Contemporary Management of the Axilla in Breast Cancer

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Abstract: The care of patients with breast cancer in the modern era involves a multimodal approach to treating locoregional and distant disease. Recent studies have demonstrated that the extent of surgical intervention in both the breast and axilla can be minimized through a personalized approach based on breast cancer stage, subtype, and planned adjuvant therapies. The older approach focused on complete removal of the axillary contents for appropriate staging and to determine the need for adjuvant systemic therapy and radiation. This approach has been replaced by sentinel lymph node biopsy, which allows for axillary staging with the removal of only the nodes most likely to contain metastatic disease. Sentinel lymph node biopsy obviates the need for complete axillary lymph node dissection in patients with node-negative disease. Clinical trials have also shown that axillary dissection can be avoided in those patients with low axillary disease burden in the sentinel nodes who are undergoing breast-conserving therapy. Radiation can also be used as an alternative to axillary dissection in patients with positive sentinel nodes, without increasing the risk for regional recurrence. Further studies are needed in patients undergoing mastectomy to determine the optimal strategy for axillary management in the setting of limited disease in the sentinel nodes. The use of neoadjuvant chemotherapy allows the ability to evaluate an individual tumor's response to therapy, thereby increasing the possibility of breast-conserving surgery and reduction in the extent of axillary surgery. This review will explore the evolution of management of the axilla in patients with clinically node-negative and node-positive disease, and will provide insights into future directions in breast cancer care.

Introduction

The surgical management of breast cancer remains an evolving paradigm in the modern era. During the time of Halsted's radical mastectomy, breast cancer was viewed as a locally aggressive disease that was best treated with extensive surgery that included resection of the breast, the pectoralis muscles, and the level 1, 2, and 3 axillary lymph nodes. Thanks to a growing understanding of tumor biology

and the emergence of more effective adjuvant therapies, there has been a shift toward a de-escalation of surgical interventions. For management of the primary tumor, it has been demonstrated that breast-conserving therapy, including partial mastectomy followed by radiation therapy to the breast, provides disease-free and overall survival comparable to that seen with complete mastectomy.[1] Even prior to this observation, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 study examined management of the axilla in patients who were clinically node-negative or node-positive.[2] Individuals presenting with clinically node-negative disease were randomly assigned to 1 of 3 groups: radical mastectomy, total mastectomy with radiation, or total mastectomy alone. Clinically node-positive patients were randomly assigned to either radical mastectomy or total mastectomy with radiation. The trial found no difference in disease-free or overall survival within the clinically node-negative cohort, whether patients had radiation treatment directed at the axilla, axillary lymph node dissection (ALND) at initial diagnosis, or no axillary treatment at all. There was no difference in survival for those patients who developed clinically evident axillary disease on follow-up and subsequently underwent axillary dissection. In those with positive nodes at presentation, no difference in survival outcomes was identified by the randomized comparison of radical mastectomy vs total mastectomy with radiation to the axillary nodes.[3] Even with the modification of ALND to remove only level 1 and 2 nodes, significant morbidity has been reported with the procedure, including lymphedema, decreased range of motion, neurosensory deficits, and other detrimental effects on quality of life.[4] The sentinel lymph node biopsy (SLNB) procedure was initially proposed as a less-invasive alternative to ALND for axillary staging in patients with early-stage breast cancer. Since the introduction of the procedure, many studies have demonstrated its accuracy in axillary staging as well as its ability to achieve regional control in patients with clinically node-negative disease. Following the publication of multiple trials to this effect, SLNB has become the preferred method for axillary staging in the clinically node-negative patient population.

Although the use of SLNB has been established in patients with a clinically node-negative axilla undergoing up-front surgery, the use of this procedure in patients receiving neoadjuvant systemic therapy has been controversial, especially in those with confirmed node-positive disease at initial presentation. Numerous neoadjuvant trials have shown that systemic therapy can eradicate biopsy-proven disease in the axilla. This finding has led to interest in a less-invasive approach to axillary staging and management following chemotherapy. The possibility of reducing the extent of axillary surgery in patients presenting with initially node-positive and more advanced disease has been an area of active study over the last decade. The accuracy of SLNB following neoadjuvant chemotherapy has been addressed and reported on in multiple trials. Current questions under study include the management of patients with residual disease after neoadjuvant chemotherapy, and how tumor subtype can be utilized to individualize care. This article will review previously published and ongoing work in the management of the axilla, in addition to exploring future directions in regional control.

