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The Landmark Series: Axillary Management in Breast Cancer

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ABSTRACT The evolution in axillary management for patients with breast cancer has resulted in multiple dramatic changes over the past several decades. The end result has been an overall deescalation of surgery in the axilla. Landmark trials that have formed the basis for the current treatment guidelines are reviewed herein.

Axillary management for patients with newly diagnosed breast cancer has undergone several practice-changing paradigm shifts over the last few decades with the ultimate goal of reducing morbidity without compromising oncologic outcomes or staging. Historically, surgical management of the axilla was viewed as a prognostic indicator of disease, and long-term survival and the axillary nodal status significantly impacted adjuvant therapy recommendations. The impact on local–regional control of surgically resecting any axillary nodal metastasis was also of importance in the era prior to screening mammography and a trend towards early-stage breast cancer diagnosis. More recently, there has been a shift towards less extensive axillary surgery in both the clinically node-negative and clinically node-positive patient populations. The increasing use of neoadjuvant therapy in early-stage breast cancer patients has presented a challenge in determining the extent of axillary surgery necessary for axillary staging and local–regional control in both clinically node-negative patients and node-positive patients. The landmark trials that have impacted the evolution of axillary management for breast cancer patients are reviewed herein.

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AXILLARY MANAGEMENT IN PATIENTS UNDERGOING PRIMARY SURGICAL THERAPY

For many patients with breast cancer, surgery is the first line of therapy for treatment and staging. When the Halsted radical mastectomy was introduced, the axilla was seen as a transit point between the breast and distant metastatic disease, and it was believed that removal of axillary nodes was necessary to prevent distant metastatic spread. As understanding of breast cancer evolved, removal of these lymph nodes was not viewed as a necessary procedure to prevent spread but rather an important component of breast cancer staging and prognosis. Identification of lymph node metastases directed clinicians to offer systemic therapy and to consider radiation therapy to the chest wall and/or the regional lymph node basins. Approximately 20 years ago, breast cancer subtypes emerged as important determinants in breast cancer prognosis. While the initial studies were performed with gene expression profiling, receptor testing (estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2) to determine approximated breast cancer subtypes emerged as critical in directing therapy and determining prognosis. It is now routine to consider approximated subtypes to inform systemic therapy recommendations, and therefore, the role of axillary staging has become less important. In this review, published studies that address the deescalation of surgical therapy of the axilla in patients undergoing upfront surgery are discussed.

NSABP B-04

Initiated in 1971, the goal of the B-04 trial was to determine whether less extensive surgery with or without radiation therapy was as effective as the Halsted radical mastectomy.[1] A total of 1079 patients with clinically negative axillary nodes were randomized to radical

mastectomy, total mastectomy without axillary dissection but with postoperative radiation, and total mastectomy alone. In terms of axillary management, these patients were essentially randomized to complete axillary lymph node dissection (ALND), axillary radiation, or no axillary treatment upfront. The trial showed no difference in overall survival, distant-disease-free survival, relapse-free survival, or disease-free survival in this group of patients. The last follow-up that was published showed these results consistent at 25-year follow-up.[2] Of note, the trial had a separate arm that included patients with clinically positive nodes who were randomized to radical mastectomy or total mastectomy with axillary radiation only. Patients with clinically positive nodes did not present any differences in survival whether the axilla was treated with surgery or radiation therapy.

In women with negative nodes, there was a difference in cumulative incidence of local or regional recurrence, and it was lowest in the patients treated with total mastectomy and radiation therapy. There was no difference in these groups related to cumulative incidence of distance recurrence as a first event. A total of 68 of the 365 women who underwent total mastectomy alone (18.6%) subsequently had axillary recurrences. Median time to axillary recurrence was 14.8 months (2–134.5 months). The investigators estimated (based on those randomized to axillary dissection at initial surgery) that approximately 40% of patients who had mastectomy alone had positive nodes that were not removed at the time of initial surgery. These data are important because they indicated that leaving positive nodes, without surgery or radiation therapy, did not significantly increase the rate of distant recurrence or breast-cancer-related mortality. These data were important in the development of American College of Surgeons Oncology Group (ACOSOG) Z0011 trial (discussed below).[3]

