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Use of sentinel lymph node biopsy to select patients for local–regional therapy after neoadjuvant chemotherapy

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Abstract

Use of sentinel lymph node biopsy for axillary staging of patients with breast cancer treated with neoadjuvant chemotherapy has been widely debated. Questions arise regarding the accuracy of sentinel lymph node biopsy in axillary staging for these patients and its use to determine further local–regional therapy, including surgery and radiation therapy. For patients who are clinically node-negative at presentation, sentinel lymph node biopsy enables accurate staging of the axilla after neoadjuvant chemotherapy, and determination of which patients should go on to further axillary surgery and regional nodal radiation therapy. Importantly, performing axillary staging after completion of chemotherapy, rather than before chemotherapy, enables assessment of response to chemotherapy and the extent of residual disease. This information can assist the planning of adjuvant treatment. Recent data indicate that sentinel node biopsy can also be used to assess disease response after neoadjuvant chemotherapy for patients with clinical N1 disease at presentation.

Keywords

Sentinel lymph node biopsy; Neoadjuvant chemotherapy; Pathological complete response; Breast cancer

Introduction

Evaluation of the axillary lymph nodes is a standard part of the staging of patients with breast cancer. The information gathered at the time of surgical staging is used to determine additional local–regional therapy. The additional therapy includes extent of surgery in the axilla and the need for adjuvant radiation therapy. As medical and surgical treatment of breast cancer has evolved, so has the approach to the axilla. Neoadjuvant chemotherapy is increasingly used, and the advantages of this approach include potential to downsize the tumor and enable breast-conserving surgery, assessment of tumor response to systemic therapy, and the opportunity to reduce the extent of axillary surgery. There has been increasing use of neoadjuvant chemotherapy, and improvements in systemic therapy have resulted in increased pathological complete response. Given these changes, re-evaluation of the approach to axillary staging in this setting is required.

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Compliance with Ethics Guidelines

Conflict of Interest

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Human and Animal Rights and Informed Consent

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History

Traditionally, the axilla was staged by axillary dissection of the level I and II lymph nodes. This is associated with significant potential for morbidity including lymphedema, reduced arm mobility, and nerve injury [1]. In twenty year follow up after breast cancer treatment utilizing mastectomy and axillary lymph node dissection, the incidence of lymphedema has been reported to be as high as 49 %, on the basis of subjective reporting by patients [2]. A more recent analysis using objective measurements found the incidence of lymphedema five years after axillary lymph node dissection was 16 % [3]. Investigators from the After Mapping of the Axilla: Radiotherapy or Surgery (AMAROS) trial recently reported one-year lymphedema incidence of 40 % with axillary dissection compared with 22 % with axillary radiation [4].

Sentinel lymph node biopsy

Sentinel lymph node biopsy is a less invasive way of obtaining axillary staging information. It enables sampling of the axillary basin with removal of the first few lymph nodes and draining the breast without removing all of the level I and II axillary lymph nodes. These lymph nodes are identified by injection of radioactive colloid labeled with technetium-99, isosulfan blue dye, methylene blue dye, patent V blue dye, or a combination of radioactive colloid and a blue dye. The advantage of sentinel lymph node biopsy is less invasive surgery and lower morbidity. A recent meta-analysis found that axillary dissection was associated with almost four times the incidence of lymphedema compared with sentinel lymph node biopsy 19.9 % (95 % CI 13.5–28.2) vs. 5.6 % (95 % CI 6.1–7.9 %) [5●].

One prospective study using objective measurements of lymphedema compared patients undergoing sentinel lymph node biopsy with those undergoing sentinel lymph node biopsy then axillary dissection. Lymphedema at a median follow up of 5 years (range 2.7–8 years) was significantly lower for sentinel lymph node biopsy (5 %) than for sentinel lymph node biopsy followed by axillary dissection (16 %). They also found that severe lymphedema was lower in the sentinel lymph node biopsy only group (0.3 % vs. 3 %) [4].

Studies have shown that use of dual mapping agents results in improved identification of sentinel nodes and fewer false negative results (FNR) than single-agent mapping. This has been shown both by use of sentinel node biopsy for patients undergoing surgery first and also in the setting of neoadjuvant chemotherapy [6●, 7].