Preoperative Axillary Imaging

The traditional means of preoperative assessment of the axilla was primarily through findings on a physical examination. Other ways of assessing the axilla in the preoperative setting include ultrasound, positron emission tomography (PET)/computed tomography (CT), and magnetic resonance imaging (MRI). Proponents of routine ultrasound of the axilla cite its low cost and noninvasiveness.[5] Ultrasound breast imaging has been added to screening mammography in women at higher risk for breast cancer to increase the ability to identify smaller cancers not seen on mammography.[6] Studies have demonstrated a correlation between nodal appearance and nodal disease burden with ultrasound. One such study, by Jackson and colleagues, evaluated 513 patients with invasive breast cancer who received preoperative axillary ultrasound. The researchers found a false-negative rate of 4% for detecting 3 or more metastatic axillary lymph nodes. Higher false-negative rates were associated with lobular tumor histology and larger tumors (pathologic classification, T2).[7] The addition of nodal sampling to axillary ultrasound has assisted in improving the accuracy of the preoperative diagnosis of metastatic disease.[8,9] This can be performed through the use of fine-needle aspiration or core needle biopsy. Further efforts are currently being made to assess whether axillary ultrasound is reliable enough to negate the need for SLNB altogether in select patients.[10] Limitations to the routine utilization of ultrasound for nodal assessment, such as operator technique, are difficult to avoid. Other imaging modalities that have been evaluated for the assessment of axillary nodes, such as MRI and PET/CT, have been shown to have limited reliability.[11,12] MRI as an isolated modality to assess axillary metastases has demonstrated sensitivity ranging from 80% to 100%, and specificity ranging from 70% to 90%.[13-15] Data published regarding PET/CT for nodal assessment has shown sensitivity ranging from 55% to 70% and specificity ranging from 90% to 100%.[12,14,16]

Axillary Staging

Historically, staging of the axilla was performed by complete resection of the nodal contents of the axilla at the time of the index breast surgery.[3] As previously stated, the routine use of axillary dissection for nodal staging results in significant morbidity—such as chronic pain, lymphedema, numbness, decreased range of motion, and diminished quality of life—in 20% to 30% of patients.[17-19]

A study by Hack and colleagues evaluated 222 women who underwent ALND as a component of their breast cancer surgery between March 1995 and February 1997. At least 6 months after surgical intervention, 73% of women continued to experience pain and limited range of motion of the involved extremity.[17] This and other studies prompted clinicians to investigate less-invasive methods of axillary staging.

SLNB, originally introduced by Morton and colleagues in melanoma patients with clinically negative nodes, is an alternative to the use of complete resection of the nodal basin to assess the possibility of nodal involvement. Although the initial study described use of blue dye alone,[20] Morton later described a dual-tracer technique to identify those nodes most likely to contain metastasis owing to direct lymphatic drainage from the primary tumor.[21] This technique has been expanded for use in multiple other solid tumor malignancies, most notably breast cancer.

Veronesi and colleagues performed one of the first randomized trials comparing SLNB with axillary dissection. Their results showed that SLNB was accurate in terms of axillary staging, and led to less morbidity. An update was published at a median follow-up of 79 months, and no significant difference in the cumulative incidence of axillary events was found between the 2 groups. In addition, there was no difference observed in all breast cancer–related events and overall survival.[22] Similar conclusions were derived from the NSABP B-32 trial, which was designed to assess whether SLNB was equivalent to ALND in achieving locoregional control, and to measure its impact on survival when used as a tool for axillary staging in patients with clinically node-negative early-stage breast cancer.[23]

