



Christine Zalewski. Orange Parrot Tulip III. Photograph.

Sentinel lymph node mapping in DCIS is controversial, and its role before and after neoadjuvant chemotherapy for locally advanced breast cancer is being defined.

The Role of Sentinel Lymph Node Biopsy in Patients With Ductal Carcinoma In Situ or With Locally Advanced Breast Cancer Receiving Neoadjuvant Chemotherapy

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Background: A significant number of patients who are initially diagnosed with pure DCIS will harbor missed or occult invasive disease at their definitive surgery. To provide more accurate staging information and to avoid a second operation, some investigators believe that SLN mapping should be performed in DCIS patients. The role of SLN biopsy after neoadjuvant chemotherapy in patients with advanced breast cancer is controversial.

Methods: A review of the literature was performed to determine the role of SLN biopsy in patients with DCIS or advanced breast cancer receiving neoadjuvant chemotherapy. The success rate of SLN biopsy after neoadjuvant chemotherapy was investigated as well as the percentage of positive SLNs in patients with DCIS.

Results: Two consecutive studies revealed metastatic disease to the regional lymph nodes in up to 13% of DCIS patients. In addition, 10% of DCIS patients were upstaged to infiltrating ductal carcinoma at their definitive therapy. The ability of the SLN to predict the status of the remaining non-SLNs after neoadjuvant chemotherapy is unknown. False-negative rates range from 0% to 33%. The success rate for SLN identification for the combined series varies from 84% to 97%.

Conclusions: SLN biopsy is a minimally invasive technique that can be used to evaluate the regional nodal status of DCIS patients. Performing a SLN biopsy during the initial surgical procedure may avoid a second operation in some DCIS patients who are diagnosed with invasive disease at their definitive operation. The success rate of sentinel node identification does not seem to be altered after neoadjuvant therapy. However, the ability of the SLN to predict the pathologic status of the adjacent non-SLNs remains unknown. Therefore, until further prospective randomized trials are conducted, it cannot be assumed that all the regional nodes have the same biologic response to chemotherapy as the SLN.

Ductal Carcinoma In Situ and Sentinel Lymph Node Biopsy

The single most important prognostic factor in breast cancer and most solid tumors is the status of the regional lymph nodes. Identifying breast cancer patients with metastatic disease to the axillary lymph nodes has diagnostic and therapeutic value, because most of these patients will benefit from adjuvant chemotherapy. SLN mapping is an effective and accurate method of evaluating the regional basin in breast cancer, and it can now be considered the standard of care. Since the status of the regional lymph nodes is the most powerful predictor of prognosis and overall survival in patients with breast cancer, it makes sense to continue to perform an axillary staging procedure.

Because the SLN biopsy technique histologically examines the lymph nodes in more detail, it has the potential of identifying patients who could harbor a focus of micrometastatic disease that would have been missed with routine methods. Other prognostic factors have been used to identify patients at risk for recurrence such as tumor size, hormonal receptor status, tumor grade, S-phase fraction, DNA index, and tumor ploidy. Currently, none of these factors predicts metastatic potential as reliably as the status of the regional lymph nodes. However, axillary nodal dissection may be associated with significant morbidity, including postoperative lymphedema, neuropathy of the arm, seroma, infection, and other local wound problems. These complications are associated with increased hospitalizations, increased overall costs, and considerable discomfort to the patient. Alternatively, the SLN technique offers patients a less invasive procedure with decreased morbidity while still providing an accurate method of staging the regional nodes.

The need to perform sentinel node biopsy in patients with DCIS is controversial. An estimated 60,000 new cases of in situ carcinoma are expected in 2004, and of these, 50,000 (85%) will be DCIS.¹ In the NSABP B-17 study, the overall local recurrence in patients treated with excision alone was 32% at 12 years. In contrast, patients treated with local excision plus irradiation had a lower local recurrence rate of 16%. This study suggests that DCIS is a heterogeneous group of breast diseases with varied potential for recurrence and metastases. Some experts believe that patients with DCIS should not undergo an SLN procedure. However, a select group of leading investigators believes that SLN biopsy should be performed in this subset of breast cancer patients.^{2,3} SLN biopsy in patients

with DCIS has demonstrated that not all DCIS tumors have the same biologic behavior and that a significant percentage of apparently pure DCIS tumors harbor missed or occult invasive disease.

One of the first studies evaluating the regional nodes in patients with DCIS using the SLN technology was conducted at the Moffitt Cancer Center (MCC). CK immunohistochemical staining was performed on 177 SLNs in 87 breast cancer patients with DCIS. Of the 87 patients with DCIS, 5 (6%) had a positive SLN.⁴ In 3 of these patients, the disease was found only on CK immunostaining, while the other 2 patients were both H&E and CK positive. Subsequently, another prospective study using the SLN biopsy technique was performed on patients with an initial diagnosis of DCIS.² Of 224 patients with a biopsy diagnosis of DCIS, 23 (10%) were upstaged to infiltrating ductal carcinoma at their definitive therapy. Furthermore, lymph node metastases were detected in 26 (13%) of 195 patients with DCIS. If nodal staging was not performed initially in DCIS patients with a final diagnosis of invasive breast cancer, then they would potentially be subjected to a more morbid operation, an axillary dissection, to obtain the nodal staging information. The authors concluded that SLN biopsy is a minimally invasive procedure that can be used to accurately stage breast cancer patients with an initial diagnosis of DCIS.² However, the study could not identify a subgroup of DCIS patients that were at high risk for invasive disease or metastatic disease to the regional lymph nodes.