Sentinel lymph node biopsy was initially adopted for clinical staging of node-negative early-stage breast cancer. Further axillary surgery was dictated by the results of the sentinel node biopsy; patients with positive sentinel nodes were recommended to undergo axillary dissection and those without disease identified in the sentinel nodes could avoid axillary dissection.

Sentinel lymph node biopsy is now the standard for axillary staging of patients with early-stage breast cancer and clinically node-negative disease. FNR for sentinel lymph node biopsy in this setting have been reported after multi-institute studies, for example the National Surgical Adjuvant Bowel and Breast Program (NSABP) B-32 trial for which 9.8 % FNR were obtained, with successful identification of sentinel lymph nodes in 97.2 % of patients [8]. A meta-analysis revealed 8 % FNR with sentinel lymph node identification of 90 % [9]. In the B-32 trial, the number of FNR was significantly different depending on the number of sentinel lymph nodes removed: 17.7 % for one sentinel node, 10 % for two sentinel nodes, 6.9 % for three sentinel nodes, 5.5 % for four sentinel nodes, and 1 % for five or more sentinel nodes ($p < 0.0001$) [8]. Studies have shown that for node-positive cases

axillary metastasis is identified 97–100 % of the time in the first three to four sentinel lymph nodes removed [10].

Adoption of sentinel lymph node biopsy as the standard for axillary staging carried with it concerns that metastases might be missed and this could be associated with increased local failure (local recurrence) and reduced survival. NSABP B-32 showed that overall survival and disease-free survival were not significantly different for sentinel node-negative patients who underwent sentinel lymph node biopsy followed by axillary dissection and those who underwent sentinel lymph node biopsy alone; mean follow up was 95.6 months [8]. Some of the patients in the sentinel lymph node only group would be expected to have axillary disease that was not detected, because these patients had not undergone surgical clearance of the axillary nodes. Additional adjuvant treatment recommendations may have been different if the nodal positivity had been known. Despite this, patient outcome was not different between the groups, which further emphasizes that use of sentinel node biopsy is reasonable for these patients in clinical practice.

Sentinel lymph node biopsy after neoadjuvant chemotherapy

Although sentinel lymph node biopsy was adopted as routine for early-stage breast cancer treated with surgery first, the timing and type of axillary surgery for nodal staging has been debated in the setting of patients receiving neoadjuvant chemotherapy.

Axillary staging after completion of chemotherapy enables assessment of extent of residual disease after chemotherapy, which correlates with outcome. Sentinel lymph node surgery before initiation of neoadjuvant chemotherapy precludes evaluation of response to chemotherapy, because it removes the sentinel nodes from the ipsilateral axilla; nodal disease response after chemotherapy cannot, therefore, be assessed. Pathologic nodal response is a critically important component of overall pathologic response and nodal status after chemotherapy correlates strongly with patient outcome. Thus, accurate nodal staging after completion of neoadjuvant chemotherapy is crucial for determination of prognosis and to guide adjuvant therapy decisions.

Regarding use of sentinel lymph node surgery after completion of neoadjuvant chemotherapy, there was initial concern that neoadjuvant chemotherapy could interfere with the accuracy of the procedure and be associated with more FNR. Although early experience showed sentinel lymph node identification was low and there were more FNR in this setting, over time and with increased experience, studies have confirmed that FNR are no different with use of sentinel node after completion of neoadjuvant chemotherapy than when performed for patients undergoing surgery as first line of treatment for clinically node negative patients.

A meta-analysis of sentinel lymph node biopsy after neoadjuvant chemotherapy for patients with clinically node negative disease at presentation revealed sentinel node identification was 90 % with 8 % FNR. This suggests sentinel node surgery can be used to stage the axilla after neoadjuvant chemotherapy [9].

The largest single-institution experience with sentinel node surgery after neoadjuvant chemotherapy was published by the MD Anderson Cancer Center. Hunt et al. [7] compared 575 clinically node-negative patients undergoing sentinel lymph node biopsy after neoadjuvant chemotherapy with 3,171 patients undergoing sentinel lymph node biopsy and surgical resection as first treatment. They found the number of FNR was not significantly different: 5.9 % for the neoadjuvant chemotherapy group and 4.1 % for the surgery first group. After adjusting for clinical stage, local–regional recurrence, disease-free survival, and overall survival were not significantly different.