NSABP B-32

NSABP B-32 confirmed that overall survival, disease-free survival, and regional control were statistically equivalent between patients with negative sentinel nodes who underwent either sentinel lymph node biopsy (SLNB) alone or ALND.[4] B-32 was a randomized controlled phase 3 trial which was performed at 80 centers in Canada and the USA between 1999 and 2005. It was the largest randomized surgical trial performed in breast cancer patients. The trial enrolled 5611 women with invasive breast cancer and clinically negative nodes. Investigators reported on outcome data for the 3989 patients with pathologically negative nodes. Surgeons were proctored in SLNB, and pathologists were required to follow specific protocols. Both ^{99m}technetium sulfur colloid and isosulfan blue were used to perform the SLNB. In the assessment of sentinel nodes, pathologists were instructed to use 2-mm sectioning of the nodes with routine hematoxylin and eosin (H&E) stains of each section. Immunohistochemistry was not permitted for routine patient care, except to confirm suspicious findings seen on routine H&E stains.

The trial was designed to detect a 2% difference in survival between the treatment arms. Regional recurrence rates were less than 1% for both groups, and the trial confirmed a low rate of regional node recurrences after SLNB surgery.

NSABP B-32 investigators also reported that patient-reported outcomes and morbidity related to range of motion, edema, pain, and sensory deficits were lower in the SLNB arm compared with ALND. A similar study, the ALMANAC trial, was published in 2006 and also noted the lower morbidity of SLNB.[5] They did not specifically address survival but did conclude that SLNB should be the treatment of choice for patients with early-stage breast cancer and clinically negative nodes.

ACOSOG Z0011

The ACOSOG Z0011 trial was designed to assess the role of completion ALND in patients found to have one or two positive sentinel nodes. Z0011 was a phase 3 noninferiority trial conducted at 115 sites and enrolled patients from 1999 to 2004. The trial enrolled women with clinical T1 or T2 invasive breast cancer with clinically negative nodes who were planned for breast conservation therapy with whole breast irradiation. Patients with one or two positive sentinel lymph nodes were randomized intraoperatively or postoperatively to undergo ALND or not. Patients with metastases identified initially or solely with immunohistochemical staining, three or more positive SLNs, matted nodes, gross extranodal disease, and patients who underwent neoadjuvant chemotherapy or endocrine therapy were not eligible. The trial sought to determine whether there was a difference in overall survival between the two groups.

Targeted enrollment was 1900 women with final analysis after 500 deaths, but the trial closed early because the mortality rate was much lower than expected. The investigators ultimately enrolled and randomized 989 patients. In addition to showing no difference in survival between the two groups, they showed very low rates of local–regional recurrence. This trial was a game changer for management of node-positive patients undergoing breast conservation. The trial was criticized for several reasons,

including not meeting the target enrollment. The ten-year follow-up data continued to show no difference in overall survival.[6]

The trial also reported on morbidity and local–regional recurrences.[7–9] Patients in the ALND group had more wound infections, seromas, and paresthesias than those in the SLNB group. At 1 year, subjective rates of lymphedema were higher in the ALND group.[9] The cumulative incidence of nodal recurrences at 10 years was 0.5% in the ALND arm and 1.5% in the SLNB alone arm ($P = 0.28$).[8]

ACOSOG Z0010

Concurrent with the Z0011 trial, ACOSOG initiated the Z0010 trial to determine the prevalence and significance of occult metastases in the SLNs and bone marrow of patients who underwent breast-conserving surgery, SLNB, and whole-breast irradiation for clinical T1 or T2 node-negative breast cancer.[10] As SLNB was still in relative infancy as a procedure, physicians were noting an increase in detection of micrometastases and isolated tumor cells with the more thorough processing of lymph nodes. Z0010 was a prospective observational study. This study enrolled 5210 eligible patients at 126 sites from 1999 to 2003. Immunohistochemistry (IHC) was performed at a central laboratory on hematoxylin–eosin-negative SLNs and bone marrow aspirates.

Of the 3325 SLN specimens that were examined by IHC, 10.5% were positive for tumor. Bone marrow metastases were rarer, with only 3.0% of the 3413 bone marrow specimens being positive. At median follow-up of 6.3 years, IHC evidence of SLN metastases was not significantly associated with a difference in overall survival. Bone marrow metastases were associated with decreased overall survival.

