should theoretically be no risk of lymph node metastases and hence no need for axillary staging. In patients who proceed to surgery with a breast core-needle biopsy diagnosis of DCIS, there is a risk of upstaging to invasive cancer upon pathological assessment of the resected specimen. The current best estimates of upstaging to either micro-invasion or invasive cancer is approximately 15%. For patients undergoing a mastectomy for the surgical treatment of DCIS due to either disease extent or patient preference, an SLNB should be performed at the time of surgery in the event that final histology reveals invasive disease, at which point an SLNB would not be feasible. Even in patients upstaged to microinvasion, the risk of sentinel node metastases is only 1%.

There is less agreement in selecting patients with DCIS who are undergoing breast-conserving surgery who may require an SLNB. One factor accepted as an indication for an SLNB is the presence of a palpable mass with a diagnosis of DCIS due to a high rate of upstaging, and other cases should be managed on an individual basis remembering that while associated with lower rates of morbidity than ALND, the morbidity from SLNB is not zero.

Elderly patients with breast cancer

In medically fit older women, standard breast cancer surgery options should be offered. For older women with clinically positive axillary adenopathy who are deemed surgical candidates, ALND is appropriate, whereas axillary radiation can be considered for those felt not to be surgical candidates. In certain clinically node-negative patients, an SLNB can be omitted if the nodal information will not affect adjuvant treatment decisions. As proof of this concept, 10-year follow-up of women over 70 years of age with a stage T1, estrogen receptor positive breast cancer and clinically negative axilla who underwent lumpectomy and received adjuvant tamoxifen showed low rates of locoregional recurrence in both the

groups that did receive radiotherapy (98%) and those that did not (90%)(20). These cases should be managed on an individual basis as opposed to purely on age terms and should merit a discussion with a medical oncologist as to whether information gleaned from a SLNB will impact adjuvant treatment decisions.

Re-operative SLNB

In patients who develop an in-breast tumor recurrence after lumpectomy and SLNB, ALND is still commonly used as the standard axillary staging procedure in the belief that the initial surgery will alter the pattern of lymphatic drainage. In theory, this would render a repeat SLNB neither feasible nor accurate. Despite this, multiple case reports and small retrospective case series have demonstrated a variable rate of success for re-operative SLNB ranging from 72–93%, suggesting the strategy is both possible and feasible. Sentinel nodes outside of the ipsilateral axilla are identified in 8% of patients; therefore, routine preoperative lymphoscintigraphy is advised. Much lower success rates for re-operative SLNB are seen in patients who have had a previous ALND.

Pregnancy-associated breast cancer

Some guidelines still suggest that SLNB should not be performed during pregnancy, but mounting clinical and pre-clinical data suggest that the procedure can be performed safely. Blue dye as a mapping agent in pregnant patients is not an option because of the low (1%) but potentially very harmful underlying risk of a maternal anaphylactic reaction as well as very limited data on potential teratogenic effects of the agents used.

While the radiocolloids used for sentinel node mapping do emit a radiation dose, the agent is administered locoregionally as opposed to systemically. Studies have demonstrated that the doses absorbed by the fetus are substantially less than the recommended fetal radiation doses. To minimize radiation exposure, it is advisable to inject the technetium radiocolloid on the morning of surgery as opposed to the preceding day.

Future Directions

The introduction of national breast cancer screening programs, in various guises, has resulted in more cases being diagnosed at an earlier stage. In patients with early breast cancer and a low probability of axillary nodal metastases coupled with excellent long-term survival outcomes based on current adjuvant therapy regimens, the need for SLNB to stage the axilla has been called into question. Surgery for the axilla for staging purposes is susceptible to improvements in preoperative imaging and more accurate predictive gene expression signatures. The SOUND trial that commenced in 2012 (sentinel node vs. observation after axillary US) hypothesizes that in patients with a low burden of axillary disease, the results of SLNB are unlikely to alter adjuvant treatment decisions. Recruited patients with clinical T1 breast cancer and a negative axillary US will be randomized to either SLNB ± axillary dissection or no axillary surgical staging with a primary endpoint of distant disease-free survival.

The advent of validated gene expression profiles promises more accurate prognostication and better predictions of response to adjuvant therapy than conventional clinic-pathological

factors. The SWOG RxPONDER Trial is assessing the ability of gene expression profiling to accurately identify patients with favorable tumor characteristics with excellent predicted long-term survival with adjuvant hormonal treatment in whom chemotherapy will not confer any additional benefit, even in the setting of lymph node positivity.

However, axillary surgery is far from obsolete. Surgical treatment for confirmed nodal metastases may be assailable by advances in radiotherapy; it is as yet unknown whether comparable rates of locoregional control can be attained through treatment with axillary radiotherapy alone in patients with a higher burden of axillary disease than those recruited to the AMAROS trial. As the indications for neoadjuvant chemotherapy expand, SLNB remains the standard for axillary staging post-treatment in the majority of patients, and ongoing study is required to validate the most accurate means of axillary assessment in node-positive patients who revert to a node-negative status with the use of neoadjuvant systemic therapy. Innovative trials such as the Alliance A11202 study may add further options to the algorithms for axillary management, and the next generation of individualized treatment programs will reflect molecular characterization of tumor biology.

Buoyed by evidence from multi-institutional randomized clinical trials, the last two decades have witnessed remarkable and practice-changing advances in our approach to the axilla. And while the landscape continues to evolve, treatment selection for the individual patient remains the focus and axillary surgery will continue to play an important role in both staging and in achieving locoregional control in selected breast cancer patients.

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Axillary pathological complete response rates in patients with biopsy proven axillary lymph node metastases after neoadjuvant systemic therapy.

Table 1

Study and Year	No of Patients	SLNB Success Rate	Axillary pCR	Molecular Subtype			
				ER+HER2-	ER+HER2+	ER-HER2+	ER-HER2-
Mantami 2016	195	98%	49%	21%	70%	97%	47%
Park 2013	178	95%	41%	24%	52%	52%	59%
Dominici 2010	109	-	-	-	67%	79%	-
Boughey 2013	689	93%	40%	-	-	-	-
Yagata 2013	95	85%	33%	-	-	-	-
Newman 2007	54	98%	32%	-	-	-	-
McVeigh 2014	78	-	37%	-	-	-	-
Total	-	93% (1067/1144)	40% (497/1236)	22% (33/148)	64% (71/111)	77% (96/125)	52% (46/89)

Randomized trials of sentinel lymph node biopsy after neoadjuvant systemic therapy in patients with biopsy proven axillary lymph node metastases at presentation.

Table 2

Study and Year	No. of patients	SLNB Identified	Average SLN removed	Patients with 3 SLN removed	False Negative Rate			
					Overall	1 SLN	2 SLN	3 SLN
Z1071 2013	689	93%	3.1	56%	13%	-	21%	9%
SENTINA Arm C 2013	592	80%	2.5	34%	15%	24%	19%	5%
SN-FNAC 2014	145	88%	2.7	-	8%	18%	5%*	-
Total	1426	87% (1240/1426)	2.8	46% (589/1281)	13% (78/619)	23% (21/92)	17% (46/270)	8% (40/490)
								10% (65/645)

* SN-FNAC study reported false negative rate only for 1 vs 2 or more SLN removed