Sentinel Lymph Node Biopsy and Management of the Axilla in Ductal Carcinoma In Situ

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Ductal carcinoma in situ (DCIS) of the breast historically has been a disease detected by physical examination, diagnosed by open surgical biopsy, and treated by mastectomy and axillary dissection. It is now increasingly detected by screening mammography, diagnosed by needle core biopsy, and treated by lumpectomy, with axillary dissection having been abandoned and sentinel node biopsy being used in axillary staging.

However, outcomes related to sentinel node biopsy in DCIS have not been validated in well-controlled clinical trials. Current guideline recommendations are to use sentinel node biopsy when needle core biopsy is highly suspicious for invasive cancer or where there is a high-risk DCIS when lumpectomy identifies invasive breast cancer with the DCIS, or when mastectomy is performed for extensive DCIS. Routine use of sentinel node biopsy for DCIS is not supported.

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Noninvasive carcinoma of the breast or ductal carcinoma in situ (DCIS) is histologically defined as proliferating malignant ductal cells limited to the ducts themselves, without evidence of invasion through the basement membrane into the surrounding stroma. It is considered a local disease with no regional involvement. The 1980s brought increased public awareness of breast cancer and improved mammography equipment and techniques that resulted in more frequent diagnoses of nonpalpable occult breast carcinoma. The diagnosis of DCIS increased from 2% of all breast cancers to as high as 30% (1); it can be detected on screening mammography in 15%–20% of cases and accounts now for 14%–30% of all diagnosed breast cancers (1–3).

Historically, noninvasive breast cancer was detected by a palpable mass on physical examination. Diagnosed pathologically by open surgical biopsy, surgical treatment recommendation consisted of mastectomy and axillary lymph node dissection (ALND). Cure rates of greater than 90% and very low mortality resulted (4,5). However, as the trend toward breast conservation for early-stage invasive breast cancers increased, the justification for mastectomy and ALND with only 1% positive nodal rate and a 1%–2% mortality rate for noninvasive cancer became a focus of attention (6). Ernster et al. (7) evaluated the treatment of DCIS using Surveillance, Epidemiology, and End Results data from 1973 to 1992 and found a decrease in the proportion of patients treated with mastectomy from 71% in 1983 to 44% in 1992. In the 1980s, Silverstein et al. questioned the need for routine ALND in patients with DCIS and recommended that it be abandoned. One hundred patients who were treated with either mastectomy (n = 49) or breast-conserving surgery and radiation therapy (n = 51) and ALND all had negative axillary lymph nodes (ALN). After a 27-month follow-up, two patients had recurrence, and no mortality was encountered (2). Following Silverstein's report, the routine use of ALND was made optional in the National Surgical Adjuvant

Breast and Bowel Project (NSABP) B-17 trial, in which patients with DCIS were randomly assigned to lumpectomy with or without whole-breast radiotherapy (8). In a review of the NSABP DCIS protocols B-17 (lumpectomy +/- whole-breast irradiation) and B-24 (lumpectomy plus whole-breast irradiation ± tamoxifen), the risk of axillary recurrence in patients was found to be less than 1% (9). A similar finding of very low axillary recurrence in the long-term follow-up of DCIS patients treated with lumpectomy and whole-breast irradiation was reported by City of Hope Cancer Center (10). The very low recurrence rates found in these studies is less than the positive axillary metastasis rate associated with undiagnosed invasive breast cancer with DCIS present (6,11–13). Thus, the routine use of sentinel node biopsy (SNB) in patients with pure DCIS does not appear to be indicated because there are no survival data of any magnitude in patients treated by SNB who have an axillary recurrence.

With the increased use of screening mammography, DCIS tumors are being detected at an earlier time, at a smaller size, as nonpalpable, and associated with a lower rate of nodal involvement, if any. Although some tumors are commonly detected by the evaluation of suspicious mammographic abnormalities such as calcifications, pathological tissue diagnosis is necessary and is routinely accomplished by image-guided percutaneous core biopsy. This minimally invasive biopsy technique has clear benefits for the patient: It is less invasive than is open surgical biopsy and can establish a diagnosis that permits patients to have definitive surgical treatment planning before they undergo surgery. As good as the diagnostic accuracy of large core needle biopsy may be, understaging of the extent of disease can range from 13% to 44% of cases. Based on the 7th edition American Joint Committee on Cancer (AJCC) guidelines, microinvasive carcinoma is the extension of cancer cells beyond the basement membrane into adjacent tissues with no focus more than 1 mm in greatest dimension.

