Point: Sentinel Lymph Node Biopsy Is Indicated for Patients With DCIS

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Key Words
Sentinel lymph node biopsy, DCIS, breast cancer surgery, lymph node metastasis

Abstract
Sentinel lymph node (SLN) biopsy, a new standard of care for staging invasive breast cancer, remains controversial for ductal carcinoma in situ (DCIS). Although DCIS has a natural history in which long-term distant disease-free survival (DDFS) is 98% to 99% and axillary node metastases are historically rare, three recent DCIS series have found SLN metastases in a surprising 6% to 13% of patients. The strongest argument for SLN biopsy in DCIS is the diagnostic uncertainty and inherent sampling error of conventional pathologic techniques. Definitive surgery (excision or mastectomy) reveals invasive cancer in 10% to 21% of patients with a preoperative core needle or surgical biopsy diagnosis of DCIS, all of whom become conventional candidates for SLN biopsy. In the absence of proven invasion, most positive SLN in DCIS are micrometastases detected by hematoxylin and eosin– and immunohistochemical-stained serial sections. An increasing body of evidence suggests that these are prognostically significant, not artifactual. We propose that DCIS patients with positive SLN have occult invasive cancers, and that the same may have been true for the 1% to 2% of DCIS patients who go on to develop distant metastasis, either after an invasive local recurrence or as a first event. We further suggest that the diagnosis of DCIS encompasses two patient populations: 1) a majority (perhaps 90%) with true in situ disease (or prognostically insignificant invasion), negative SLNs, and an expected DDFS of 100%; and 2) a minority (perhaps 10%) with occult invasion, positive SLNs, and an expected DDFS of perhaps 90%. Pending the development of predictive models for preoperative identification of this SLN-positive minority of DCIS patients, SLN biopsy is indicated in any DCIS patient who may have an underlying invasive cancer, especially those who require mastectomy. In DCIS, SLN biopsy may ultimately prove to be a more sensitive screening test for occult invasion than examination of the breast itself. (JNCCN 2003;1:199–206)

Sentinel lymph node (SLN) biopsy is a new standard of care for axillary node staging in patients with invasive breast cancer. Since its introduction by Krag et al in 1993 and Giuliano et al in 1994, early caution has rapidly given way to enthusiastic acceptance, and numerous validation studies worldwide have confirmed its feasibility and accuracy in a wide range of practice settings. Compared with conventional axillary dissection (ALND), SLN biopsy has greater sensitivity, and substantially less morbidity. Initially limited to patients with small invasive cancers, it has since proven suitable in virtually all patients with nonmetastatic disease, including T2/3 tumors, after neoadjuvant chemotherapy, and even in the setting of prophylactic mastectomy (in which occult invasive cancers are found in about 5% of cases). Less clear, and far more controversial, is the role of SLN biopsy in ductal carcinoma in situ (DCIS). DCIS is by definition a local process and cannot metastasize. The emphasis of all treatment is local control, and local control should equal cure. Regional lymph node staging should have no role in a disease where axillary metastasis occurs in fewer than 1% of patients and long-term survival approaches 100%. Indeed, the overwhelming body of opinion supports this position. Four European and two American consensus meetings, three major randomized trials, large retrospective datasets, the definitive text, and the current NCCN treatment guidelines (this issue) collectively find no role for axillary nodal staging in DCIS. Some even suggest that SLN biopsy for DCIS is “dangerous and unwarranted.” However, this article argues the opposite position. Three published studies of SLN biopsy for DCIS have found SLN metastases in a surprising 6% to 13% of cases.
We propose that, compared with conventional approaches, SLN biopsy in selected (and perhaps all) patients with DCIS can substantially improve the accuracy of diagnosis, staging, and prognostication, potentially changing treatment and outcome in some patients.

Is It Really DCIS?

As we have previously argued,\(^2\) the strongest basis for nodal staging in patients with DCIS is the diagnostic uncertainty of conventional pathologic techniques. The experienced clinician will be skeptical in accepting any diagnosis of DCIS, and with good cause.

First, a cytologic diagnosis of malignancy on fine needle aspiration (FNA) simply cannot differentiate between DCIS and invasive cancer. A substantial proportion of malignant FNA results, especially in the setting of a palpable mass,\(^1\) will prove to be invasive cancer and not DCIS.

Second, regardless of biopsy method, the pathologic diagnosis may be wrong. Expert pathologic review of DCIS cases from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17\(^3\) and the European Organization for Research and Treatment of Cancer (EORTC) 10853\(^4\) trials found invasive cancer in 2% and 3% of cases, respectively (Table 1). Equally significant was the downstaging of 7% of the NSABP and 4% of the EORTC DCIS patients to a benign diagnosis.