Prior to the advent of screening mammography, DCIS presented as a palpable mass, nipple discharge, or an incidental finding in another benign breast lesion. At that time, the recommended treatment for DCIS was the same as invasive breast cancer because of the 2% to 10% recurrence rate of associated axillary nodal metastasis and the presence of microinvasion.⁵ In the past, a 5% incidence rate of nodal metastases was noted in DCIS patients who underwent a level 1 or 2 axillary dissection. In addition, it was found that comedo DCIS and extensive intraductal component histology were more likely to have nodal involvement and microinvasion.⁶ However, now that screening mammography is a routine procedure, symptomatic DCIS is an uncommon presentation, and less importance is placed on the assessment of the axilla.

The significance of DCIS with an occult focus of microinvasive disease has not been determined. Prior studies from the Memorial Sloan-Kettering Cancer Center found invasive disease in 12 (11%) of 110 patients undergoing mastectomy for DCIS.⁷ Other studies have found

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Submitted September 11, 2003; accepted January 5, 2004.

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other authors report no significant relationship with the companies/organizations whose products or services may be referenced in this article.

Abbreviations used in this paper: SLN = sentinel lymph node; DCIS = ductal carcinoma in situ; H&E = hematoxylin and eosin; CK = cytokeratin; AJCC = American Joint Committee on Cancer.

residual invasive disease in 21% of mastectomy specimens after a previous diagnostic breast biopsy revealed pure DCIS.^{8,9} These studies have also demonstrated that patients with DCIS and occult microinvasive disease can have metastatic disease to the regional lymph nodes. Furthermore, patients with comedo carcinoma histology have a higher incidence of microinvasive disease and are more likely to present with clinical signs, such as a palpable mass, nipple discharge, or Paget's change.^{7,10} Therefore, it is important to understand that patients with pure DCIS lesions on diagnostic breast biopsy can harbor an occult focus of microinvasive disease that may have not been detected histologically. Only a prospective, randomized study with a large population of DCIS patients who are studied over a long period of time will determine the true significance of lymph node metastases in DCIS patients.

Currently, the single most important prognostic factor in patients with breast cancer continues to be the status of the regional lymph nodes. However, evaluation of the axillary lymph nodes is not routinely performed on DCIS patients since regional nodal metastases is relatively low in patients who appear to have pure intraductal lesions. Recently, investigators have discovered that a significant percentage of DCIS patients have occult foci of microinvasive disease and that a certain subgroup of these patients will harbor metastatic disease to the regional lymph nodes. Experts at MCC and our center believe that if SLN biopsy is not carried out at the initial operation, then 10% to 21% of DCIS patients will require a second operation to evaluate their regional lymph nodes because of previously undetected infiltrating ductal carcinoma.^{2,4} Furthermore, all patients with DCIS who plan to have a mastectomy should undergo sentinel node biopsy since a small but significant percentage of these patients will harbor an invasive ductal component. These patients will require a complete axillary lymphadenectomy if a sentinel node biopsy is not performed at the initial operation, as the mapping procedure is impossible after a simple mastectomy. It is true that most patients with DCIS have a favorable prognosis, but the unidentified patients with metastases to the regional nodes may have a more aggressive clinical course. These patients must be identified and treated appropriately. This controversial issue can be resolved with the minimally invasive technology of SLN biopsy and CK staining of the sentinel lymph nodes. As a result, DCIS patients are accurately staged with minimal morbidity or complications. Furthermore, possible high-risk DCIS patients with a focus of microinvasive disease or metastatic disease to the axillary lymph nodes are identified early and treated in a more selective fashion.

A majority of the patients with metastatic breast cancer found in the SLN have low-volume disease and the disease is found at least initially with the CK stains. The interpretation of CK stains in the SLN is controversial. Many clinicians will use the CK stains to locate the

metastatic cells in the SLN, particularly if the H&E stains are negative and the disease is low-volume. However, they will require that the identified cells be documented to have malignant cytology by finding the cells with a follow-up section and an H&E stain, since cytology of cells is difficult to evaluate with the immunostains. The new AJCC staging system for breast cancer¹¹ incorporates CK staining in the pathologic N staging of the patient, but the metastatic focus has to be greater than 0.2 mm in size to classify the patient as N1. If cells are identified with either an H&E or CK stain and the focus does not reach this size criterion, the patient is given the N0 stage.

