Published in final edited form as:

Curr Oncol Rep. 2009 January ; 11(1): 15–20.

Completion of Axillary Dissection for a Positive Sentinel Node: Necessary or Not?

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Abstract

Sentinel node excision has been widely accepted as the initial surgical step for evaluating the axilla for metastatic breast cancer. When the nodes are positive, the standard of care is to complete the axillary node dissection, a more extended procedure that carries an increased risk for morbidity. This article reviews data from sentinel lymph node trials, case series reports of outcomes when axillary node dissection was not performed in the setting of positive sentinel nodes, models for predicting the status of nonsentinel nodes, and the morbidity associated with axillary operations. Despite an approximate 10% false-negative rate, early results indicate that there is a much lower local recurrence rate after sentinel node excision alone and that systemic therapy may sterilize the axilla. In selected patients, it may be appropriate to forgo an axillary node dissection, although there are no randomized clinical trial data to support or refute this suggestion.

Introduction

As the use of sentinel lymph node (SLN) excision has become more widespread, some have questioned whether an axillary lymph node dissection (ALND) should be performed when the SLN has been proven positive. This is particularly an issue when the positive status of the node is not confirmed until after surgery. By that time, the patient often has been told that the nodes removed were negative, although she is cautioned to await the permanent hematoxylin-eosin (H&E) staining or immunohistochemical (IHC) review.

The perceived benefits to completing the axillary dissection are 1) decreased local recurrence, 2) improved survival, and 3) completion of staging, which may change therapy. The main disadvantages are the immediate risk of another operation and the long-term sequelae of the removal of the axillary content, such as lymphedema (LE) and pain. Moreover, in select cases it is probable that systemic or radiation therapy (RT) may control residual cancer without further operation.

Evidence From SLN Trials

There are well documented cases in which a false-negative rate associated with SNL dissections allowed positive nonsentinel lymph nodes (NSLNs) to remain unrecognized and therefore not removed. The National Surgical Adjuvant Breast and Bowel Project (NSABP) [1•] recently

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Disclosures No potential conflicts of interest relevant to this article were reported.

reported technical data from its randomized B-32 trial comparing SLN excision plus ALND even if the SLN was negative (group 1) to SLN excision alone (group 2). ALND was required for women in group 1 with a positive SLN. A false-negative rate of 9.8% was present in the group 1 patients. For an SLN to be considered positive, the metastatic focus had to be identified by H&E staining. Among patients in the SLN-positive group, at least one involved NSLN was found at ALND in 38.6%. Predictive factors for a positive NSLN on multivariate analysis included undergoing mastectomy rather than lumpectomy, clinical tumor size, tumor location, number of involved SLNs, and lymphovascular invasion (LVI); the latter was particularly significant [2]. Age was inversely related. Eventually, the data from this study should reveal the clinical significance of a false-negative SLN.

Recent reports address the issue of axillary recurrences after SLN excision alone. A population study from Sweden examined 3534 breast cancer patients, 2246 of whom had a negative SLN and did not undergo ALND [3]. At a median of 37 months, the rate of isolated axillary recurrence was 0.6%, local and axillary recurrence was 0.3%, and axillary plus metastatic disease was 0.3%. From their data, these investigators found an estimated isolated 5-year axillary recurrence risk of 1.1%. The axillary recurrence risk in Sweden in the pre-SLN era, after a negative ALND, was reported to be 1% at 5 years and 1.6% at 10 years.

A report from Amsterdam on 1019 breast cancer patients with 755 negative SLN excisions followed up for a median of 46 months further illustrates the good control of disease in the axilla with a negative SLN and no ALND [4]. These researchers found a rate of 0.25% for axillary nodal recurrence and for extranodal recurrence. The authors predicted a 0.4% axillary recurrence rate at 5 years. Overall survival (OS) was 95.9%, and disease-free survival (DFS) was 89.7%.

In a meta-analysis of axillary recurrence after negative SLN surgery only, van der Ploeg et al. [5•] looked at the outcomes for 14,959 patients in 48 published reports. At a median of 34 months of follow-up, there were only 67 axillary recurrences (0.3%). In the subgroup with more than 3 years of follow-up, results were similar. Recurrence was lower with the use of technetium Tc 99m sulfur colloid, superficial injection of the localizing agent, performance at a cancer center, and use of intraoperative frozen section. The authors mention the possibility that the use of RT with breast-conserving therapy and systemic agents contributed to the low recurrence rate.

