Counterpoint: Sentinel Lymph Node Biopsy Is Not Indicated for Ductal Carcinoma In Situ

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Abstract
The purpose of axillary surgery in breast cancer is to provide prognostic information to guide the choice of adjuvant systemic therapy. Axillary surgery for ductal carcinoma in situ (DCIS) was abandoned in the 1980s because of the extremely low risk of lymph node metastases and high survival rates. Most women with metastases probably harbored an unrecognized focus of invasion or had metastases subsequent to an invasive local recurrence. Increased use of the less morbid sentinel node biopsy (SNB) for axillary staging of invasive cancer and the recognition that many patients will harbor micrometastases in nodes only recognized by cytokeratin immunohistochemistry (IHC) led two groups to perform SNB with IHC in women with DCIS. One group included all subtypes of DCIS and found metastases in 13% (half of which were detected only on IHC). The other group studied only patients with “high-risk” DCIS. They found metastases in 12% (7 of 9 by IHC only). These groups recommend SNB for women with DCIS. However, the use of SNB in DCIS should be tempered by the uncertainty of the prognostic significance of IHC-detected metastases, the conflicting results of these 2 studies, and the real potential to cause more harm than good from the morbidity of the procedure, the application of unnecessary axillary dissection, and the use of unwarranted adjuvant systemic chemotherapy. These results should be used to generate hypotheses for clinical trials addressing these problems. However, SNB for DCIS remains investigational and should not be generally applied. (JNCCN 2003;1:207–212)

The increased use of sentinel node biopsy (SNB) for staging breast cancer, with its lower morbidity compared with axillary dissection, has renewed interest in axillary staging for ductal carcinoma in situ (DCIS). Two groups have reported high rates of positive axillary nodes in women with DCIS studied using SNB. Most of these positive nodes were involved only by micrometastases detected only by cytokeratin immunohistochemistry.1–3 One group studied women with all histologic subtypes of DCIS and the other applied SNB to a subset believed to be more likely to have nodal metastases. Based on these data, another group recommended guidelines for the use of SNB with DCIS.4 Unfortunately, SNB for DCIS is not without cost. In addition to the substantial expense, SNB carries some risk of long-term morbidity, including lymphedema.5,6 Furthermore, the finding of “positive” nodes may lead to the use of cytotoxic chemotherapy, with its short- and long-term risks, despite the absence of evidence that such therapy is warranted. Although the results of these two pilot studies should promptly lead to further research, there is a potential for real harm with routine use of SNB in DCIS.

Purpose of Axillary Dissection
The main purpose of axillary lymph node surgery for invasive breast cancer is to provide prognostic information to guide the choice of adjuvant systemic therapy. Axillary surgery also prevents progression of cancer in the axillary basin in women with positive nodes. Axillary surgery itself only affects survival by guiding the choice of adjuvant systemic therapy. Evidence, including the long-term results of a large randomized clinical trial, clearly shows that, in and of itself, axillary surgery does not affect survival.7

Axillary Staging in DCIS
A large body of evidence shows that the incidence of nodal metastases with DCIS is extremely low. Although
there are isolated cases of DCIS in which axillary metastases are identified, in most series the rate of involvement of lymph nodes with DCIS is zero or close to zero. In a series of 20,556 patients with DCIS treated from 1985 to 1991 reported by the American College of Surgeons National Cancer Data Base, about one half of the cases had axillary dissection. Of these, 1% had positive nodes. It is generally believed that the incidence of node metastases is higher in cases of DCIS with high histologic grade and necrosis (eg, comedo-type DCIS). It is difficult to define the rate of node metastases for different subtypes of DCIS because of the very low numbers of cases with positive nodes in all reported series. However, more extensive lesions seen in cases in which DCIS was diagnosed as a palpable mass are more likely to harbor undiagnosed foci of invasive cancer than the smaller, mammographically detected lesions seen today. Therefore, it may not be appropriate to extrapolate the findings of such series to the less extensive DCIS that is diagnosed more often in the current era.