Third, the substantial advantages and increasing popularity of percutaneous image-guided core breast biopsy (fewer operative procedures and lower treatment cost) have not completely eliminated the main disadvantage: histologic underestimation.\(^5\) The two largest studies\(^5,\) of underestimation in patients with an image-guided core biopsy diagnosis of DCIS show a striking similarity of results (Table 1), with invasive cancer subsequently found in 10% to 21% of cases. In general, underestimation occurs less often with vacuum-assisted (“mammotome”) than with automated large-core biopsy devices,\(^6\) with 11-gauge than with 14-gauge cores,\(^7\) with more than than with 10 or fewer specimens,\(^8\) with calcifications than with masses,\(^9\) with smaller lesions,\(^10\) and with experience.\(^11\)

Fourth, a diagnosis of DCIS by surgical biopsy does not preclude underestimation. At definitive surgery, Cox et al\(^12\) and Morrow et al\(^13\) found invasive cancer in 12% and 7% of patients, respectively, after a surgi-

<table>
<thead>
<tr>
<th>DCIS Identified By</th>
<th>Invasive Cancer Found By</th>
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<tbody>
<tr>
<td>Initial pathologic interpretation</td>
<td>Pathologic re-review</td>
</tr>
<tr>
<td>Fisher et al(^14)</td>
<td>17/790 (2%)</td>
</tr>
<tr>
<td>Bijker et al(^15)</td>
<td>27/863 (3%)</td>
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<tr>
<td>14 gauge ALCBB</td>
<td>Surgical excision</td>
</tr>
<tr>
<td>Darling et al(^16)</td>
<td>14/67 (21%)</td>
</tr>
<tr>
<td>Jackman et al(^17)</td>
<td>76/373 (20%)</td>
</tr>
<tr>
<td>14 gauge DVABB</td>
<td>Surgical excision</td>
</tr>
<tr>
<td>Darling et al(^18)</td>
<td>8/47 (17%)</td>
</tr>
<tr>
<td>Jackman et al(^19)</td>
<td>38/348 (11%)</td>
</tr>
<tr>
<td>11 gauge DVABB</td>
<td>Surgical excision</td>
</tr>
<tr>
<td>Darling et al(^20)</td>
<td>18/175 (10%)</td>
</tr>
<tr>
<td>Jackman et al(^21)</td>
<td>69/605 (11%)</td>
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<tr>
<td>Core biopsy</td>
<td>Surgical excision or mastectomy</td>
</tr>
<tr>
<td>Cox et al(^22)</td>
<td>ns (13%)</td>
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<tr>
<td>Morrow et al(^23)</td>
<td>13/90 (14%)</td>
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<tr>
<td>Surgical biopsy</td>
<td>Surgical excision or mastectomy</td>
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<tr>
<td>Cox et al(^24)</td>
<td>ns (12%)</td>
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<tr>
<td>Morrow et al(^25)</td>
<td>9/61 (7%)</td>
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<tr>
<td>Surgical or core biopsy</td>
<td>Mastectomy</td>
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<tr>
<td>Cox et al(^22)</td>
<td>8/73 (11%)</td>
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<tr>
<td>Morrow et al(^23)</td>
<td>ns (12%)</td>
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<tr>
<td>Mastectomy**</td>
<td>Positive SLN biopsy</td>
</tr>
<tr>
<td>Cox et al(^22)</td>
<td>11/61 (18%)</td>
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</table>

Abbreviations are: ALCBB, automated large-core breast biopsy; DVABB, directional vacuum-assisted breast biopsy; N, number; ns, not stated.

*Underestimation, the proportion of patients with a DCIS diagnosis found on definitive surgery to have invasive cancer.

**Patients with a final pathologic diagnosis of DCIS (no invasion found in the mastectomy specimen).
diagnosis of DCIS (ie, no invasion found in the mastectomy specimen), 18% had positive SLN. In our own series (K Van Zee, personal communication), the SLN was positive in 15% of comparable patients. Perhaps the most striking example of underestimation is the observation that in about 30% of patients undergoing mastectomy for an occult breast cancer that presented as an axillary metastasis, no tumor is found in the breast. Assuming that the axillary metastasis could only have come from an occult focus of invasion in the breast, the ultimate cause of underestimation is the sampling error inherent in conventional histopathologic techniques and not the biopsy method.

This observation, although counterintuitive, is not at all surprising. Standard examination of a core biopsy specimen involves one or two slides; complete examination of the same 2-mm tissue core by standard 5 µm sections would require a total of 400 slides. If only the smallest proportion of the smallest tissue specimen is ever actually examined, the prospects for complete sampling of a surgical biopsy or even a mastectomy specimen are even more discouraging.