Although the low local recurrence rate is very encouraging, it may be too soon to know the long-term impact on survival. This is especially true with the results from the meta-analysis of the Early Breast Cancer Trialists Collaborative Group (EBCTCG), which showed that local breast cancer recurrence did influence OS [6]. The results of 78 randomized trials including 48,000 patients were reviewed for the effect of RT and extent of surgery. When the difference in the local recurrence rate between treatment groups at 5 years was greater than 10%, at 15 years, there were differences in breast cancer mortality—44.6% versus 49.5% (a 5.0% absolute reduction). Although 75% of local recurrences were seen in the first 5 years, it took longer to demonstrate an effect on survival.

Prediction Models

When the sentinel nodes contain metastasis, there is a reluctance to leave potentially positive NSLNs in the axilla; therefore, the recommendation is to complete the ALND. However, in most of these axillae, there will be no residual cancer in the NSLN. Attempts have been made to predict that the axilla is free of disease in the hope of avoiding ALND, but all these models are based on information gathered from examining the nodes.

Van Zee et al. [7] published a nomogram to help predict the likelihood of positive NSLNs. This nomogram assigned value to various tumor and nodal characteristics. Points were assigned to each variable, added, and converted into a predicted probability of positive NSLN. Size of the nodal metastasis was not used. The area under the receiver operating characteristic (ROC) curve was 0.76 in the retrospective group and 0.77 in a later, prospective group. An area under the curve of 0.7 to 0.8 is considered to represent reasonable discrimination between disease and nondisease states. The nomogram these investigators devised is available online at www.mskcc.org/nomograms.

Other institutional groups have used their own data to validate this nomogram and to devise and compare predictive models of their own. Data from 200 consecutive patients at MD Anderson Cancer Center were used to validate this nomogram, and the area under the ROC curve was 0.71 [8]. A patient with a relatively low prediction for a positive NSLN by nomogram may be more likely to rely on this information to avoid an ALND. The nomogram's sensitivity in predicting a 10% or 15% probability of a positive NSLN was 94% and 80%, respectively, and its specificity was 26% and 43%. The authors caution that this tool does not determine who should or should not undergo ALND, but their work lends validity to its use in counseling patients.

From the Institut Curie, a study of the Memorial Sloan-Kettering Cancer Center (MSKCC) nomogram using 588 consecutive patients with positive SLNs and ALND showed it to be valid [9]. Twenty-seven percent of these patients had positive NSLNs. However, when the nomogram was applied to the 213 SLNs that contained only micrometastases, the area under the ROC curve was 0.538 (not much better than flipping a coin). A micrometastasis, defined here as less than 2 mm focus, was detected by IHC review in 44% of this subset but in only 5% to 9% of the population at MSKCC. In the original nomogram, it was the method of detection and not the size of the metastatic implant that mattered. The authors postulated that a different model might be needed for patients with micrometastases.

Kohrt et al. [10] devised an online calculator (<https://www3-hrpdcc.stanford.edu/nsln-calculator/>) for predicting NSLN status based on the population from the Bay Area SLN Study. The women in this study had a 40% SLN-positive rate, 9.8% false-negative rate, and 35.4% positive-NSLN rate. The authors tested three statistical techniques to develop their model. They included primary tumor size, LVI, and size of SLN metastasis and emphasized the synergistic interaction among these characteristics. Using their patient database and calculator, the authors found the area under the curve to be 0.83; it was 0.77 if they applied the MSKCC nomogram to the same database. They tested these two predictive models using a different database from Northwestern University and found areas under the curve of 0.74 and 0.62, respectively. The authors raised concerns about the generalization of any model because each is developed based on the characteristics of the population used in its development.

Most women with invasive cancer who are having SLN excision are prepared, following informed consent, to have the ALND during the same operation, which limits the usefulness of these models. Regardless of the model used, if the ALND is not performed, there is a risk of leaving behind positive NSLNs. Even if one of these predictor models is used to help in decision making, some patients without residual axillary metastases will continue to be subjected to the ALND because only a probability of significant pathology is produced.

