



An update of sentinel lymph node mapping in patients with ductal carcinoma in situ

Caren Wilkie, M.D.^{a,*}, Laura White, B.S.^a, Elisabeth Dupont, M.D.^a, Alan Cantor, Ph.D.^b, Charles E. Cox, M.D.^a

^aDepartment of Surgery, H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, 12902 Magnolia Drive, Suite 3157, Tampa, FL 33612, USA

^bDepartment of Biostatistics, H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, Tampa, FL, USA

Manuscript received June 5, 2005; revised manuscript June 10, 2005

Presented at the Sixth Annual Meeting of the American Society of Breast Surgeons, Los Angeles, California, March 16–20, 2005

Abstract

Objective: The purpose of our study is to further clarify the incidence of ductal carcinoma in situ (DCIS) patients that are upstaged upon final pathology and/or have metastatic disease in the axilla.

Methods: All patients were diagnosed with DCIS or DCIS with microinvasion (DCISm) on their diagnostic biopsy and received a sentinel lymph node (SLN) biopsy between 1994 and 2004. Six hundred seventy-five patients were divided into 613 patients with DCIS and 62 patients with DCISm.

Results: Sixty-six of 675 (10%) were upstaged to invasive cancer. Fifty-five of 613 (9%) patients with DCIS were upstaged, whereas 11 of 62 (18%) patients with DCISm were upstaged. Forty-nine of 675 (7%) patients had +SLN. Twenty-two of 49 (45%) patients with +SLN had invasive carcinoma or DCISm on final histology.

Conclusions: After review of histology, grade, type of biopsy, and mammographic findings, the combined findings of high grade, mass by mammography, and microinvasion predict patients at higher risk for invasive carcinoma. Selective utilization of SLN biopsy in DCIS is recommended. © 2005 Excerpta Medica Inc. All rights reserved.

Keywords: Ductal carcinoma in situ; Sentinel lymph node mapping; Breast cancer; Lymphatic mapping; Upstaging; DCISm; DCIS with microinvasion

Sentinel lymph node biopsy has evolved to become the primary means of axillary lymph node evaluation in patients with node negative breast cancer [1–3]. The morbidity of the procedure is low [4,5], and a negative sentinel lymph node reliably predicts node negative disease, allowing 60% to 70% of breast cancer patients to avoid axillary lymph node dissection [1].

Ductal carcinoma in situ (DCIS) comprises 25% to 30% of breast cancers detected by mammographic imaging [6]. Ductal carcinoma in situ with microinvasion (DCISm) is less frequent [7] and is defined as ductal carcinoma cells extending beyond the myoepithelial layer of the duct in foci less than 1 mm. The published axillary nodal metastases rate in DCIS is less than 1% [8], and because of this low

metastatic potential, nodal evaluation in patients with DCIS is not routine. However, published studies have relied on tumor registry data, where the definitive diagnosis of DCIS is established [9,10] to draw conclusions about treatment planning. Herein lies a major flaw because definitive diagnosis cannot be achieved until the final pathology review and may vary greatly from the biopsy diagnosis. The focus of this investigation is based on the data derived from the initial biopsy report as the patient would present to the surgeon for preoperative decision making.

Because DCIS and DCISm are not usually palpable and are mammographically detected calcifications, the diagnosis is usually based on stereotactic core biopsy. There is a high degree of concordance between histopathology of specimens obtained at stereotactic core biopsy and surgical open biopsy, but in 20% of cases of DCIS diagnosed by stereotactic core biopsy, invasive cancer is found after definitive surgical resection [11,12]. Surgeons make treatment deci-

* Corresponding author. Tel.: +1-813-972-8480; fax: +1-813-979-7287.

E-mail address: coxce@moffitt.usf.edu

sions based on stereotactic core biopsy data, and the presence of invasive cancer at the time of lumpectomy would require a second operation to evaluate axillary sentinel nodes. In addition, if a mastectomy is performed for DCIS and invasive cancer is found in the mastectomy specimen, a sentinel lymph node biopsy is no longer possible and an axillary dissection would be required.

Currently, there are no reliable prognostic factors to accurately predict the probability of invasive carcinoma in patients with a biopsy diagnosis of DCIS or DCISm [13]. There is some correlation with a palpable or mammographic mass [14,15] and microinvasion on biopsy histology [13,15]. The purpose of this study was to clarify the incidence of patients with a biopsy diagnosis of DCIS and DCISm who are upstaged to invasive carcinoma at the time of definitive resection and the incidence of axillary metastases. Prognostic factors were also evaluated to determine if selective sentinel lymph node biopsy could be recommended in subgroups of patients with a biopsy diagnosis of DCIS who are at highest risk for being upstaged to invasive carcinoma.