Likewise, the treatment of patients with micro-metastatic disease in the SLN (by the new AJCC staging criteria the focus has to be greater than 0.2 mm in size to be termed N1 and micrometastatic) is controversial, particularly in patients with primary tumors with good prognostic factors, such as the primary tumor being DCIS. However, in patients who are found to have N1 disease, a strong recommendation is usually made for systemic therapy — either adjuvant chemotherapy or hormonal therapy or both. If the focus of metastases does not reach 0.2 mm, the patient is not deemed to have N1 and with DCIS, the patient is usually observed.

The Role of SLN Biopsy in Patients Receiving Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy is being utilized with increasing frequency. The role of SLN biopsy in this group of patients is not clear. There appears to be little role for SLN biopsy in patients with palpable lymphadenopathy. However, in patients with locally advanced breast cancer and a clinically negative axilla, lymphatic mapping with SLN biopsy is debated. In a patient with inflammatory breast cancer, lymphedema of the breast results from the lymphatics being occluded by metastatic cells, resulting in inadequate lymphatic drainage. It would be anticipated that the mapping agents would also remain trapped in the breast and not travel to the SLN, making this a contraindication to mapping. In the two series in the literature specifically reporting on sentinel node biopsy in this group of patients, the false-negative rate was high.^{12,13}

A false negative is defined as a negative SLN but higher nodes in the lymphatic basin being positive. It is necessary to understand the convention for reporting false-negative results in the lymphatic mapping literature. This is defined as the false-negative cases ÷ (true positives + false negatives). In other words, in the patient population, what is the percentage of the positive patients that would be missed by performing the mapping procedure? This calculation includes only the patients who have positive nodal disease. One must take this into account when reviewing false-negative rates in the literature. Of 100 patients mapped, only 3 would have to have

a false-negative examination to result in a 10% false-negative rate by the standard false-negative definition applied to lymphatic mapping and SLN biopsy.

The false-negative rate is therefore dependent on the pretest probability of a positive node. The risk of axillary metastasis is related to primary tumor size, and this relationship is almost linear. A tumor less than 2 cm has approximately a 30% risk of axillary metastasis, and a tumor greater than 5 cm has a 70% risk.¹⁴ Mathematically, if 100 breast cancer patients were operated on and the pretest probability of a positive lymph node was 30%, a 10% false-negative rate would translate into 3 of the 30 node-positive patients incorrectly staged as node-negative. Therefore, 97 of the entire 100 patients would be accurately staged. On the other hand, if the pretest probability of a positive node is 70%, a 10% false-negative rate would translate into 7 of the 70 node-positive patients incorrectly staged as node negative and only 93 of the 100 patients would be accurately staged. Thus, it is recommended that a physician have significant experience with this procedure prior to embarking on SLN biopsy in individuals with large primary tumors.

The ability of the SLN to predict the status of the remainder of the axillary basin after neoadjuvant therapy is not known at this time. Kuerer et al¹⁵ reviewed a series of 191 patients with positive axillary lymph nodes at diagnosis. Following neoadjuvant chemotherapy, 23% were converted to a negative pathologic axillary status. Eleven series were identified in the literature that reported on SLN biopsy after neoadjuvant chemotherapy.^{12,13,15-24} The SLN identification rate for the combined series was 89.7% (322/359) and varied from 84.3% to 97.6%. Though series have reported on the successful identification of a SLN after neoadjuvant therapy, the question remains: Is the SLN reflective of the pathologic status of the remaining nodes? Could there possibly be a differential response to the neoadjuvant chemotherapy in the SLN vs neighboring non-SLNs? The false-negative rates reported in the literature range from 0% to 33%.^{12,13,15-24} Five of the series reported false-negative rates greater than 10%, and 5 of the series reported no false negatives. All the series are relatively small, varying between 14 and 51 patients.

It is difficult at this point to believe that all the lymph nodes would respond to chemotherapy equally well and if the SLN has been rendered pathologically free of disease, the higher echelon nodes will also have had a complete pathologic response. For this reason, we believe it makes intuitive sense to proceed with SLN biopsy prior to initiation of neoadjuvant therapy. This is the approach utilized at our center. Even with a large primary tumor, the presence of nodal disease has a significant impact on prognosis and may alter treatment recommendations. If an axillary lymph node were clinically positive, we would proceed with fine-needle aspiration in the office setting for confirmation. However, if the patient is clinically node negative, we proceed with SLN biopsy prior to neoadjuvant

chemotherapy. SLN biopsy can be performed in conjunction with placement of a port and open breast biopsy if needed. If the SLN were positive, a complete axillary lymph node dissection (CALND) would be recommended at the time of the definitive surgical therapy; if the SLN was negative, a CALND at the completion of neoadjuvant therapy may not be necessary.

Our approach of proceeding with SLN biopsy prior to neoadjuvant therapy is based on the premise that all lymph nodes may not necessarily respond uniformly to chemotherapy. Therefore, if the SLN was sterilized of metastatic disease by neoadjuvant chemotherapy, we do not feel confident this represents the status of all the regional nodes. We contend that the literature as outlined above does support a low false-negative rate in this setting for many of the studies. This remains a viable area for future research.

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