Series of Positive SLNs Without ALND

There are retrospective observational series on outcomes in the cohort of women who did not undergo ALND despite having positive SLNs. Zakaria et al. [11•] from the Mayo Clinic looked retrospectively at patients with positive SLNs treated between 1998 and 2004. In 625 cases,

86 did not undergo ALND. In only one of these 86 cases was the metastatic focus diagnosed intraoperatively. Based on the MSKCC nomogram, the ALND group in this study had a mean chance for a positive NSLN of 46.9% (range, 4%-95%), versus 20% (range, 5%-65%) in those who elected not to undergo ALND. In general, the patients who did not undergo ALND were older and had smaller tumors with a small metastatic focus and a solitary positive SLN. Among the stage II patients, 50 had breast-conserving therapy, and full treatment data on 40 showed that 40% received nodal RT. Thirty-three patients underwent a mastectomy, 29 without RT. No axillary recurrences were noted, but distant metastases occurred in two patients, one with isolated chest wall recurrence and the other with local recurrence with distant disease. Thus far, there has been one cancer-related death. Follow-up data were not provided for the ALND group.

Between 1993 and 2005, 196 SLN-positive patients were treated without ALND at MD Anderson Cancer Center [12•]. Sixty-seven had N0[i+], 90 had N1mi, and 39 had N1 disease. Some of these women were enrolled in the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial and were randomly assigned to the group not receiving an ALND. Otherwise, the lack of ALND in this group was reported to be the result of patient preference expressed during consultation with their physician. At a median 29.5-month follow-up, none of the patients had developed an axillary recurrence. Standard adjuvant chemotherapy, usually anthracycline based, was offered to stage II patients, and the use of nodal RT was at the discretion of the radiation oncologist. Nearly 60% of the patients received chemotherapy and/or extended RT. There were three recurrences—one supraclavicular and three metastatic—and no breast cancer deaths. The authors speculated on the role of these modalities in controlling residual local disease.

In their report on 287 patients at MSKCC, Park et al. [13] noted that an increasing proportion did not have ALND if the sentinel nodes were not deemed positive on frozen section intraoperatively or when the nodes were not examined intraoperatively. In 1997, the authors' rate of completion ALND in this setting was 69% and decreased to 62% by 2003 to 2004. Using their nomogram, they found that the median predicted risk of a positive NSLN was 9% in those who did not have an ALND and 37% in those who underwent the procedure. The axillary local recurrence risk was 2% and 0.4%, respectively. LVI was present in the primary tumors of the patients who developed axillary local recurrence.

Takei et al. [14] reported on 1670 breast cancer patients who had undergone SLN excision. Their report included 127 patients, 107 with negative intraoperative pathology, who had a positive SLN and did not undergo ALND. Fifty-four percent of these 127 patients received nodal irradiation, and 92% received systemic therapy. In contrast, only 22% of the women undergoing ALND for a positive SLN had nodal RT, and 95% received systemic therapy. No patients who underwent nodal RT using a third radiation field had an axillary recurrence. The researchers found that a nuclear grade of 3+ and negative hormone receptor status increased the risk for regional nodal recurrence in the SLN excision-only group.

Common to the series discussed in this section are patients perceived to be at “low risk” for residual cancer in the axilla, namely those who are older and have small tumors with lower nuclear grade and estrogen receptor positivity. These nonrandomized, retrospective case series include patients who elected not to undergo ALND, often because the metastatic focus was not identified intraoperatively. Frequently, radiation fields were extended or ports were added to local therapy to include nodal regions.

Morbidity of Axillary Operations

Besides the fact that ALND may be unnecessary when the NSLNs are negative, the fear of morbidity from the operation may influence a patient's decision. The surgeon may also be reluctant to venture into the axilla a second time.

The risk of complications has been reported with SLN excision alone and with one- and two-stage ALND. This issue was addressed by the ACOSOG Z0011 study, which randomly assigned women with up to two positive SLNs to an ALND or no further axillary operation [15•]. The patients were assessed at 30 days and at 6 and 12 months. At 6 months, LE, determined by one arm circumference measurement, was found in 6% of those who underwent an SLN excision and in 11% who underwent ALND. Based on arm measurement, there was no statistically significant difference at 12 months; however, 13% of patients subjectively reported symptoms of arm swelling after ALND and only 2% reported swelling after SLN removal. There were more subjective complaints of paresthesia in the ALND group, particularly in younger women. Overall, 70% of those in the ALND group had a postoperative adverse effect, versus 25% of those in the SLN-removal cohort. A more recent evaluation of the data from the ACOSOG Z0010 and Z0011 studies comparing complications of single versus two-stage ALND showed that the number of nodes recovered and long-term complications were similar between the two groups [16]. There was no statistically significant difference in LE at any time point.