The current accepted standard for axillary staging in breast cancer is SLNB.[24,25] The procedure is performed by injection of the breast parenchyma in a peritumoral, subareolar, or subdermal fashion with either a technetium-labeled (Tc99m) radiocolloid and/or a vital blue dye (methylene blue or isosulfan blue). Following injection, the mapping agent travels to the first nodes (usually 2 or 3) in the regional nodal basins. If no metastatic disease is found on pathologic examination of the sentinel nodes, the chance of metastatic disease being present in the remaining axillary nodes (false-negative sentinel node) is less than 10%.[23,26] Factors associated with an increased false-negative rate include identification of less than 2 sentinel nodes and prior excisional biopsy.[27-29] Failed identification of the sentinel node has been described in obese patients, in patients with upper inner quadrant tumor location, and with increasing decade of age after 50 years.[28-31]

Some groups have used lymphoscintigraphy for identification of the sentinel node to assist in predicting successful operative sentinel node localization. A study by Veronesi and colleagues described successful identification of the sentinel node using preoperative lymphoscintigraphy in 97.5% of patients. Their study population consisted of 163 patients with operable breast cancers (T1-T3) at the time of diagnosis.[32] Techniques such as utilization of a dual tracer and identification of more than 2 sentinel nodes when present have been described as means of improving the accuracy of SLNB.[27,30] Application of these techniques has been extended to include those patients receiving systemic therapy prior to surgical resection, who have false-negative rates comparable to those of patients who do not receive neoadjuvant therapy.[33]

Clinically Node-Negative Disease

With the emergence of breast cancer screening programs, breast cancer patients are presenting on average with smaller tumors and earlier disease stage compared with patients in earlier decades.[34,35] The designation of negative nodes on clinical examination is determined by the absence of palpable disease in the regional nodal basins, and in some centers by the lack of abnormal-appearing nodes on ultrasound or MRI imaging. These patients traditionally have been treated with surgery first, but more recent management has included neoadjuvant systemic therapy that depends on tumor subtype (ie, triple-negative or human epidermal growth factor receptor 2–positive).[36]

Some of the early trials of SLNB in breast cancer were designed to assess the accuracy of staging of the axilla compared with ALND. Another important endpoint to consider is the risk of locoregional recurrence following a negative SLNB. The American College of Surgeons Oncology Group (ACOSOG) Z0010 trial (A Multicenter Prognostic Study of Sentinel Node and Bone Marrow Micrometastases in Women With Clinical T1/T2 N0 M0 Breast Cancer) was designed to determine the incidence of occult disease in the sentinel nodes and bone marrow in patients with early-stage breast cancer who were undergoing breast-conserving surgery and SLNB. Patients without an identified sentinel node intraoperatively or with a positive sentinel node on hematoxylin and eosin (H&E) staining were required to continue with completion axillary