Upstaging from DCIS on the core biopsy to microinvasive or invasive disease in the final pathology review of the resected tissue can occur and therefore may eliminate the benefit of a one-stage surgical procedure (14–17). In a study by Jackman et al. (14) in patients with core biopsy–proven DCIS, underestimations for microinvasive or invasive disease were 1.9 times more likely with masses than with calcifications, 1.8 times greater with large core biopsy than with vacuum-assisted devices, and 1.5 times more frequent with 10 or fewer specimens per lesion than with more than 10 specimens. Understaging can present a problem for surgeons when nondiagnosed invasive cancer coexists with DCIS or if an undetected invasive tumor is present in other parts of the breast with potential axillary node involvement. The question then is, if one can predict the likelihood of microinvasive or invasive breast cancer in patients with an initial diagnosis of DCIS, then which patients should undergo axillary evaluation with sentinel lymph node biopsy (SLNB)?

As a result of the probability of upstaging after initial diagnosis, multiple investigators have stressed the need for SLNB in patients with high-risk DCIS (Table 1) (18–20). Independent predictors on final pathology have been established that indicate an increased likelihood of a microinvasive or invasive cancer being present. These include age 55 years or younger, mammographic abnormality greater than 4 cm, high grade, or comedo necrosis on histological evaluation (11,21–23). In addition, the presence of a palpable tumor has been found to be an independent predictor of a positive sentinel lymph node (21). The rationale for this view is based on reports that DCIS is frequently upstaged to microinvasion or invasive breast cancer on final surgical pathology (10%–38%) after a core biopsy is done that has been diagnosed otherwise (Table 2) (14–17,24–26). In these instances, SLNB has been used as a diagnostic tool to rule out invasive disease and as such allows the investigators the option of not having to return the patients to the operating room for a second procedure. Additionally, it serves as a fallback mechanism for a less than thorough analysis of the resected surgical specimen for invasive cancer.

Based on current 7th edition AJCC Cancer Staging Manual guidelines, DCIS is stage 0 (Tis, N0, M0). Within new guidelines, nodal micrometastases have been separated not only by size but also by method of detection (hematoxylin and eosin, immunohistochemical stain (IHC), and molecular). Pathological TNM staging can be described as: pN0 (i+), with a metastatic cell no greater than 0.2 mm (hematoxylin and eosin or IHC including isolated tumor cells); pN1mi with micrometastases greater than 0.2 mm and/or more than 200 cells but not more greater than 2.0 mm; and pN1a, metastases greater than 2.0 mm. This means that there is the possibility of staging DCIS as stage IB (T0N1mi) or stage IIA (T0N1) because T0 is designated as no evidence of invasive cancer

Table 2. Rationale for sentinel lymph node biopsy based on upgrading of ductal carcinoma in situ following core biopsy

Researcher	Number of patients	Upgrading after surgical biopsy, %
Wilke	675	13
Yee	398	25
Goyal	587	37.5
Jackman	1326	13.8
Lee	59	29
Dillon	93	47

(27). The high proportion of sentinel lymph node (SLN) involvement in patients with DCIS may be explained in that it represents either micrometastasis or isolated tumor cells that can only be identified by IHC used in sentinel lymph node evaluation. In a Memorial Sloan-Kettering review of 76 high-risk DCIS patients, 12% had metastases in the SLN, 77% of these diagnosed by IHC (19). The Moffit Cancer Center reported on 613 patients and showed a positive SLN rate of 5% with pure DCIS, with 77% of these found only by IHC staining (24). At this time, the clinical significance of IHC only–detected micrometastasis with invasive breast cancer is unknown and is even more questionable in patients with DCIS.