Not surprisingly, the trial provided significant weight to the data, emphasizing that SLN micrometastases were likely not clinically significant for early-stage breast cancer patients. This would further be confirmed with two large and important clinical trials reviewing the role of ALND in patients with micrometastases.[11,12]

AMAROS

The goal of the AMAROS trial was to assess whether axillary radiotherapy provides comparable regional control with fewer side effects compared with ALND.[13] It was a randomized, multicenter, open-label, phase 3 non-inferiority trial which enrolled patients with T1 or T2 invasive breast cancer and no palpable lymphadenopathy. Patients undergoing neoadjuvant chemotherapy or endocrine therapy were ineligible. Patients with a positive sentinel node were randomized to receive either ALND or axillary radiotherapy. Between 2001 and 2010, 4806 patients were enrolled and randomized at 34 centers across Europe. In the ALND group, 33% of the patients had additional positive nodes. At 5 years, axillary recurrence was 0.43% after ALND and 1.19% after axillary radiotherapy. Lymphedema was noted to occur significantly more often with ALND compared with radiation at 1-, 3-, and 5-year follow-up. Based on these data, patients with clinically negative nodes but positive sentinel lymph nodes could forgo ALND and receive axillary radiation with less morbidity. There are limited data regarding the management of patients who undergo mastectomy and are found to have positive SLN(s). In the AMAROS trial, 248 patients underwent mastectomy as their primary breast surgical procedure. Although the numbers were small, axillary recurrence rates were similar in patients undergoing mastectomy with three or fewer SLN(s), regardless of whether patients underwent completion ALND or simply had adjuvant chest wall irradiation.[13]

AXILLARY MANAGEMENT AFTER NEOADJUVANT CHEMOTHERAPY

While the initial use of neoadjuvant chemotherapy (NAC) was largely in patients with inoperable breast cancers, its indications subsequently broadened to facilitate breast conserving surgery in women with large tumors. All clinical trials on axillary management have been performed on patients undergoing upfront surgical management, and their applicability to those receiving NAC is not well defined. The most accurate way to assess the status of the axilla after NAC is also uncertain. Axillary evaluation should be performed at the time of diagnosis with a clinical exam. As the accuracy of clinical axillary exam is remarkably low—negative predictive value (NPV) 60–70%, positive predictive value (PPV) $\sim$ 80%[14–16]—ultrasound of the axilla is also regularly implemented as part of the preoperative diagnostic imaging workup.

CLINICALLY NODE-NEGATIVE PRIOR TO NEOADJUVANT CHEMOTHERAPY

A clinically node-negative patient is defined as one who has no abnormal axillary lymph nodes on examination or has undergone a needle biopsy of a lymph node that showed no evidence of metastatic disease. Although there was initially concern regarding the reliability of SLNB after NAC, its feasibility and accuracy has been demonstrated in multiple studies, including NSABP B-27.[17] The FNR and SLN identification rate were optimized following NAC with the use of dual tracers and removal of at least

three SLNs, which would include all blue nodes and all radioactive nodes > 10% of the count of the hottest node. Current recommendations for the patient who is clinically node negative prior to and following NAC, axillary staging with a SLNB, using dual tracers, is done at the time of the definitive breast operation. If the SLN(s) is negative, no further axillary surgery is needed. If the SLN(s) is positive, an ALND should be performed. If a SLN could not be identified, an ALND should be performed.

CLINICALLY NODE-POSITIVE PRIOR TO NEOADJUVANT CHEMOTHERAPY

A clinically node-positive patient is defined as one who has abnormal axillary lymph nodes identified via clinical exam and/or sonographic evaluation with a needle biopsy confirming metastatic disease. Historically, all clinically node-positive patients underwent an ALND following NAC, regardless of the observed response to treatment. Current data suggest that a pathologic complete response can be seen in the axilla in 12–65% of patients, depending on tumor subtype, with nearly 50% of triple negative cancers and 65% of Her2 positive cancers showing no residual disease on ALND following NAC.[18,19]

The morbidity of an ALND has been well described. Since the response rates to NAC are quite good, the need to immediately proceed to an ALND has been called into question.

ACOSOG Z1071

The ACOSOG Z1071 investigators sought to determine the utility of SLNB in patients who were initially clinically node positive prior to NAC. This phase 2 clinical trial enrolled 756 women over the age of 18 with cT0–4, N1–2, M0 primary breast cancer with nodal metastases confirmed by needle biopsy who were undergoing NAC. All patients underwent an axillary exam as well as an axillary ultrasound at the completion of NAC. Clip placement into the biopsy-proven positive node was optional. Dual tracer use, with both blue dye and radioactive colloid mapping agents, was recommended. The protocol required resection of at least two SLNs. All patients underwent a SLNB followed by an ALND.