These data stand in contrast to findings by Husen et al. [17], who examined morbidity with one- or two-stage ALND in 370 patients who responded to a survey concerning arm symptoms. These women were also asked to measure their arms at three different levels. The lowest reported morbidity was in the group of women who had undergone only an SLN excision. There were significantly higher reports of swelling and numbness among the women who required a second operation to complete the ALND. The self-reported arm measurements were randomly distributed.

In a prospective multicenter Swiss study examining morbidity after axillary surgery, decreased mobility and more pain, seroma formation, and numbness were described in patients who underwent ALND versus SLN removal [18]. LE was diagnosed by subjective symptoms, objective signs, or arm measurements. At a median follow-up of 29 to 31 months, 3.5% of patients who had SLN excision, 15.7% who had ALND without RT, and 18.9% who had ALND plus RT had LE. There was no statistical difference in postoperative arm motion, pain, or LE between those who underwent ALND immediately and those who required a second operation. The incidence of postoperative wound infection was low in each group.

If SLNs are initially reported as negative, a second operation to complete the ALND may increase early postoperative complications. It appears that subjective patient complaints are more common after ALND, although even limited axillary node procedures cause morbidity.

Treatment Alternatives to ALND

If an ALND is not performed, the impact on treatment decisions must be evaluated; there may be alternative means to control residual disease in the axilla. RT for regional control has been suggested as an adjunct to surgery. Version 2.2008 of the National Comprehensive Cancer Network (NCCN) guidelines recommend (category 1) chest wall and supraclavicular nodal RT post mastectomy for patients with more than four positive nodes. The guidelines also recommend supraclavicular RT in conjunction with breast RT for women with four positive nodes who undergo breast-conserving therapy. The NCCN also strongly recommends adding this RT regime for postmastectomy patients with one to three involved nodes. Adding

supraclavicular RT is considered a category 2B recommendation, even when only one to three nodes are positive, which has led investigators to postulate substituting RT for ALND.

To evaluate the clinicopathologic features associated with having four or more positive nodes, Rivers et al. [19] looked at the records of 285 patients who had had ALND for positive SLNs. The authors estimated a 0.2% chance of finding four or more involved nodes in a T1 tumor with a single metastatic SLN, no LVI, and no extranodal extension. The presence of these tumor characteristics could be used as a surrogate for an ALND in planning regional therapy in this subset of women.

Data from the NSAPB B-04 trial support the use of RT as primary treatment of the axillae [20]. In this study, there was no significant difference during 25 years of follow-up in distant DFS or OS among women who were axillary node negative clinically and were randomly assigned to radical mastectomy, total mastectomy plus postoperative RT, or total mastectomy with ALND only if the axilla became positive. About 40% of these clinically node-negative axillae were positive on pathology review of the tissue from radical mastectomy. In the groups of women with clinically positive axillary nodes, there was no significant difference in distant DFS or OS, regardless of treatment with a radical mastectomy or total mastectomy plus RT.

The Italian Oncological Senology Group randomly assigned women with clinically negative nodes and invasive breast cancer up to 1.2 cm to no axillary treatment or axillary RT [21]. At a mean follow-up of 63 months, there were three cases of axillary metastasis (1.5%) in the untreated group and one case (0.5%) in the RT group. There was no difference in DFS at 5 years. A striking feature was the low axillary failure rate in both groups.

In their randomized trial with 15 years of follow-up, Louis-Sylvestre et al. [22] at the Institut Curie showed that long-term survival was identical in patients who underwent axillary dissection and those who had RT. The axillary recurrence rate was 1% in the surgery group and 3% in the RT group. The axillary dissection group had a 21% positive node rate, and these patients also received RT to the supraclavicular and internal mammary chains. In the RT group, the axilla and internal mammary chains were treated. Morbidity between the two groups was not recorded.

The European Organization for Research and Treatment in Cancer is conducting a study titled After Mapping of the Axilla: Radiotherapy or Surgery (AMAROS). The investigators are randomly assigning women with positive SLNs to ALND or axillary RT. This study should offer more definitive information on tumor recurrence after different treatment modalities.