Mortality of DCIS

Pathologic underestimation is almost certainly an element of DCIS-related breast cancer mortality. Retrospective series of DCIS treated by mastectomy, more recent data from the era of breast conservation, and three major prospective randomized trials all cite a breast cancer-specific mortality of 1% to 2%. In Silverstein et al’s carefully documented report of their experience, all distant metastases and breast cancer deaths occurred after the development of an invasive local recurrence and might therefore be attributed entirely to the invasive disease. However, in both the NSABP and the EORTC trials (Table 2), among patients who developed distant metastasis, 28% of the metastases appeared as a first event or after non-breast locoregional relapse. These DCIS patients almost certainly had occult invasive disease undetected by conventional pathologic techniques. Therefore, the challenge for the clinician is to identify this subset of patients in advance.

Significance of Micrometastases

Lymph node micrometastases associated with invasive breast cancer are a well recognized phenomenon, but their prognostic significance remains a matter of debate. Many retrospective studies have addressed this issue using pathologic reanalysis (using serial sections [SS] or immunohistochemical [IHC] staining for cytokeratins) of axillary nodes initially read as negative. In a comprehensive 50-year review, Dowlatshahi et al showed that six of the seven largest studies (those with the statistical power to detect small differences in survival) found that patients with micrometastases had a 10% to 15% worse disease-free survival (DFS) or overall survival (OS) than patients whose nodes were truly negative. The five- and ten-year results of the largest study (International Breast Cancer Study Group [Ludwig]) found adverse prognostic significance for micrometastases detected by hematoxylin and eosin (H&E)-stained SS (10-year DFS, 23% worse; \( P = .001 \)), and marginal significance for those found by single-section IHC (10-year DFS, 8% worse; \( P = .09 \)).

Data from Memorial Sloan-Kettering Cancer Center support this conclusion as well. Tan et al used our current pathologic protocol for examining axillary SLNs to re-examine axillary nodes of 368 “node-negative” patients with invasive breast cancer. These patients were treated between 1976 and 1978 using mastectomy or ALND and no systemic therapy. Median follow-up was 17.6 years. Comparing patients who were truly node-negative, node-positive only on IHC, or node-positive on H&E, they observed 10-year DFS rates of 83%, 71%, and 50% (\( P < .001 \)), respectively.

| Table 2 Frequenty of Distant Metastasis and Breast Cancer-specific Death for DCIS Patients in Randomized Trials |
|---------------------------------|------------------|------------------|
|                                 | NSABP B-17* (8 year results) | EORTC 10853* (5 year results) |
| \( N \) patients                | 814               | 1002             |
| \( N \) with distant metastases | 19 (2.3%)         | 24 (2.4%)        |
| As first event                  | 5                 | 3                |
| after locoregional non-breast recurrence | 3 | 1 |
| after invasive breast recurrence (ipsilateral or contralateral) | 7 | 20 |
| \( N \) breast cancer deaths    | 14 (1.7%)         | 15 (1.5%)        |

Abbreviation is: \( N \), number.
Taken together, these results suggest that: 1) nodal micrometastases occupy the mid-range of a prognostic continuum, with expected associated long-term survival somewhere between that of patients who are truly node negative and those with macrometastases conventionally detected by single-section H&E; and 2) prognosis is better for patients with low-volume micrometastases detected only on IHC than for those with larger-volume micrometastases detected on SS/H&E.

The Logistical Barrier

Enhanced pathologic examination of ALND specimens was logistically prohibitive in the era before SLN biopsy. The first Ludwig study\textsuperscript{45} required about 1,600 slides to identify one additional node-positive patient. At the time of its publication in 1990, few institutions had the resources to pursue this methodology. SLN biopsy, a targeted examination of those few nodes (a median of 2 per patient) most likely to contain metastasis, now makes enhanced pathologic analysis by SS or IHC stains feasible on a routine basis.

For invasive cancers, the prognostic significance of SLN micrometastases remains a matter of debate and is the subject of prospective trials by both the American College of Surgeons Oncology Group (ACOSOG)\textsuperscript{48} and the NSABP.\textsuperscript{49} Enhanced pathologic analysis has other clear benefits for patients with invasive cancer: improved staging accuracy,\textsuperscript{4} a reduction in the rate of false-negative SLN,\textsuperscript{10} and a role in predicting the likelihood of non-SLN involvement in SLN-positive patients.\textsuperscript{31} However, all of these studies apply to patients with invasive cancer. How frequent and how significant are SLN micrometastases in DCIS?