A similarly large body of literature shows that survival for women with DCIS is extremely high. In many case series with long-term follow-up, cause-specific survival approaches 100%. A few women in large series DCIS die from metastatic breast cancer. However, in most (though perhaps not all) of these patients, the source of metastatic breast cancer was probably recurrent disease or a new primary cancer. For example, only 1 of 270 patients with long-term follow-up after breast conserving therapy for DCIS developed distant metastases as a first recurrence. Similarly, none of the 707 women reported on by the Van Nuys Breast Center developed distant metastases as a first recurrence. Distant metastases were always preceded by an invasive local recurrence. In the few patients who have lymph node metastases with DCIS or who die from distant metastatic disease after a previous diagnosis of DCIS, it is likely that the original tumor harbored at least a small focus of invasive cancer that was the source of the metastases and that was not recognized pathologically.

The very low incidence of lymph node metastases and death with DCIS combined with 1) the increasing use of breast-conserving surgery for DCIS and 2) the substantial morbidity of axillary dissection led most authorities in the mid-1980s to recommend against axillary dissection for DCIS. Concrete evidence of this change in the standard of care is reflected in the design of the NSABP B-17 study of radiation with excision. When the study was begun in 1985, axillary dissection was required; however, it was dropped as a requirement after about one third of the patients were entered into the study. Current treatment guidelines specifically call for omission of axillary dissection for DCIS.

**Sentinel Lymph Node Biopsy**

Until recently, the only reliable method for determining the status of axillary nodes was dissection of the lymph nodes extending from the latissimus muscle to the medial border of the pectoralis minor muscle. Although this operation is safe, it carries a substantial risk of short- and long-term morbidity. As many as 10% to 20% of women develop permanent lymphedema after axillary dissection. Axillary dissection would not be necessary if the status of the lymph nodes could be defined without surgery. Unfortunately, no anatomic or functional imaging is accurate enough to replace axillary surgery for defining axillary node involvement with tumor. For example, \(^{18}F\)-deoxyglucose positron emission tomography detected metastatic disease in only 20% and 25% of nodes identified as positive by SNB.

Recently, sentinel node biopsy was introduced as a possible replacement for axillary dissection for invasive cancer. SNB involves mapping the lymphatic drainage from the breast to the axilla followed by removal of the lymph nodes identified by this mapping. Lymphatic mapping identifies an average of three nodes, most often in the low axilla. SNB has proven highly accurate in staging the axilla for invasive breast cancer. SNB has rapidly gained acceptance in high-volume centers. Analysis of practice patterns at NCCN centers from 1997 to 2000 showed that the breast teams at member institutions use SNB as routine care for invasive cancer. The NCCN incorporated SNB into its breast cancer guidelines as an alternative to full axillary lymph node dissection in 1998.

The accuracy of sentinel node biopsy may be due in part to the degree of pathologic scrutiny given to the sentinel nodes. Most groups section sentinel nodes at 2- to 3-mm intervals, whereas the routine examination of axillary nodes with dissection is limited to 1 or 2 sections of each node. Many groups supplement hematoxylin and eosin (H&E) staining of the node with immunohistochemistry (IHC) examination for
cytokeratin-expressing cells to identify very small metastatic deposits or individual epithelial cells. IHC identifies micrometastases or isolated tumor cells in the sentinel nodes in 5% to 20% of cases deemed negative on standard H&E examination. In one study in which nodes from 200 women with negative nodes on standard H&E were sectioned at 0.25-mm intervals, micrometastases or isolated tumor cells were found in 85 (42%). The ability to detect “metastases” on enhanced pathology, including cytokeratin IHC, led at least one author to state that this enhanced pathologic examination makes SNB more accurate than axillary lymph node dissection.

The prognostic significance of such metastases is not clear. Data conflict regarding whether such solely IHC-detected micrometastases convey the same risk of distant metastases as lymph node involvement defined by standard pathologic evaluation with invasive cancer. Some case series suggest that such metastases provide important prognostic information and others show no difference in prognosis for women with H&E-negative nodes regardless of the results of cytokeratin IHC.