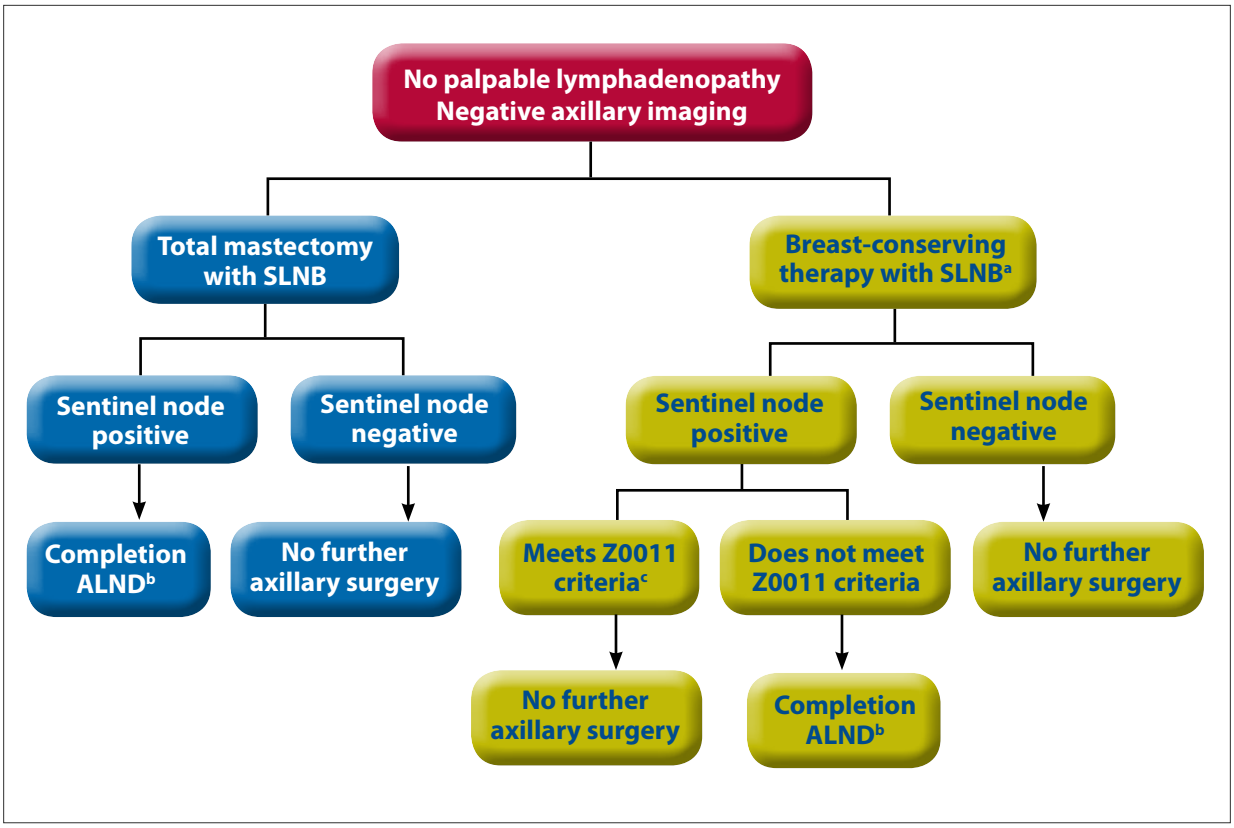

Figure 1. Management of clinically node-negative disease.

[a] Breast-conserving therapy denotes breast-conserving surgery in conjunction with whole-breast irradiation.

[b] The AMAROS trial demonstrated equivalent axillary recurrence rates between patients treated with ALND and those treated with axillary radiation. AMAROS and the IBCSG 23-01 trial (micrometastases in 1-2 SLNs) enrolled patients undergoing mastectomy or breast-conserving therapy.

[c] Inclusion criteria for patients in the ACOSOG Z0011 study included T1-T2 invasive carcinoma, clinically negative nodes, breast-conserving surgery, and 1 to 2 positive sentinel nodes.

ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy.

dissection if not enrolled in the companion ACOSOG Z0011 study (Lymph Node Removal in Treating Women Who Have Stage I or Stage IIA Breast Cancer). There was no significant difference in disease-free or overall survival in patients in the Z0010 study regardless of the presence of micrometastatic disease in the bone marrow or in the sentinel nodes on immunohistochemistry staining. A secondary endpoint of the study was locoregional recurrence in early-stage breast cancer patients with clinically negative axillary lymph nodes. A total of 5119 patients were evaluated in the trial; approximately 24% had positive sentinel nodes on H&E staining and 10.5% had positive sentinel nodes on immunohistochemistry staining. At a median follow-up of 8.4 years, local and regional recurrences were rare, and were found to be associated with hormone receptor–negative disease and younger patient age at presentation. Lymphovascular invasion and grade 2 or 3 disease were associated with distant recurrences. This study highlighted the importance of tumor subtype in predicting local treatment failure, and found that local recurrence was associated with a worse overall survival.[37]