Patients and Methods

Patient population

From April 1994 until September 2004, 675 patients with a biopsy diagnosis of DCIS or DCISm were prospectively entered into a database at the H. Lee Moffitt Cancer Center and Research Institute. Current compliance guidelines were followed, and institutional review board approval was obtained to review this series of patients. All biopsy slides were reviewed by breast pathologists at the H. Lee Moffitt Cancer Center and Research Institute to confirm the diagnosis. Patient clinical characteristics, pathologic data, treatment methods, and mammographic data were prospectively recorded into a computer database, and a retrospective review was then performed. All patients received a lumpectomy or mastectomy and sentinel lymph node biopsy.

Prognostic factors such as grade, type of biopsy, histological subtype of DCIS at biopsy, presence of necrosis, presence of a palpable mass, and mammographic findings were all analyzed to correlate with presence of invasive carcinoma after definitive resection. When categorizing DCIS grade, patients were placed into the highest grade category seen in the biopsy specimen. When evaluating histologic subtype, patients were placed into the comedo category if any necrosis or comedo histology was noted in the specimen. When evaluating mammography data, patients with findings of a density, architectural distortion or a mass were all categorized as a mass. All patients with findings of calcification only were categorized as calcifications, but in the subgroup of patients with calcifications who were upstaged to invasive carcinoma at the time of definitive surgical resection, the extent of the calcifications was noted. Extensive calcifications were defined as multifocal

areas of suspicious calcifications or calcifications involving more than 1 quadrant of the breast by mammography.

Surgical and pathological techniques

Lymphatic mapping was performed using a combined blue dye and radiocolloid technique followed by breast massage as described previously [13,16]. Imprint cytology was utilized for intraoperative sentinel lymph node evaluation and the node(s) was then processed by sectioning into 2-mm sections. All sections were then submitted for paraffin blocks. Step sectioning was then performed and hematoxylin and eosin staining as well as monoclonal antibody staining against low-molecular weight cytokeratin (CK; CAM 5.2, Becton Dickinson Immunocytometry System, San Jose, CA) was then performed as previously described [13].

Statistical analysis

The chi-square test for proportions was used to determine significance with respect to DCIS grade analysis as a predictive factor for invasive carcinoma. The chi-square test was also used to compare core biopsy histology concordance and surgical biopsy histology concordance. Logistic regression analysis and the chi-square test for proportions were used to correlate specific mammographic findings with risk of invasive carcinoma and determine statistical significance.

Results

Six hundred thirteen patients (91%) had a biopsy diagnosis of DCIS, and 62 (9%) had a biopsy diagnosis of DCISm.

Rate of invasive carcinoma with surgical resection

Overall, 66 out of 675 patients (10%) were upstaged to invasive carcinoma upon definitive surgical resection. Within the DCIS subgroup of 613 patients, 55 (9%) were upstaged, and 11 out of 62 (18%) of patients with a biopsy diagnosis of DCISm were upstaged. Analysis of invasive tumor size revealed that 58 patients had T₁ lesions, 7 had T₂ lesions, and 1 had a T₃ lesion.

Sentinel lymph node metastases

Of the 559 patients with a definitive diagnosis of DCIS, 27 (5%) had a positive sentinel lymph node. Nineteen (70%) were detected only by immunohistochemical (IHC) staining (Table 1). Fifty-one patients had a definitive diagnosis of DCISm. This included 34 patients with a biopsy diagnosis of DCISm and 17 patients who were upstaged after a biopsy diagnosis of DCIS. Seven of the 51 patients (14%) had a

Table 1
Final pathology and correlation with lymph node metastases

Final pathology	Positive node (%)	IHC ⁺ (%)
DCIS	27/559 (5)	19/27 (70)
DCISm	7/51 (14)	5/7 (71)
IDC	15/66 (23)	4/15 (27)

positive sentinel lymph node, and 5 (71%) were detected only by IHC staining (Table 1).

A total of 66 patients had a definitive diagnosis of invasive carcinoma. Fifteen (23%) of these patients had a positive sentinel lymph node, and 11 (73%) were detected by hematoxylin and eosin staining (Table 1).

The biopsy diagnosis was established using stereotactic core biopsy or open surgical biopsy. Among the 613 patients with a biopsy diagnosis of DCIS, 290 (47%) underwent core biopsy and 301 (49%) had excisional biopsy. Nine patients (2%) had an incisional biopsy or fine-needle aspiration. In the 62 patients with a biopsy diagnosis of DCISm, 20 (32%) had a core biopsy, 40 (65%) underwent excisional biopsy, and 2 patients had an incisional biopsy. In 13 patients, type of biopsy was unavailable.