### Studies of SLN Biopsy in DCIS

Pendas \textit{et al}\textsuperscript{26} first reported on SLN biopsy in DCIS, finding positive SLN in five of 87 (6%) consecutive patients with pure DCIS (Table 3). Of these five patients, two were found using H&E and three using IHC only. A completion ALND was negative in all five. Four of these five patients had high histologic grade and the remaining patient had a low-grade but extensive lesion. The authors concluded that SLN biopsy was suitable for DCIS patients with large or poorly differentiated tumors, and that SLN biopsy might be the most efficient way to screen the breast for occult invasive disease.

Klauber-DeMore \textit{et al}\textsuperscript{28} reported positive SLN in 9 of 76 (12%) patients with “high-risk DCIS.” Comprising about 20% of all DCIS diagnosed patients, all these patients were selected for SLN biopsy on the basis of suspected invasion and had one or more of the following: a palpable or mammographic mass, pathology suggestive (but not diagnostic) of invasion, high-grade histology, or extensive disease requiring mastectomy. Two of these nine patients were positive according to H&E and seven according to IHC only. A completion ALND was positive in one of six. The authors concluded that SLN biopsy was reasonable in a subset of DCIS patients at high risk of occult invasive disease, especially those needing mastectomy. An unpublished update of this experience (Table 3) has yielded similar results. We continue to perform SLN biopsy in high-risk DCIS (or about 25% of our DCIS diagnoses overall) and have found positive SLN in 32 of 325 (10%) patients.

Cox \textit{et al}\textsuperscript{27} recently updated the experience with SLN biopsy for DCIS at the H. Lee Moffitt Cancer Center. Among patients with a preoperative biopsy diagnosis of

<table>
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<tr>
<th>Study</th>
<th>Case selection method</th>
<th>N</th>
<th>SLN+/total</th>
<th>H&amp;E+/total</th>
<th>IHC+/total</th>
<th>ALND+/total</th>
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<tr>
<td>Pendas \textit{et al}\textsuperscript{26}</td>
<td>consecutive cases</td>
<td>87</td>
<td>5 (6%)</td>
<td>2 (2%)</td>
<td>3 (4%)</td>
<td>0</td>
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<tr>
<td>Klauber-Demore \textit{et al}\textsuperscript{28}</td>
<td>“high risk” (20% of all DCIS)</td>
<td>76</td>
<td>9 (12%)</td>
<td>2 (3%)</td>
<td>7 (9%)*</td>
<td>1/6 (17%)</td>
</tr>
<tr>
<td>Cox \textit{et al}\textsuperscript{27}</td>
<td>consecutive (70% of all DCIS)</td>
<td>195</td>
<td>26 (13%)</td>
<td>13 (7%)</td>
<td>13 (7%)</td>
<td>not stated</td>
</tr>
<tr>
<td>Moore \textit{et al}\textsuperscript{52}</td>
<td>“high risk” (25% of all DCIS)</td>
<td>325</td>
<td>32 (10%)</td>
<td>25 (8%)**</td>
<td>7 (2%)*</td>
<td>1/17 (6%)</td>
</tr>
</tbody>
</table>

Abbreviations are: SLN, sentinel lymph node; H&E, hematoxylin and eosin; IHC, immunohistochemistry; ALND, axillary lymph node dissection; N, number.

*SLN positive only on IHC.

**Four (1%) had macrometastases found on routine H&E and 21 (6%) had micrometastases found on serial sectioning.
DCIS, 23 of 224 (10%) were upstaged to invasive cancer by the definitive surgery. As was noted previously, upstaging was equally frequent after diagnosis by core biopsy (13%) and surgical biopsy (12%; Table 2). By final pathologic status, positive SLN were found in 26 of 195 (13%) patients with DCIS, 3 of 13 (20%) with microinvasive DCIS, and 8 of 20 (27%) with invasive cancer. Histologic type or grade of DCIS was not predictive of SLN metastasis. The authors concluded that SLN biopsy is suitable in all patients with DCIS, based on: 1) the high incidence of unsuspected invasion in patients with biopsy-proven DCIS; 2) the inability of histologic type or grade to predict SLN metastasis; and 3) the avoidance of reoperative ALND in DCIS patients found at mastectomy to have invasion.

Prognostic Significance of Positive SLN in DCIS

Some argue that the positive SLN in DCIS is not a biologic metastases at all, but rather an artifact reflecting the passive lymphatic transport of tumor cells and epithelial debris dislodged by manipulation of the breast. Others argue that a 10% rate of SLN metastasis in DCIS is meaningless, because “10% of DCIS patients do not die of distant disease.”