Although SLNB has been relatively well accepted for axillary staging, the need for additional axillary surgery has been questioned for patients with minimal nodal disease found in the sentinel nodes. Many investigators have reported that the sentinel node is the only positive node in the axilla in approximately 60% of patients who present with early-stage, clinically node-negative disease. With publication of the Z0011 trial, the ACOSOG investigator group was instrumental in changing the way in which patients with limited nodal disease in the sentinel nodes are managed. Patients included in this trial had T1/T2 disease without evidence of palpable nodal disease on clinical examination. Patients underwent breast-conserving surgery

with SLNB followed by adjuvant whole-breast irradiation. Patients found to have 1 or 2 sentinel nodes with metastatic disease on SLNB were eligible to be randomly assigned to either completion ALND or no further axillary surgery. A total of 893 patients were randomized, and at a median follow-up of 6.3 years, there was no significant difference in overall survival between those patients undergoing ALND (88.8%) and those undergoing SLNB alone (89.9%). A recent update corroborated these findings with a median 9.3-year follow-up. The 10-year disease-free survival was 80.2% in the ALND group vs 78.2% in the SLND-alone group. The 10-year overall survival was 83.6% in the ALND group and 86.3% in the SLND-alone group.[38] This study has been instrumental in decreasing the extent of axillary surgery in patients with a low burden of disease in the axillary nodal basin. Criticism towards the trial has centered around the limited representation of younger patients and those with hormone receptor–negative tumors, human epidermal growth factor receptor 2–positive tumors, or tumors with lobular histology.[39] Despite this, many institutions have embraced this paradigm, suggesting that axillary dissection may soon become obsolete in this patient population.[40,41] The POSNOC trial (Positive Sentinel Node: Adjuvant Therapy Alone Versus Adjuvant Therapy Plus Clearance or Axillary Radiotherapy) is an ongoing study in the United Kingdom that is addressing a question similar to that explored by the Z0011 trial. The trial is expected to complete accrual in 2019.

Alternatives to Axillary Dissection

One of the often-cited limitations of ACOSOG Z0011 is that only patients undergoing breast-conserving therapy were eligible for participation. Other criticisms concern the lack of adherence to protocol requirements with respect to radiation field design, and the possibility that potential radiation to the nodal basins may have influenced the rates of regional recurrence.[42] A study evaluating the radiation fields in ACOSOG Z0011 patients demonstrated equivalent rates of nodal irradiation between the ALND and SLND groups.[42]

The role of radiation as an alternative to axillary dissection was the focus of the OTOASOR study (Optimal Treatment of the Axilla - Surgery or Radiotherapy) and the AMAROS trial (Comparison of Complete Axillary Lymph Node Dissection With Axillary Radiation Therapy in Treating Women With Invasive Breast Cancer).[43,44] These studies included patients with T1/T2 disease undergoing breast-conserving therapy or mastectomy with SLNB. The OTOASOR trial was a single-institution study comparing ALND and axillary radiotherapy in patients with a positive sentinel node. Axillary recurrence rates in the recent 8-year update were comparable in the ALND and radiotherapy arms, at 2.0% and 1.7%, respectively. The AMAROS trial was a multicenter study that evaluated 4806 patients with T1/T2 tumors and clinical N0 disease, 30% of whom were found to have a positive sentinel node. Patients were randomly assigned to either ALND or axillary radiation therapy, with a primary endpoint of axillary recurrence. Their findings demonstrated that there was no difference in axillary recurrence between the 2 treatment arms, with a 5-year recurrence rate of 0.43% in the ALND group compared with 1.19% in the axillary radiation group. There was a reduction in ipsilateral arm lymphedema in those patients randomly assigned to axillary radiation. Approximately 17% of patients in this trial underwent mastectomy, with similar locoregional recurrence rates.[44] Sixty percent of patients enrolled in the AMAROS study were found to have macrometastatic disease on SLNB.

Patients with micrometastatic disease (<2 mm) were the focus of the International Breast Cancer Study Group (IBCSG) 23-01 trial. This trial demonstrated that observation alone is similar to completion axillary dissection in rates of locoregional recurrence, with less morbidity in the sentinel node–only group.[45]