Analysis of biopsy type and correlation with subsequent invasive carcinoma at surgical resection revealed that in the subgroup of patients with a biopsy diagnosis of DCIS, 15 of 301 (5%) of patients who had an excisional biopsy and 38 of 290 (13%) of patients who had a core biopsy were upstaged to invasive carcinoma, and this difference was statistically significant ($P \leq .002$). However, in the subgroup of patients with a biopsy diagnosis of DCISm, 4 of 40 (10%) of patients who had an excisional biopsy were upstaged and 6 of 20 (30%) of patients who had a core biopsy were upstaged. This difference was not statistically significant ($P = .061$).

A total of 603 patients had biopsy grade data available, and this was correlated with subsequent invasive carcinoma at definitive resection. Grade III biopsy histology was noted in 37% of the DCIS subgroup. As noted in Table 2, 30 of 228 (13%) patients with grade III biopsy histology were upstaged to invasive carcinoma, and this was statistically significant ($P \leq .003$). Histopathologic subtype analysis failed to show a clear correlation between comedo histology/necrosis and risk of invasive carcinoma or axillary metastases (Table 3).

Mammography data were available for 434 patients, including all 66 patients who were upstaged to invasive carcinoma. These results are summarized in Table 4. Logistical

Table 2
Biopsy grade and risk of IDC

Grade of DCIS on biopsy	No. of patients*	No. of upstaged (%)
I, I/II, II	313	21 (7)
II/III, III	228	30 (13)

$P = .003$.

* Grade unavailable in 72 patients (3 upstaged to invasive).

Table 3
Biopsy histology and risk of IDC or +SLN

Histopathologic subtype	IDC (%)	+SLN (%)
Comedo (195)	16/195 (8)	12/195 (6)
Cribriform (131)	12/131 (9)	16/131 (12)
Micropapillary (13)	0/13	4/13 (31)
Papillary (7)	0/7	2/7 (29)
Solid and other (264)	26/264 (10)	11/264 (4)

regression analysis was then performed to determine the odds ratio for presence of a mass and risk of upstaging as well as the presence of calcifications with risk of upstaging. This analysis revealed that patients with a mass by mammography were twice as likely as patients with microcalcifications to be upstaged to invasive carcinoma (95% confidence interval 1.08–4.65, $P = .0298$), which was statistically significant.

A review of clinical examination findings was also performed. This showed that in the 66 patients who were upstaged to invasive carcinoma, 8 (12%) had a palpable mass. Sixteen (4%) out of 368 patients who were not upstaged had a palpable mass.

Comments

Sentinel lymph node biopsy is not currently recommended for the surgical management of DCIS, and the low incidence of nodal involvement (5% in this study) does not support routine use of sentinel node evaluation. In fact, the majority of positive sentinel lymph nodes in patients with a biopsy diagnosis of both DCIS and DCISm were positive only by cytokeratin staining, and the clinical significance of IHC positive lymph nodes is uncertain. However, Lara et al [17] showed axillary micrometastases in 13% of DCIS patients. These patients were followed clinically for a minimum of 10 years, and none developed recurrence or systemic disease. Therefore, the presence of micrometastases (IHC+) in sentinel lymph nodes of patients with DCIS does not mandate an axillary lymph node dissection.

As an update to a previous sentinel node mapping study in DCIS [13], it is important to compare data to validate or refute results and conclusions. This analysis is summarized in Table 5. In the previous analysis, there were no strong prognostic factors to correlate with a final diagnosis of invasive carcinoma. The current update includes 675 patients, and the numbers are large enough to provide the

Table 4
Risk of IDC based on mammography findings

X-ray findings	No. of patients	No. of upstaged (%)
Calcifications	327	43 (13)
Mass	55	9 (16)
Mass + calcification	52	13 (25)

Table 5
Comparison of upstaging and +SLN analysis

	Cox et al, 2001 (%)	Current update (%)
Initial diagnosis		
No. with DCIS upstaged	23/224 (10)	55/613 (9)
No. with DCISm upstaged	7/16 (44)	11/62 (18)
Final diagnosis		
No. with DCIS, +SLN	26/195 (13)	27/559 (5)
No. with DCISm, +SLN	3/15 (20)	7/51 (14)
No. with IDC, +SLN	8/30 (27)	15/66 (23)

power to detect significance. In addition, clinical and mammographic findings were analyzed in this update and the presence of a mass was significant.

DCIS is not one disease. The behavior and prognosis are a function of tumor biology, and some types of DCIS tumors are more aggressive than others. These higher-risk tumors are more likely to be associated with invasive carcinoma when definitive resection is performed, and sentinel lymph node evaluation is important in these patients.

Predictive factors such as microinvasion at the time of biopsy and high grade are associated with a higher incidence of upstaging (16% and 13%, respectively) to invasive carcinoma. Presence of a mass by mammography doubled the risk of invasive carcinoma, and core biopsy is also associated with a greater risk for upstaging in DCIS (20%–25%) [11]. However, our previous report [13] and the report of Lee et al [18] showed no difference between vacuum-assisted core biopsy and surgical biopsy when comparing the risk of upstaging DCIS to invasive carcinoma.