Because of the uncertainty of the prognostic significance of IHC-detected metastases, cytokeratin IHC for evaluation of the sentinel node is still considered investigational. The National Cancer Institute clearly takes this position, as evidenced by the use of IHC analysis in the ongoing NSABP and American College of Surgeons Oncology Group studies. In both studies, cytokeratin IHC is performed on all sentinel nodes at a central laboratory, but patients and treating physicians are blinded to the results. The American Joint Committee on Cancer classifies limited disease (micrometastases or isolated tumor cells [ITC]) in axillary nodes as node negative. (Micrometastases are defined as tumor deposits greater than 0.2 but not greater than 2.0 mm. ITC are defined as single cells or small clusters of cells not greater than 0.2 mm, usually with no histologic evidence of malignant activity such as proliferation or stromal reaction.)

Sentinel Node Biopsy in DCIS

In 2 recent series of patients with DCIS who underwent SNB, the rates of node involvement were 12% and 13%, respectively. The majority of involved nodes were positive only on cytokeratin IHC. To date, there are no other reported case series of SNB with DCIS, and there is no long-term follow-up of patients with nodal micrometastases with DCIS.

The first study is from the H. Lee Moffitt Cancer Center. This group performed SNB on 224 women with DCIS and 16 with DCIS and microinvasion. The study included women with all pathologic subtypes of DCIS. Among the women with DCIS, 23 (10%) had true invasive cancer on the final excision. Of the remaining 195 women available for evaluation, node metastases were found in 26 (13%). Among these women, 13 of 26 (50%) were identified using IHC only. This study found no correlation between pathologic subtype or grade and the rate of node involvement.

The second study is from the Memorial Sloan Kettering Cancer Center. This group performed SNB on 76 women with DCIS and 31 women with DCIS and microinvasion. They selected women with DCIS for whom they thought there was “sufficient evidence that invasive cancer will be identified,” including those with a palpable or mammographic mass (55%), a core biopsy “suspicious for microinvasion” (24%), micrometastasis (53%), and pathologic characteristics of high grade and necrosis (72%). The node was positive in 9 (12%) cases of DCIS and 3 cases of DCIS and microinvasion. The node was only positive on cytokeratin IHC in 7 of 9 cases of DCIS and 1 of 3 cases of DCIS and microinvasion. This group did not report how many patients with DCIS identified on core biopsy had invasive cancer on surgical excision.

These groups suggest routine use of SNB for women with DCIS based on a number of arguments: 1) patients need to be provided with any therapy that may help them; 2) a substantial number of patients will have invasive cancer on final pathology, performing SNB at the initial operation avoids a second operation, and SNB may be less accurate after a previous excision; 3) SNB as a second operation leads to an unnecessary delay in treatment with substantial emotional and fiscal cost; and 4) IHC examination of the sentinel node may be a better indicator of the biologic potential of breast cancer than extensive pathologic examination of the tumor in the breast.

Each of these arguments has flaws. The first, that all advantages must be provided to our patients, is more than equally balanced by our commitment to “first do no harm.” Though SNB is safe, it causes real morbidity. In addition to surgical complications of
seroma and wound infection, as many as 1% of patients develop intraoperative anaphylactic shock from the isosulfan blue dye used to find the node. Furthermore, many women will have paresthesias and numbness in the distribution of the intercostal brachial nerves. There is also a risk of lymphedema.

In addition to surgical morbidity, there is a real risk that the finding of “positive” nodes by SNB in DCIS will result in additional therapy that is inappropriate and/or harmful. These women are likely to undergo completion axillary dissection with its known morbidity. Further, although neither of the two groups reporting these findings recommended adjuvant systemic chemotherapy for women with IHC-only metastases with DCIS, its use is the extension of the argument of offering anything that may help. If SNB is broadly applied in DCIS, undoubtedly many women will receive chemotherapy, with its recognized short- and long-term morbidity, for minimal or no gain. This practice is already being reported. Therefore, although SNB is safe, broad application in DCIS has as much potential to cause harm as it has to provide useful information.