Clinically Node-Positive Disease

More recently, controversy has arisen regarding the management of the axilla in breast cancer patients who have clinically positive axillary nodes at presentation. These patients are sometimes treated with surgery as initial management, although other patients receive neoadjuvant systemic therapy. Neoadjuvant therapy has become the preferred approach at many institutions, given that the timing of systemic therapy does not affect survival.[46,47] Systemic therapy leads to a reduction in tumor burden in both the primary tumor and the regional nodes in many patients. The neoadjuvant approach has the benefit of allowing the opportunity to assess tumor response to systemic therapy, and can increase the number of patients eligible for breast-conserving surgery as well. The response to systemic therapy has demonstrated prognostic value, especially in the setting of a pathologic complete response.[48-50] Symmans and colleagues described the residual cancer burden index, a composite of pathologic characteristics of the primary tumor and regional nodes, as a prognostic indicator of distant relapse-free survival.[51] In addition to downstaging the primary tumor, neoadjuvant systemic therapy may also eradicate nodal disease in those with either clinically node-negative or clinically node-positive axillary nodes at presentation.[52,53] SLNB has been shown to be accurate for axillary staging following neoadjuvant systemic therapy in patients presenting with a clinically node-negative axilla.[33,54]

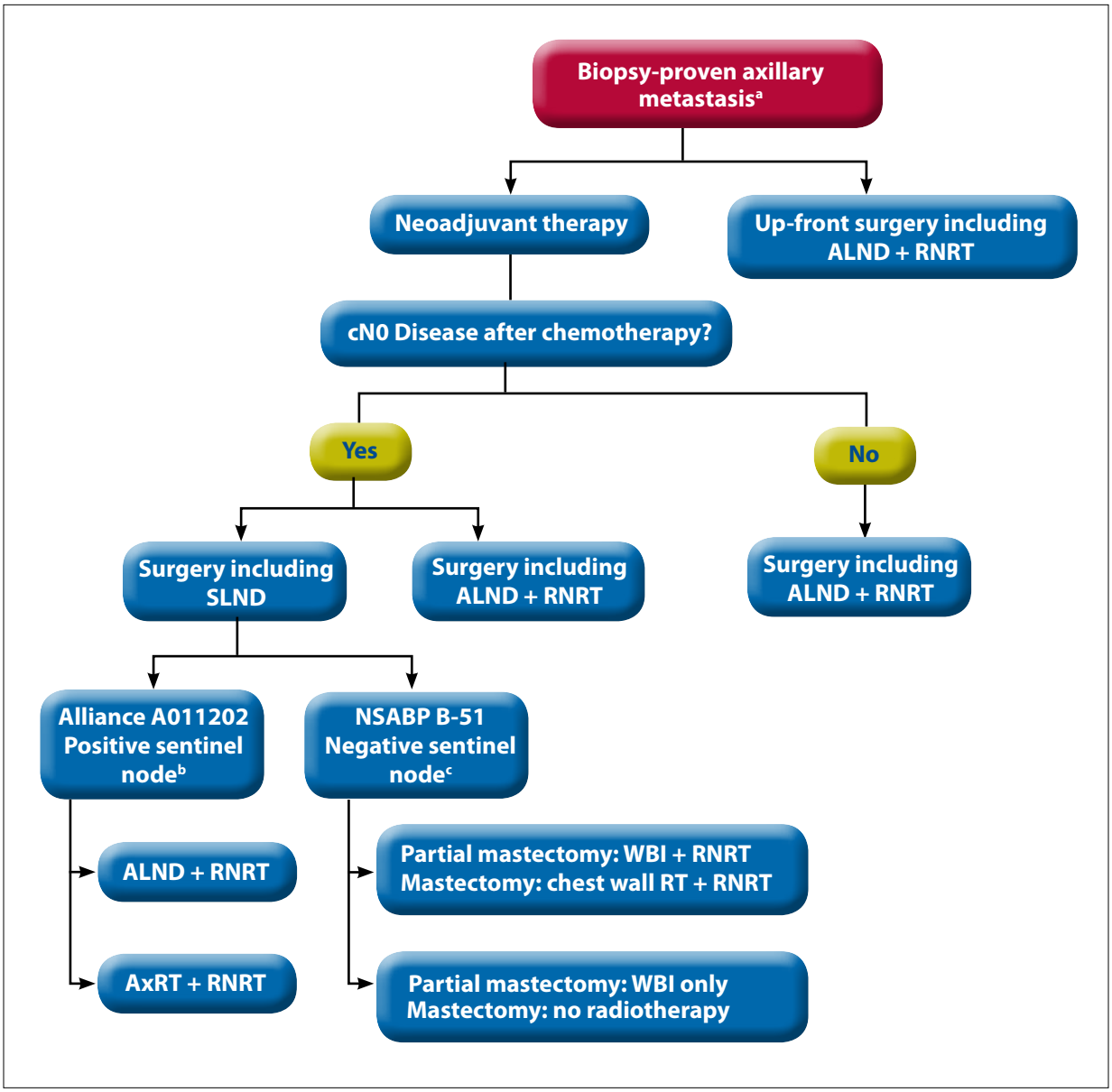

Figure 2. Management of clinically node-positive disease.