The tumor biology of DCIS is still poorly understood, and diagnostic technology to accurately predict DCIS behavior is lacking. The traditional surgical paradigm in DCIS, which concludes that nodal evaluation is never required, fails to consider higher-risk disease and the associated higher incidence of invasive carcinoma when definitive resection is performed. Selective utilization of sentinel lymph node biopsy in DCIS is optimal. Based on current data, we would recommend sentinel node biopsy in patients who are undergoing mastectomy for DCIS, patients who have DCIS with microinvasion, patients who have high-grade DCIS at the time of biopsy, and patients who have a mass by mammography. If the patient has had a core biopsy diagnosis of DCIS, the possibility of upstaging to invasive carcinoma should be discussed and the need for possible nodal evaluation should also be addressed. In our own series, when all patients with these risk factors are considered (including core biopsy in the DCIS subgroup), the total number of patients meeting criteria for sentinel lymph node biopsy is 534 of 675 (79%). The combination of low morbidity and greater risk for invasive carcinoma at the time of definitive resection make sentinel lymph node biopsy an

important consideration in high-risk patients with DCIS, whereas the actual finding of micrometastatic disease on immunohistochemical analysis is of little or no consequence in patients with a noninvasive diagnosis of DCIS.

References

- [1] Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med* 2003;349:546–53.
- [2] Giuliano AE, Kirgan DM, Guenther JM, et al. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg* 1994;220:391–8; discussion 398–401.
- [3] Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer—a multicenter validation study. *N Engl J Med* 1998;339:941–6.
- [4] Burak WE, Hollenbeck ST, Zervos EE, et al. Sentinel lymph node biopsy results in less postoperative morbidity compared with axillary lymph node dissection for breast cancer. *Am J Surg* 2002;183:23–7.
- [5] Swenson KK, Nissen MJ, Cernovsky C, et al. Comparison of side effects between sentinel lymph node and axillary lymph node dissection for breast cancer. *Ann Surg Oncol* 2002;9:745–53.
- [6] Jemal A, Murray T, Samuels A, et al. Cancer statistics, 2003. *CA Cancer J Clin* 2003;53:5–26.
- [7] Adamovich TL, Simmons RM. Ductal carcinoma in situ with microinvasion. *Am J Surg* 2003;186:112–6.
- [8] Silverstein MJ, Rosser RJ, Gierson ED, et al. Axillary lymph node dissection for intraductal breast carcinoma—is it indicated? *Cancer* 1987;59:1819–24.
- [9] Kelly TA, Kim JA, Patrick R, et al. Axillary lymph node metastases in patients with a final diagnosis of ductal carcinoma in situ. *Am J Surg* 2003;186:368–70.
- [10] Farkas EA, Stolier AJ, Teng SC, et al. An argument against routine sentinel node mapping for DCIS. *Am Surg* 2004;70:13–7; discussion 17–8.
- [11] Jackman RJ, Burbank F, Parker SH, et al. Stereotactic breast biopsy of nonpalpable lesions: determinants of ductal carcinoma in situ underestimation rates. *Radiology* 2001;218:497–502.
- [12] Liberman L, Dershaw DD, Rosen PP, et al. Stereotaxic core biopsy of breast carcinoma: accuracy at predicting invasion. *Radiology* 1995;194:379–81.
- [13] Cox CE, Nguyen K, Gray RJ, et al. Importance of lymphatic mapping in ductal carcinoma in situ (DCIS): why map DCIS? *Am Surg* 2001;67:513–9.
- [14] King TA, Farr GH Jr, Cederbom GJ, et al. A mass on breast imaging predicts coexisting invasive carcinoma in patients with a core biopsy diagnosis of ductal carcinoma in situ. *Am Surg* 2001;67:907–12.
- [15] Klauber-DeMore N, Tan LK, Liberman L, et al. Sentinel lymph node biopsy: is it indicated in patients with high-risk ductal carcinoma-in-situ and ductal carcinoma-in-situ with microinvasion? *Ann Surg Oncol* 2000;7:636–42.
- [16] Pendas S, Dauway E, Giuliano R, et al. Sentinel node biopsy in ductal carcinoma in situ patients. *Ann Surg Oncol* 2000;7:15–20.
- [17] Lara JF, Young SM, Velilla RE, et al. The relevance of occult axillary micrometastasis in ductal carcinoma in situ: a clinicopathologic study with long-term follow-up. *Cancer* 2003;98:2105–13.
- [18] Lee CH, Carter D, Philpotts LE, et al. Ductal carcinoma in situ diagnosed with stereotactic core needle biopsy: can invasion be predicted? *Radiology* 2000;217:466–70.