ACOSOG Z0011 was designed to look at the survival impact of observation versus ALND in women with up to two positive axillary SLNs [15•]. However, accrual was slow and the study was closed prematurely. Survival data are not available.

The American Society of Clinical Oncology and the NCCN currently recommend that an ALND be completed if an SLN containing a metastatic focus beyond isolated IHC-positive cells is found [23]. However, most recommendations for systemic therapy take into account tumor-specific factors and node status and do not rely on the number of involved nodes.

Systemic therapy can also “sterilize” the axillary nodes. In the NSAPB B-18 trial, women receiving preoperative chemotherapy with doxorubicin and cyclophosphamide (AC) had a significantly higher incidence of pathologically negative nodes (58%) compared with those who had surgery first (42%) [24]. The preoperative addition of docetaxel to AC in NSAPB B-27 resulted in a 16% increase in negative axillary nodes [25].

The evaluation of patients before neoadjuvant chemotherapy may include a needle biopsy to pathologically confirm axillary metastases. After systemic therapy, the axillary lymph nodes usually are resected. Khan et al. [26] comprehensively evaluated the axilla before treatment; of 38 patients with confirmed positive nodes, one third had a completely negative ALND. Likewise, Newman et al. [27] reported a conversion to negative nodes in 32% of their patients who had had biopsy-proven positive nodes. Therefore, adjuvant chemotherapy and hormonal therapy may treat small amounts of residual disease in NSLNs.

Conclusions

Is completion of axillary dissection necessary for patients with a positive SLN? The knowledge gained so far from randomized trials cannot provide an absolute answer to that question. However, a qualified response is that a complete ALND may not be necessary for all breast cancer patients with positive SLNs. Thirty percent or more of women with a positive SLN will have negative NSLNs and are not likely to benefit from ALND. In addition, the prescribed systemic therapy and RT may sterilize the axilla, although prospective data are inconclusive.

ALND is also associated with increased morbidity, including LE, paresthesia, pain, and decreased mobility, symptoms that may affect quality of life. A second operation, if needed, may add short-term limited morbidity.

Axillary recurrence risk is low after SLN removal alone, even with a predicted false-negative rate of approximately 10%. Case series outcomes data from node-positive SLN patients who did not undergo ALND are encouraging. These patients generally were highly selected and often received more extended nodal radiation in addition to systemic therapy. On an individual basis, a patient and her physician may choose, given the information available, to forgo an ALND.

Although none of the prediction models is absolute in determining who has no further disease in the axilla, these tools can be used as a guide for the physician and patient. The prediction models cannot be used before the primary tumor and SLNs are removed. Therefore, most patients are prepared to undergo ALND as part of the breast operation and SLN excision. The dilemma over whether ALND should be completed arises most often when the nodal status is not definitively determined at the time of breast surgery. If the intention is to complete an ALND when SLNs are positive, efforts should be made to confirm the true nature of the axillary nodes in a manner that allows for a single operation.

At our center, patients with invasive breast cancer undergo a thorough preoperative evaluation of the axilla, including an ultrasound-guided core biopsy of any abnormal nodes. With this workup, we subsequently find positive axillary lymph nodes only 21% of the time [28]. During surgery, when the SLN is removed, an intraoperative touch preparation cytologic examination is performed. Patients with a positive node are prepared for an immediate ALND. Our intraoperative false-negative rate is 10% [29]. Results from a recently published study using the Breast Lymph Node Assay (GeneSearch; Veridex, Raritan, NJ), a rapid molecular reverse transcriptase polymerase chain reaction assay, show promise for decreasing the intraoperative false-negative SLN rate using this approach, with an observed sensitivity of 0.876 and specificity of 0.942, allowing for a better-informed intraoperative decision [30].

For the breast cancer patient who, despite these efforts, is found to have metastases in the SLN after her primary operation, treatment can be individualized based on her wishes, the characteristics of her tumor, and her physician's perception of the risks and benefits of the various options discussed in this review. It appears that for older women with T1a or T1b primary estrogen receptor-positive tumors, a solitary positive node, and no LVI, a low local or

distant recurrence rate may be expected if an ALND is not performed. Results from trials such as AMAROS and NSABP B-32 may provide future guidelines.

Acknowledgments

This work is supported in part by Public Health Service Grants U10CA-12027, U10CA-69974, U10CA-37377, and U10CA-69651 from the National Cancer Institute, Department of Health and Human Services.

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