[a] Biopsy performed owing to suspicious nodes on physical examination or on ultrasound, magnetic resonance imaging, or another imaging modality.

[b] Patients eligible for participation in the Alliance A011202 trial.

[c] Patients eligible for participation in the NSABP B-51 trial.

ALND, axillary lymph node dissection; AxRT, axillary radiation therapy; RNRT, regional nodal radiation therapy; RT, radiation therapy; SLND, sentinel lymph node dissection; WBI, whole-breast irradiation.

For those patients who present with initially node-positive disease, there has been concern that SLNB is not accurate for axillary staging following chemotherapy. The initial studies exploring SLNB in this patient population were small, single-institution studies that did not require a standard approach to the sentinel node procedure or the pathologic assessment of the sentinel nodes. Early reports had relatively high false-negative rates, but also had wide variation in the surgical techniques that were used and the patient populations that were included. Several groups

advocated for the use of SLNB prior to chemotherapy, whereas others advocated for SLNB after chemotherapy to reduce the number of axillary dissections needed in those with clinically node-positive disease downstaged with systemic therapy.

Some investigators have explored the use of SLNB before and after chemotherapy; however, SENTINA (Sentinel Lymph Node Biopsy in Patients With Breast Cancer Before and After Neoadjuvant Chemotherapy) found that this resulted in false-negative rates as high as 52%.[55] Recently, 3 multicenter trials—SENTINA, ACOSOG Z1071 (Surgery to Remove the Sentinel Lymph Node and Axillary Lymph Nodes After Chemotherapy in Treating Women With Stage II, Stage IIIA, or Stage IIIB Breast Cancer), and SN FNAC (Sentinel Node Biopsy Following Neoadjuvant Chemotherapy in Biopsy Proven Node Positive Breast Cancer), reported false-negative rates of SLNB after chemotherapy in patients with initially node-positive disease treated with neoadjuvant chemotherapy.[55-57] The SENTINA study reported a false-negative rate of 14.2% for patients who converted to clinically node-negative disease, but noted that this rate was decreased with the use of a dual-tracer technique (false-negative rate, 8.6%) and removal of at least 3 sentinel nodes (false-negative rate, 7.3%).

In the ACOSOG Z1071 trial, investigators found that a false-negative rate of 12.6% was reduced to 10.8% with use of a dual-tracer technique and to 9.1% with retrieval of at least 3 sentinel nodes. Similar findings were reported by investigators from the SN FNAC study.[56,57] Although these studies demonstrated that SLNB is feasible following neoadjuvant chemotherapy, the researchers cautioned against using the technique when only 1 sentinel node is identified. False-negative rates ranging from 18.2% to 31.5% were reported in this patient population. A subset of 170 patients in the ACOSOG Z1071 population had a clip placed at the time of SLNB. All patients subsequently underwent sentinel node surgery with eventual completion axillary dissection. The biopsy clip was identified in the sentinel node in 75.9% of cases, and in the axillary contents in 24.1% of cases. The false-negative rate with the sentinel node surgery was 6.8% in patients whose clip was found in the sentinel node vs 19.0% in patients whose clip was found in the ALND specimen.[58]