Conversely, other investigators have not seen the benefit of subjecting patients to additional surgical intervention unless invasive disease is confirmed, either on core needle biopsy or by final surgical pathology (28–30). In addition to the previously cited NSABP B-17/24 report and City of Hope Cancer Center experience, Murphy et al. (30) at Massachusetts General Hospital and Lara et al. (31) at St Barnabas Medical Center confirmed that in patients with DCIS or DCIS with microinvasion, a positive SLNB was not associated with a high risk of local or distant recurrence (8–10). Murphy reviewed 322 patients who underwent SLNB for DCIS or DCIS with microinvasion. Twenty-nine were found to have a positive SLN, 18 (5.6%) identified by IHC alone and 11 (3.4%) by hematoxylin and eosin. Seven positive SLNB patients had complete ALND, and no additional positive nodes were found. After a 47.9-month median follow-up, only 1 of 13 patients with local recurrence had a positive SLN (30). Lara reported on 102 patients and found 13 (13%) patients with a positive SLN. However, when the group with micrometastasis was compared with the group that experienced tumor recurrence, neither shared a common patient. The authors concluded that disease recurrence seemed totally unrelated to microscopic tumor deposition in the lymph node(s) (31).

The most common and dreaded morbidities following either SLNB or ALND, which may compromise the patient’s quality of life, are as follows: lymphedema, pain, nerve injury, paresthesias,

Table 1. Rationale for SLNB in high-risk DCIS*

Researcher	Number of patients	SLNB positive, n (%)
Pendas	87	5 (6)
Klauber-Demore	76	9 (12)
Cox	240	37 (15.4)

* DCIS = ductal carcinoma in situ; high risk = high grade, comedo necrosis, or large size; SLNB = sentinel lymph node biopsy.

Table 3. Functional and quality of life outcomes from the Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial of SLNB vs ALND*

Group	Sensory loss	Edema	Drains	Days in hospital
SLNB, %	14	4.5	17	4.1
ALND, %	37	17	79	5.4

* ALND = axillary lymph node dissection; SLNB = sentinel lymph node biopsy.

Table 4. Morbidity outcomes from the ACOSOG Z-11 trial comparing SLNB vs SLNB + ALND

Group	Wound infection	Seroma	Paresthesias (1 y)	Lymphedema (subjective, 1 y)	Total
SLNB, %	3	6	9	2	25
SLNB + ALND, %	8	14	39	13	70

* ALND = axillary lymph node dissection; SLNB = sentinel lymph node biopsy.

numbness, decreased limb use and shoulder dysfunction, and persistent pain. SLNB has become the primary means of axillary staging evaluation in patients with clinically node-negative invasive breast cancer because it is as accurate as axillary dissection but is less morbid. The NSABP B-32 trial, which completed accrual in 2004, randomized 5611 patients to receive SLNB alone vs SLNB plus ALND. In this trial, at least one SLN was identified in more than 97% of patients and was positive in 26%. The false-negative rate in the group who underwent an ALND was 9.7%. The SLN was the only positive node in 61.5%, and only 0.6% of patients had a positive SLN outside the axilla (32,33). The morbidity risk with this procedure is not zero. In both single institutional studies as well as in prospective trials, the sequelae of lymphedema, paresthesias, decreased limb use, persistent pain, and seroma have been reported (34–39).

The benefits of completing an SLNB over complete ALND reported by the Axillary Lymphatic Mapping Against Nodal Axillary Clearance trial included a decrease in axillary operative time, drain usage, hospital length of stay, and time to return to normal activities of daily living, but symptoms in the SNB group persisted in the follow-up period (Table 3) (35). The ACOSOG Z0011 trial, a phase III randomized study of axillary lymph node dissection in women with stage I or IIA breast cancer with a positive sentinel node, was designed to determine if observation alone was equivalent to ALND in overall survival. Patients with positive SLNs were randomized to undergo either ALND of level I and II nodes or observation. Unfortunately, this study was terminated early because of poor accrual. However, Lucci et al. reported data related to morbidity that revealed a significant difference of 25% to 70%, respectively, when comparing SLNB alone to SLNB plus ALND (Table 4). Up to a year following SLNB alone, symptoms of lymphedema and paresthesia persisted (40). The Swiss Multicenter Study, which revealed a benefit of SLNB over ALND with an overall decrease in morbidity from 68.6% to 39%, also demonstrated persistent morbidity following SLNB only. Long-term findings were numbness (37.7%–10.9%) and lymphedema (19.1%–3.5%) (Table 5) (41). Therefore, although SLNB shows a benefit over ALND, surgeons must consider the risk and benefits of this procedure in patients with minimal disease. Clearly, the risk

for quality of life and the burden of morbidity still persist in the SLNB group despite the lesser surgery. Patients should undergo SLNB only when the diagnosis of invasion or microinvasive disease is established either on core needle biopsy, on final surgical pathology, or in selected cases of high-risk or large tumors.

