



Sentinel node mapping and ductal carcinoma in situ

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Abstract

Background Pure ductal carcinoma in situ (DCIS) is typically unassociated with a risk of regional lymph node involvement. Retrospective series maintain that larger tumors or high-grade histopathology may harbor a risk of lymph node involvement.

Purpose Our community hospital retrospectively reviewed a series wherein women with DCIS were subjected to sentinel lymph node biopsy based on large tumor size and/or high-grade histopathology.

Materials and methods 232 consecutive women with a diagnosis of pure DCIS were evaluated independently by two breast surgeons, one who typically offers sentinel node mapping to patients with tumors larger than 10 mm and the other who offers sentinel node mapping to women with grade 3 tumors. 60 women (26%) underwent sentinel node mapping along with appropriate surgery directed to the breast. Women were offered risk-adjusted adjuvant radiotherapy and anti-endocrine therapy.

Results At a median follow-up of 18 months (range 6–132 months), 9 women (15%) were identified with regional axillary nodal disease. A statistical analysis was conducted between women who did or did not undergo sentinel node mapping because there was overlap in large tumor size and high grade between the two groups. A univariate logistic regression statistic showed a trend toward a significant relationship between grade 3 tumors and a risk of occult nodal involvement. This was not confirmed by multivariate analysis.

Conclusions In our moderate-sized surgical experience evaluating women with pure DCIS who underwent a sentinel node mapping due to large tumor size or high grade histology, we were unable to confirm that either is predictive of occult node involvement.

Keywords DCIS · Sentinel node mapping · Tumor grade · Tumor diameter

Introduction

Due to improvements in imaging techniques and technology, patient education, and an interest in screening among patients and their providers, ductal carcinoma in situ (DCIS) represents 30% of all breast cancer diagnoses in the US [1]. Controversy surrounds this diagnosis as incidental and subject to overtreatment; however, a recent study suggested screen detection of DCIS reduces the subsequent diagnosis

of invasive breast cancer [2]. Pure DCIS is unassociated with a risk of regional lymph node metastases and, as such, surgical assessment of the axilla has not typically been pursued [3]. However, several series have documented a low, albeit real risk of sentinel node involvement in patients with pure DCIS based on tumor size [4–6], histological grade [7, 8], and mammographic appearance [9]. Herein we report our single institutional experience of patients diagnosed with pure DCIS, a number of whom went onto sentinel lymph node mapping based on tumor dimension and or histological tumor grade.

Materials and methods

232 consecutive patients with a biopsy-proven diagnosis of DCIS were evaluated in our coordinated multi-disciplinary breast cancer clinic from 2005 to 2015. All new breast cancer patients were prospectively discussed in a weekly tumor

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board with attention paid to surgical treatment planning. Following the coordinated discussion, patients were offered an appropriate surgical recommendation and, based on surgeon and patient preference, either mastectomy or breast conservation with or without sentinel node mapping. One breast surgeon was inclined to recommend sentinel node mapping for tumors larger than 10 mm in size regardless of grade while the other was more inclined to offer mapping for all grade 3 tumors, regardless of tumor volume.

The majority of patients (228 or 98%) were diagnosed by either stereotactic or ultrasound-guided core biopsy. Breast conserving surgery was accomplished with needle-localization with the intent to remove the index lesion and at least 1 cm of grossly normal breast parenchyma. In women opting for a simple mastectomy, none chose immediate reconstruction. Those women undergoing sentinel node mapping received both technetium 99 and isosulfan blue dye.

Patients were re-presented at the tumor board following the definitive surgical procedure where appropriate adjuvant therapies and chemoprevention were discussed. Of the 232 women treated, 60 (26%) underwent a sentinel node mapping while the remaining 172 women did not proceed to nodal evaluation due to physician and/or patient choice.

Appropriate adjuvant therapies were offered; women undergoing breast conservation received radiotherapy either to the whole (group 1: 46%; group 2: 55%) or partial breast (group 1: 15%; group 2: 41%). Simple mastectomies were performed in 39% of the women in group 1 and 4% in group 2. Adjuvant radiotherapy was delivered to one patient in group 1 because of her large tumor volume of 16 cm, while it was not offered in the postmastectomy setting otherwise.

The median follow-up for group 1 (sentinel node mapping performed) was 18 months (range 6–132 months) while group 2 (no sentinel node biopsy performed) was followed for a median 30 months (range 6–132 months). Follow-up consisted of semi-annual physical examinations in all women, and diagnostic mammography in women maintaining the breast 6 months following the radiotherapy course and then at annual intervals thereafter.