The primary endpoint of Z1071[20] was to determine the false-negative rate (FNR) of SLNB after neoadjuvant chemotherapy in women who were initially node positive. They set a prespecified FNR threshold of 10%. Of the 756 study patients, 525 had cN1 disease with at least two SLNs removed. Following chemotherapy, 215 (41%) had a nodal pathologic complete response. Of the 310 patients with residual nodal disease, it was confined to the SLNs in 108 patients (20.6%). In these 310 patients, 39 had a false-negative SLNB, resulting in an FNR of 12.6%. The FNR was decreased to 10.8% when dual tracers were used for mapping.

The secondary endpoint of the study[21] was to determine if axillary ultrasound after NAC could identify abnormal nodes and guide patient selection for SLNB. There were 470 cN1 patients who underwent an axillary ultrasound after NAC followed by removal of two or more SLNs followed by subsequent ALND. An axillary lymph node was considered abnormal if the cortex was either focally or diffusely thickened (> 3 mm) and the fatty hilum was deformed or absent. Patients with abnormal nodes on axillary ultrasound after NAC were significantly more likely to have a positive SLN (71.8%) than those with normal nodes on axillary ultrasound after NAC (56.5%). The combination of dual tracers, removal of at least two SLNs, and patient selection with axillary ultrasound decreased the FNR to 9.8%.

A recent analysis of the Z1071 study patients[22] sought to determine if clip placement in the biopsy-proven positive node with confirmation of removal of the clipped node at the time of surgery would improve the FNR of a SLNB. Of the 170 patients with a clip placed into the biopsy-proven positive node at the time of diagnosis, 141 had the clipped node resected in the SLN specimen (75.9%). If the clipped node was within the SLN specimen, the FNR was 6.8%.

Additional prospective, multiinstitutional trials—SENTINA and SN FNAC—have been published with similar results.[23,24]

CLINICAL IMPLICATIONS

In the initially cN1 patient who undergoes NAC, a SLNB can be safely performed for nodal staging using the following criteria:

- Use of clinical axillary exam and axillary ultrasound to guide patient selection to attempt SLNB
- Dual tracer lymphatic mapping
- Placement of a clip in the biopsy-proven positive node at diagnosis and ensuring resection of the clipped node at the time of the SLNB
- Ensuring at least two SLNs are removed

ROLE OF REGIONAL NODAL RADIATION THERAPY FOLLOWING NAC

Although a significant body of literature is available to guide radiation therapy (RT) recommendations in patients who undergo upfront surgical management of their breast

cancer, the same cannot be said for initially clinically node-positive patients who receive NAC. The studies described below are ongoing with no results currently available.

ALLIANCE A11202 (NCT01901094)

This phase III, randomized, clinical trial[25] is currently comparing regional nodal irradiation (RNI) in addition to axillary RT versus ALND in patients who are persistently node positive following NAC. A011202 began accruing in February 2014 with an expected trial completion in January 2024. The estimated enrollment is 2918 patients over the age of 18 with cT1–T3, N1, M0 disease before NAC. All patients must have an axillary ultrasound as well as histologic confirmation of metastatic disease via needle biopsy. No SLNB can be performed prior to NAC. Assessment of nodal status following NAC is done via clinical exam—repeat axillary ultrasound is not required—and a SLNB performed if clinically node negative. A positive SLN is defined as having at least a 0.2-mm metastatic focus. Patients with a positive SLN(s) after NAC are then randomized to ALND plus RNI or axillary RT plus RNI. The primary endpoint for this study is determining invasive-recurrence-free survival. The secondary endpoints are overall survival and locoregional recurrence.

NSABP B-51/RTOG 1304 (NCT01872975)

This phase III, randomized, controlled clinical trial[26] is designed to investigate whether the addition of RNI improves the recurrence-free interval rate in women with cT1–T3, N1 disease prior to NAC who are found to be pathologically node negative by SLNB or ALND. Enrollment began in August 2013 with expected study completion in August 2028. Planned enrollment is 1636 female participants over the age of 18 who had nodal status determined prior to NAC via exam, ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET)/CT with histologic confirmation of metastatic nodal disease via needle biopsy. The primary endpoint is invasive breast cancer recurrence-free interval. The secondary endpoints include overall survival, locoregional recurrence, and time to development of a second primary breast cancer.

CONCLUSIONS

Axillary management for breast cancer patients has changed tremendously over the past few decades. The use of sentinel node biopsy over ALND has the benefit of reduction in morbidity while not compromising staging, survival, or local–regional recurrence. The increasing effectiveness of adjuvant systemic and local therapies has been key to these advances in surgical care. Ongoing trials and future studies will further delineate the extent of axillary management for select subsets of breast cancer patients.

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