The final scenario for SNB in patients with DCIS is related to those patients undergoing mastectomy for extensive DCIS. Tumor characteristics that favor choosing mastectomy include the inability to obtain clear margins with breast conservation, large tumor size, multicentric disease, and contraindication to radiation therapy. These contraindications to breast conservation can also be considered risk factors for the presence of or progression to invasive cancer. In these patients who undergo mastectomy, the use of SLNB at the time of surgery has been evaluated (19–21,42). In a series by Tan et al. (42), upstaging to invasive cancer was seen in 33% of patients who underwent mastectomy for DCIS. Dominguez et al. (43) reported an 11% positive SLNB rate in such patients. SLNB has been reported to have a high identification rate (>96%) in patients who undergo mastectomy for invasive cancer (44,45), although it is less efficacious after mastectomy (46). The presence or risk of invasive cancer would indicate the need for ALND for nodal staging, even though most of these patients will have node-negative disease. Therefore, since SLNB following mastectomy is not uniformly effective, and due to an apparent increased risk for invasive cancer in patients undergoing mastectomy for DCIS, SLNB is a very reasonable procedure to carry out at the time of mastectomy.

DCIS with microinvasion is a distinct pathological entity with an unclear metastatic potential. Detailed sentinel node analysis with the use of hematoxylin and eosin stains as well as immunohistology (IHC) have generated controversy regarding outcomes related to micrometastases and nanometastases in patients with invasive breast cancer. These small clusters of cells may be more a result of displacement from biopsy than to the actual tumor biology of dissemination (47,48). IHC analysis for DCIS has resulted in the detection of cells that are of questionable prognostic significance. As previously described, in a review of 102 patients with a previous diagnosis of DCIS and negative ALND, Lara et al. (31) identified 13 patients with micrometastatic disease found only by IHC. In clinical follow-up ranging from 10 to 28 years, the overall disease recurrence rate was 12%, but no disease was detected in the micrometastatic group. Although serial IHC evaluation improved the ability to identify occult micrometastasis in this DCIS patient population, no apparent clinical significance was observed. Thus, the need to fanatically pursue these nodes becomes less clear and of questionable necessity.

The current American Society of Clinical Oncology guidelines for SLNB in early-stage breast cancer also recommend SLNB for patients undergoing mastectomy for DCIS because of the technical difficulty of performing SLNB after mastectomy, but

Table 5. Morbidity outcomes from the Swiss Multi-Center Study comparing SLNB vs SLNB + ALND*

Group	Impaired ROM	Numbness	Shoulder pain	Lymphedema	Total
SLNB, %	3.5	10.9	8.1	3.5	39
SLNB + ALND, %	11.3	37.7	21.1	19.1	68.6

* ALND = axillary lymph node dissection; ROM = range of motion; SLNB = sentinel lymph node biopsy.

the routine use of SLNB in patients who undergo breast-conserving surgery is not recommended. In circumstances of high-risk DCIS or large tumors, SLNB should be considered on a case-by-case basis (49). The 2001 Sentinel Lymph Node Biopsy Consensus Conference recommendations were similar. However, the Consensus generated a clearer statement recommending the use of SNB in patients who have DCIS with the presence of any type of invasive breast cancer but against its use in patients with DCIS without any type of invasive breast cancer (50).

In summary, at the present time, based on currently available data, the routine use of SLNB in all patients with pure DCIS is not warranted. For patients with proven invasive or microinvasive disease with DCIS, SLNB is supported. In those who undergo mastectomy for DCIS, SLNB is recommended at the time of mastectomy. A case-by-case decision should be made for the use of SLNB in patients who have high-risk DCIS or large tumors.

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