However, we propose, based on the previous evidence, that DCIS patients with positive SLN have unrecognized invasive cancer and that the same may have been true for those few DCIS patients who develop distant metastasis as a first event. This hypothesis is consistent with the natural history of DCIS. In fact, if nodal micrometastases confer a survival disadvantage of about 10% and are present in about 10% of patients with DCIS, then it can be predicted that about 1% (10% of 10%) of patients with DCIS might die of distant disease. We further propose that the diagnosis of “DCIS” comprises two populations of patients: 1) a majority (perhaps 90%) with true in situ disease (or prognostically insignificant invasion), negative SLN, and an expected DFS of 100%, and 2) a minority (perhaps 10%) with occult invasion, positive SLN, and an expected DFS of perhaps 90%.

Treatment Implications of the Positive SLN in DCIS

Standard surgical treatment for patients with SLN-positive invasive cancer is to perform a completion ALND, because non-SLN metastases are present in about half of SLN-positive patients. The limited data available suggest that this may not be necessary in SLN-positive DCIS; residual non-SLN disease was found in completion ALND in only 1 of 17 (6%) of our SLN-positive DCIS patients.

Patients with invasive cancer and SLN micrometastases found on H&E staining (whether on routine single section or SS) have a substantially worse prognosis than those who are node-negative. We suggest that DCIS patients with SLN micrometastases found on H&E should be considered to have occult invasive cancers and should be treated the same as any node-positive breast cancer patient, with systemic adjuvant therapy.

The prognostic significance of SLN micrometastases found only by IHC is probably intermediate between that of truly node-negative and H&E node-positive disease. Both our own data and that of Cote et al suggest that micrometastases found only on IHC will reduce 10-year DFS by about 10%. Two prospective trials, the ACOSOG Z0011 and the NSABP B-32, promise a definitive answer to this question. After SLN biopsy, physician and patient are blinded to the IHC results, and treatment decisions are made only on the basis of H&E staining.

The American Joint Committee on Cancer (AJCC) Staging Manual has begun to incorporate the above information. In the earlier fifth edition (1997), micrometastases 2 mm or less were classified as pN1a disease. These patients were stated to have a prognosis “similar to that of patients with pN0.” The current edition (2002) includes a lengthy discussion on micrometastases and subcategorizes them into “pN1mic” (micrometastases > 0.2 mm and ≤ 2 mm in size) and “pN0(i +)” (micrometastases ≤ 0.2 mm detected only by IHC). The editors acknowledge the possibility of prognostic significance, at least for pN1mic disease, and encourage H&E confirmation of IHC-detected micrometastases whenever possible.

Pending further study and the results of prospective trials, it is reasonable to assume that the DCIS patient whose SLN is positive only on IHC has an expected 10-year DFS somewhere between 99% and 90% (the threshold at which current guidelines dictate systemic adjuvant therapy) and to counsel the patient accordingly. In questionnaire studies, as many as half of all surveyed patients were willing to accept substantial treatment-related morbidity for a survival gain as small as 1%. This may be especially true for DCIS,
where the significance of a positive SLN is controversial and the exact magnitude of the risk is unknown.

**Conclusions and Future Directions**

For patients with a core needle or surgical biopsy diagnosis of DCIS: 1) 10% to 21% on definitive surgery prove to have invasive cancer; 2) SLN metastases are found in 6% to 13%; and 3) 1% to 2% will develop distant metastases, some of these as the first evidence of treatment failure.

We propose that SLN biopsy in high-risk (or perhaps even all) patients with DCIS will prove to be a more efficient and reliable screening test for invasion than examination of the breast itself. The positive SLN in DCIS indicates not only the presence of an occult invasive cancer, but an occult invasive cancer that is prognostically significant and may put as many as 10% of SLN-positive DCIS patients at risk of systemic disease. SLN biopsy is indicated in all DCIS patients suspected of having an underlying invasive cancer, especially those who require mastectomy.

The subject of SLN biopsy in DCIS requires further study with larger numbers of patients. Significant questions remain unanswered. Should SLN biopsy in DCIS be done selectively in high-risk patients or in all cases? Are there histopathologic or clinical features of DCIS that (singly or in combination) predict SLN metastasis? Are these features the same or different from those that predict local relapse after breast conservation? Finally, does a positive SLN in DCIS adversely affect survival, and if so, to what extent?

**References**


47. Tan LK, Giri D, Panageas K et al. Occult micrometastases in axillary lymph nodes of breast cancer patients are significant: A retrospective study with long-term follow-up (Abstr). Proc ASCO 2002;21:37a, #146.