Similarly, in the multi-institutional clinical trial setting, for patients on NSABP B-27 who underwent sentinel node surgery and axillary dissection, the number of FNR was 10.7 % for sentinel lymph node biopsy after neoadjuvant chemotherapy [11]. This is similar to 9.8 % FNR in NSABP B-32, in which patients had surgery as initial therapy [8].

Sentinel lymph node biopsy after neoadjuvant chemotherapy for clinically node-positive patients

With improvements in systemic therapy and patient selection for use of neoadjuvant chemotherapy, achievement of pathological complete response has been increasing. Patients who are clinically node positive before chemotherapy may become clinically node negative after neoadjuvant treatment; nodal conversion from clinical N1 to pathologic N0 is approximately 40 % [6●]. These improvements in nodal conversion makes it important for clinicians to re-assess the need for axillary dissection for all patients who are node positive at presentation, because those who had axillary disease prechemotherapy do not necessarily have persistent disease at the time of surgery and, therefore, may not require axillary dissection. These patients could be spared unnecessary surgery and morbidity by performing sentinel lymph node biopsy as an alternative to axillary dissection. However, the importance of axillary staging for determining additional local–regional therapy requires careful examination of the results of sentinel lymph node biopsy for staging the axilla.

The American College of Surgeons Oncology Group (ACOSOG) Z1071 trial was designed to evaluate the accuracy of sentinel node surgery for staging the axilla after neoadjuvant chemotherapy for women with nodal metastasis at initial presentation. A total of 756 patients with histologically or cytologically proved node-positive disease at presentation were enrolled and treated with neoadjuvant chemotherapy. The primary endpoint was the incidence of false-negative sentinel node surgery, as measured for study patients who underwent axillary staging after neoadjuvant chemotherapy with sentinel lymph node biopsy followed by axillary dissection. Overall FNR for cN1 patients with two or more sentinel nodes resected was 12.6 %. Fewer FNR were obtained when three or more lymph nodes were removed; use of dual-mapping was also associated with fewer FNR [6●].

Similar results were obtained for sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proved node-positive breast cancer—in the SN FNAC study FNR were 9.6 % for sentinel lymph node biopsy after chemotherapy for node-positive breast cancer patients [12].

The SENTINA study reported 14.2 % FNR in a similar trial; they did not, however, require pathologic confirmation of nodal positivity before onset of chemotherapy and included cases with a single sentinel node resected. In cases with two or more sentinel nodes resected the number of FNR was 9.6 % [13●].

All three of these studies demonstrated that as the number of sentinel nodes resected increases the number of FNR decreased, with most FNR obtained in cases in which a single sentinel node was removed [6●, 7]. This has also been reported in the setting of sentinel lymph node surgery with surgery first [8]. For sentinel node surgery to be an accurate staging tool, it is important that all sentinel nodes are removed; studies suggest that most patients will have more than 1 sentinel node. For high-risk patients who have proved node-positive disease before chemotherapy, especially, careful examination of the axilla with removal of all lymph nodes that are radioactive, blue, or palpably abnormal is important.

Performance of sentinel node biopsy for patients who have received neoadjuvant chemotherapy is known to result in identification of fewer sentinel nodes, especially for patients with node-positive disease at presentation. The ACOSOG Z1071 study evaluated

factors affecting the success of sentinel node identification. Sentinel node identification was improved when mapping was performed by use of radiolabelled colloid alone or with blue dye compared to blue dye alone [14●]. Sentinel lymph node identification with blue dye alone was 79.3 % which was significantly lower than when radiolabelled colloid (91.3 %) or dual mapping agents (93.8 %) were used. Patient age, body mass index, clinical T stage at presentation, clinical N stage at presentation, and pathologic nodal response to chemotherapy did not affect the ability to identify sentinel lymph node(s). Use of the optimum tracer is important to successful identification of sentinel lymph nodes, especially in the setting of neoadjuvant chemotherapy.