The second argument, that SNB should be performed because invasive cancer may be found when the lesion is completely excised, is also not valid in patients undergoing lumpectomy. It is true that a percentage of women with DCIS on core biopsy will be found to have invasive cancer when the lesion is excised, and in many or most of these cases, the invasion will not be limited to microinvasion. However, SNB can be performed in women after excision of the breast lesion. Substantial literature shows that SNB is equally accurate after a previous excision. This is logical because our current concept is that the same node is a sentinel for the majority of the breast. This is evidenced by the accuracy of SNB with subareolar injection regardless of the location of the breast cancer. The exception to this argument is when mastectomy is used to treat DCIS because mastectomy precludes subsequent SNB.

No evidence indicates that the time delay of 2 to 3 weeks from delayed SNB has any impact on outcome. The short delay also gives patients the opportunity to research these issues and make informed decisions regarding treatment. It also is argued that the return to the operating room to perform SNB on the 10% to 15% who have invasive cancer incurs at least half the cost of performing SNB on all patients at the time of initial excision. The issue of cost is not clear, and no formal cost analysis of using SNB in all women versus selective return to surgery has been reported.

The argument that enhanced pathologic examination of the sentinel node may supplement or even replace careful examination of the primary tumor is also spurious. With standard pathologic evaluation of the tumor, patients with true DCIS have a remarkably high survival rate. However, more than half of the women with known invasive breast cancer and positive nodes die of breast cancer. Therefore, if as many as 13% of patients with DCIS had invasive cancer that was evidenced by positive nodes, the death rate from DCIS should be much higher. Yet, in no series of DCIS with long-term follow-up does a death rate even approach 10%. This is true even though these studies include a higher fraction of the “high-risk” DCIS associated with multicentricity or a palpable mass as seen more commonly in the past. It also is likely that most patients who died in these older series had less than optimal pathologic examination of the primary tumor and likely had invasive cancer that was not noted.

Serious caution also must be applied to the interpretation that IHC-detected epithelial cells in axillary nodes represent invasive cancer in the primary breast lesion. Recent reports suggest that these may simply be cells displaced into lymphatics at the time of needle biopsy or possibly by massaging the breast at the time of SNB. In another recent report, Tamhane et al examined lymph nodes on IHC from 26 women treated for DCIS using mastectomy. Most of these women had large, high-grade lesions with necrosis. On repeat review of the breast pathology, none had invasive cancer. There was an average of 5 lymph nodes in each mastectomy specimen. None of the women had positive nodes on H&E, even after examination after serial sectioning of the nodes for this study. However, in 6 women at least one node contained clusters of cytokeratin-positive cells in the peripheral sinus and cytokeratin-positive cell fragments in the node itself. The women had been followed up for an average of 5 years, and none had suffered a local or distant cancer recurrence. The authors hypothesized that these cells were displaced into lymphatics at the time of the previous diagnostic biopsy. They cautioned against overinterpretation of the presence of cytokeratin-positive cells in the lymph nodes with DCIS.
One additional cautionary note in interpreting these studies is that although these two series seem to show the same result (positive rates of 12% and 13%) on the surface, close examination shows that the results are actually somewhat conflicting. In reality, the series include distinctly different patient populations. The “positive” node rate was the same in both studies even though one study looked at “high-risk” cases and the other included all women with DCIS. If one group is “high risk,” we would expect this group to have a substantially higher rate of node involvement. This highlights the shortcomings of our understanding of DCIS and the uncertainty about the significance of SNB in DCIS. Conflicting data from the limited literature regarding SNB in DCIS should temper enthusiasm for its broad application.

In some circumstances performing SNB in women with DCIS may be reasonable. The most logical situation is when the primary breast operation will preclude subsequent SNB, such as with mastectomy. In addition, when the mammogram shows a spiculated mass that strongly suggests an invasive cancer, it may be reasonable in selected cases to proceed with lymph node staging at the primary procedure even if the needle biopsy showed only DCIS.

**Conclusions**

Broad application of SNB in DCIS will probably cause substantially more harm than good. There is clear evidence that survival with DCIS is much better than would be predicted if these lymph node “metastases” were clinically relevant. Previously, few patients died of DCIS. It is unlikely that they are dying now because physicians have a new technology. The only reasonable conclusion is that these preliminary results should be used to generate the hypotheses for prospective clinical trials to address the significance of nodal micrometastases in DCIS. The oncology community should move quickly to design and execute appropriate studies.

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