In an effort to further improve the accuracy of axillary staging following neoadjuvant therapy, investigators from the MD Anderson Cancer Center have described the technique of targeted axillary dissection. This procedure requires the placement of a clip in the biopsy-proven metastatic lymph node at the time of initial presentation. Following neoadjuvant therapy, a radioactive seed or other marker can be placed in the clipped node to assure removal at the time of axillary surgery. Caudle and colleagues showed that when resection of the clipped node is confirmed in addition to SLNB (targeted axillary dissection), the false-negative rate drops to 2.0%. It is important to note that the clipped node was not identified as a sentinel node in 23% of patients; therefore, localizing the clipped node increases the accuracy of axillary staging when combined with SLNB.[59] A similar technique of localizing the biopsy-proven metastatic nodes in conjunction with SLNB was described by Diego and colleagues.[60] In this study, the patients also underwent localization with a radioactive seed preoperatively, with resection of the clipped node in addition to SLNB. All retrieved nodes were assessed with serial H&E evaluation, with only intermittent use of immunohistochemistry. The use of immunohistochemistry has demonstrated benefit in reducing the false-negative rate in the neoadjuvant setting.[57,61] This was demonstrated by the reduction in the false-negative rate from 12.6% to 8.7% in the ACOSOG Z1071 study when immunohistochemistry evaluation was performed on sentinel nodes negative for metastasis based on standard H&E staining.[61]

There is also literature to suggest that the presence of treatment effect in sentinel nodes resected following neoadjuvant chemotherapy may be more predictive of a true negative result.[62] Eighty-six patients with node-positive disease who underwent SLNB with completion ALND were evaluated retrospectively by Brown and colleagues. In this study, the researchers found that 65% of patients with true negative sentinel nodes had associated histologic changes of focal fibrosis, fat necrosis, and foamy parenchymal histiocytes on pathologic evaluation. This effect was seen in only 18% of patients with false-negative sentinel nodes. The absence of these findings resulted in a sensitivity of 82% and a specificity of 65% in identifying a false-negative sentinel node.[62] In order to further guide the use of SLNB following neoadjuvant therapy, several groups have evaluated the use of post-therapy ultrasound to predict persistent nodal burden. A secondary outcome of ACOSOG Z1071 was the ability of axillary ultrasound to identify abnormal nodes following chemotherapy. The false-negative rate of 12.6% was reduced to 9.8% when SLNB was used selectively in patients with normalization of the nodes on ultrasound imaging following chemotherapy.[63] Imaging characteristics found to be related to residual nodal burden in this population included increased cortical thickness, increased lymph node short-axis and long-axis diameters, and absence of a fatty hilum.[64]

Future Directions

Surgeons are growing increasingly comfortable with omitting completion ALND in patients with planned

breast-conserving surgery and whole-breast irradiation who have limited nodal disease based on SLNB as the initial staging procedure. Additional data are needed before broader adoption of this approach is routinely extended to patients undergoing mastectomy. The use of SLNB and targeted ALND is gaining popularity for patients with initially node-positive disease; however, outcomes data regarding regional recurrences are lacking in this patient population. Small, single-institution studies have suggested that omission of completion ALND and use of axillary radiation therapy in initially clinically node-positive patients treated with neoadjuvant chemotherapy have similar rates of disease-free and overall survival when a pathologic complete response is achieved.[65]

There are 2 important cooperative group trials addressing the role of surgery and radiation therapy in these patients. NSABP B-51 (Standard or Comprehensive Radiation Therapy in Treating Patients With Early-Stage Breast Cancer Previously Treated With Chemotherapy and Surgery) is a randomized prospective trial looking specifically at patients with initially node-positive disease who achieve a pathologic complete response following chemotherapy. These patients are randomly assigned to nodal irradiation or observation. Patients undergoing mastectomy who are randomly assigned to regional radiation will also receive treatment to the chest wall. Those undergoing breast-conserving therapy will still receive whole-breast irradiation, but will be randomly assigned to receipt or omission of nodal irradiation.

Another concern for patients undergoing neoadjuvant therapy is how to manage those with residual disease in the sentinel nodes. The Alliance A011202 trial (Comparison of Axillary Lymph Node Dissection With Axillary Radiation for Patients With Node-Positive Breast Cancer Treated With Chemotherapy) addresses this population by randomly assigning patients to ALND vs axillary nodal irradiation. These ongoing studies speak to the increasing need to individualize locoregional management in patients with breast cancer.

Disclosures

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