Radiocolloid and blue dye should, therefore, both be used when performing sentinel lymph node biopsy after neoadjuvant chemotherapy to improve sentinel lymph node identification and minimize the number of FNR.

Directing local–regional treatment—sentinel lymph node biopsy to guide the extent of axillary surgery

Nodal evaluation after completion of neoadjuvant chemotherapy enables assessment of response to chemotherapy and evaluation of the extent of residual nodal disease. An excellent response to chemotherapy can reduce the extent of surgery needed both in the breast and the axilla.

Patients with clinically node negative disease at initial presentation

For clinically node-negative patients, sentinel lymph node biopsy should be performed after completion of neoadjuvant chemotherapy, given the acceptable number of FNR and the fact that multiple studies have revealed lower incidence of nodal positivity after neoadjuvant chemotherapy compared with those undergoing surgery first. This results in reduction of the need for axillary dissection.

When a sentinel node cannot be identified at surgery, axillary dissection should be performed for accurate axillary staging and local control. Intraoperative evaluation of the sentinel nodes to direct the extent of axillary surgery is recommended. Patients with negative sentinel lymph node(s) need no further axillary surgery.

Use of frozen section or touch prep intraoperatively can enable intraoperative detection of positive sentinel nodes. When a positive sentinel node is identified intraoperatively, completion axillary dissection can be performed during the same operation. When identified after surgery on final pathology, completion axillary dissection is still recommended; outcome is no different whether completion axillary lymph node dissection is delayed or immediate [15]. In cases with residual nodal disease after completion of chemotherapy, axillary dissection is recommended (Fig. 1). This is to provide additional staging information regarding the nodal disease burden, and for local regional control of the disease. Residual disease in the nodal basin despite optimum systemic therapy is different from positive sentinel nodes in a patient who has yet to receive systemic therapy. Therefore, standard practice in this situation is to resect those nodes with thorough surgery in the form of axillary lymph node dissection.

Jeruss et al. [16] found that of patients with a positive sentinel lymph node biopsy after neoadjuvant chemotherapy, 44 % had no additional axillary disease on completion axillary dissection. They developed a nomogram for predicting additional axillary disease after positive sentinel lymph node biopsy. Factors associated with increased risk of positive non-sentinel nodes included lymphovascular invasion, multicentricity, and pathologic tumor size.

Patients with clinically node positive disease at presentation

Patients who present with nodal involvement and receive neoadjuvant chemotherapy should be assessed for disease response on clinical and radiological examination after chemotherapy. Patients at high likelihood of pathologic complete response may not require axillary dissection for disease control. Sentinel lymph node biopsy is a method of staging the axilla with less morbidity and which provides information indicating the extent of axillary surgery needed, as outlined in Fig. 1. Several factors can increase the accuracy of the sentinel node procedure in this setting. As already discussed, if sentinel lymph node biopsy is undertaken in this setting, use of a dual-tracer procedure and thorough evaluation of the axilla are recommended. Resection of a minimum of two sentinel nodes is recommended with the understanding that the number of FNR decreases as more sentinel nodes are identified. Because the pathologist can assess the nodes for the presence or absence of histological changes consistent with therapeutic effect in the node, collaboration is important. The presence of histological changes indicates that the node previously contained metastasis and has been converted to negative by systemic therapy. Identification of biopsy site changes in the sentinel node can also indicate that the sentinel node is, indeed, the node sampled before chemotherapy, which was positive for metastasis at presentation.

If persistent nodal disease is seen in the sentinel node(s) axillary dissection is recommended (Fig. 1). Thus, intraoperative assessment of the sentinel nodes to direct the extent of surgery is beneficial and can enable axillary dissection to be performed during the same operation.

Patients who are cN1 at presentation and for whom two or more sentinel lymph nodes cannot be identified or for whom sentinel lymph node surgery is unsuccessful and no sentinel lymph node can be identified should undergo axillary dissection (Fig. 1).

For patients with cN2 disease at presentation, the standard of care is still axillary dissection. In the ACOSOG Z1071 study, the number of FNR for this subgroup was 0 %; however, this was a small subgroup and, therefore, not large enough to draw the conclusion that sentinel lymph node biopsy is accurate for axillary staging of these patients. Further study is needed to determine if some patients with cN2 disease can be accurately staged by use of sentinel lymph node biopsy. This is particularly important, because the incidence of axillary pCR in the Z1071 study for cN2 patients was 46.1 %.

Further work is in progress to assess the effect of axillary ultrasound after completion of neoadjuvant chemotherapy, to determine whether this reliably reflects the nodal response to neoadjuvant chemotherapy and can be used to guide the selection of patients for sentinel node biopsy. If axillary ultrasound can be used to identify patients with resolution of their nodal disease on imaging, this may help ensure that sentinel node biopsy is used for the most appropriate patients. Axillary dissection would remain standard practice for patients at high risk of significant residual nodal disease.

Surgery to guide adjuvant radiation therapy

Nodal staging both at presentation and after completion of chemotherapy are major factors in determining which patients should receive local–regional radiation therapy. Although regional nodal radiation therapy is well-tolerated overall by breast cancer patients, thoughtful selection of patients is important to avoid the small but significant morbidities of treatment. Side effects include an increased risk of arm lymphedema, breast or chest wall edema, and death from cardiac and cerebrovascular events [4, 17, 18].

Node-negative after sentinel lymph node biopsy

Patients who are clinically node negative at presentation (cN0) and have no axillary lymph node metastases on sentinel lymph node biopsy post-chemotherapy (ypN0) do not require adjuvant regional nodal irradiation. Studies including NSABP B-18 and B-27 have shown local–regional recurrence is low for patients who are ypN0 after neoadjuvant chemotherapy [19, 20●]. The evidence suggests that some patients who are clinically node positive (cN+) and convert to pathologically node negative (ypN0) with neoadjuvant chemotherapy can avoid nodal radiation therapy [20●]. Patients at higher risk of recurrence, on the basis of poor prognostic factors, should be considered for nodal radiation therapy to include the axillary, the supraclavicular, and possibly the internal mammary lymph nodes [19, 21●]. These include patients with cN2-3 disease, lymphovascular invasion, pathologic tumor size >2 cm, or multifocal disease on pathology. These can be evaluated by use of the MD Anderson prognostic index which incorporates multiple factors to give a score from 0–4 [22●]. Local–regional recurrence-free survival at 10 years is 92 % for patients with a score of 0 or 1. This decreases to 84 % for patients with a score of 2 and 68% for patients with a score of 3 or 4. Other factors including estrogen receptor negative or triple-negative disease should also be considered when assessing prognosis for local–regional recurrence.

The NSABP B-51/RTOG 1304 protocol is investigating use of regional nodal radiation therapy for patients who convert from node-positive at presentation to node-negative after neoadjuvant chemotherapy [23]. Completion of this trial may aid further determination of the benefits of regional nodal radiation in this subgroup of ypN0 patients.

Node-positive

In the setting of surgery after neoadjuvant chemotherapy, the finding of positive lymph nodes during surgery indicates persistent disease after systemic therapy. Current standard practice in this setting includes both axillary dissection and regional nodal radiation. Further examination of the most appropriate management of the axilla for these patients is being evaluated in the Alliance A011202 trial. This study randomizes patients with positive sentinel lymph node(s) after chemotherapy to either level I and II axillary lymph node dissection or radiation therapy of the axilla to level I and II [24]. For all these patients, regional nodal radiation including the breast, the chest wall, the supraclavicular fossa, and internal mammary nodes is recommended.

Conclusions

Sentinel lymph node biopsy can accurately identify residual nodal disease after neoadjuvant chemotherapy, with acceptable sentinel lymph node identification and FNR for patients with clinically node-negative disease at presentation. In addition, sentinel node surgery can also be considered for axillary staging after chemotherapy for patients with node-positive disease at presentation. The information from sentinel lymph node biopsy can then be used to select patients for completion axillary dissection and adjuvant radiotherapy, on the basis of evolving evidence for nodal radiation for selected patients.

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Fig. 1. Sentinel lymph node biopsy to guide extent of axillary surgery after neoadjuvant chemotherapy. *SLN*, sentinel lymph node; *ALND*, axillary lymph node dissection; *cN0*, clinical N0 (node-negative); *cN+*, clinical node-positive; *cN1*, clinical N1 status; *cN2*, clinical N2 status