Results

Table 1 summarizes patient characteristics of group 1 (women undergoing sentinel node mapping) and group 2 (women whose axilla was not surgically addressed). Because of the surgeons' preference to more frequently offer sentinel node mapping to women with higher grade and/or larger tumors, the 60 women who underwent sentinel node mapping had more grade 3 tumors (67% vs 24%) or larger mean tumors (17.5 mm vs 5.75 mm) than the 172 women not undergoing nodal evaluation. Table 2 depicts the univariate analysis by logistic regression demonstrating a trend toward

occult lymph node involvement by immunohistochemistry and grade 3 histopathology. No such trend was seen with larger tumors. Table 3 shows the multivariate analysis which failed to confirm a statistically significant relationship between tumor grade, diameter, and sentinel node disease. Of the 9 (15% overall) of patients with nodal metastases, 2 (3% overall) had micrometastases with a nodal deposit measuring 0.4 mm. One patient (1.7% overall) had a deposit 0.1 mm in size and the remaining 6 (10% overall) had nodal tumor foci described as a few subcapsular pan-keratin positive cells.

To determine if there was a relationship between architectural pattern and necrosis to account for the higher than expected incidence of nodal disease, an analysis was performed. With regard to tumor-specific architectural pattern, 13 individual groups were identified and described in Table 4. A Fisher's exact test failed to establish a relationship between a specific tumor morphology and the presence of nodal disease. In Table 5, we reviewed the presence or absence of necrosis in the primary tumor and, by statistical analysis, were unable to relate either to nodal disease.

After a median follow-up of 18 months (group 1) and 30 months (group 2), no patients were identified with a regional axillary recurrence.

Discussion

Our moderate volume single institutional series evaluated 60 women with pure DCIS who, because of high-risk features identified by their surgical oncologists, underwent sentinel node mapping at the time of definitive breast surgery. Sentinel node biopsy revealed 9 (15%) with immunohistochemical evidence of nodal disease. These women were compared to 172 contemporaneously treated women with pure DCIS who did not undergo sentinel node biopsy and, by multivariate analysis, neither tumor grade nor tumor diameter proved to be predictive of occult regional nodal involvement. These findings corroborate the literature consensus wherein pure DCIS has not been shown to metastasize to regional lymphatics, associated with either high tumor grade or large diameter.

Some have argued that, with increasing tumor volume, there is a potential increased risk of undetected microinvasive disease and, for this reason, regional lymphatics may be at risk. Indeed, the previous standard surgical approach in pure DCIS was to evaluate the axilla; this approach was generally abandoned following the publication of NSABP-B17 and the Van Nuys experience when neither showed a significant risk of occult nodal disease [10]. Today's pure DCIS is often identified as an occult mammographic lesion, unlike the much larger tumors found prior to regular screening

Table 1 Sentinel versus non-sentinel node biopsy group differences

	SNM (<i>n</i> = 60)		Non-SNM (<i>n</i> = 172)		<i>t</i> test
	Mean (Mdn)	SD	Mean (Mdn)	SD	
Age (years)	56.4 (57.5)	10.3	61.3 (61.5)	10.6	−3.10*
Tumor size (mm)	17.5 (15)	20.3	7.0 (5.75)	5.6	6.15**
Margin status ^a (mm)	2.6 (1.1)	3.9	3.8 (2.3)	3.8	ns
	Count (%)				χ^2
Tumor grade					
Grade 1	4 (6.7)		50 (29.1)		36.29**
Grade 2	16 (26.7)		80 (46.5)		
Grade 3	40 (66.7)		42 (24.4)		
Tumor lateralization					ns
Right	32 (53.3)		99 (57.6)		
Left	28 (46.7)		73 (42.4)		
Estrogen receptor status (+)	48 (80.0)		156 (90.7)		4.80*

SNM sentinel node mapping

p* < 0.01*p* < 0.001^aReported for patients with quantified margins (SNM *n* = 32; non-SNM *n* = 89)

Table 2 Univariate logistic regression of tumor diameter and grade on positive sentinel node biopsy

Variable	Coefficient (β)	SE	Wald χ^2	<i>p</i> value	95% CI
Tumor diameter	0.07	0.05	1.55	0.122	−0.02 to 0.16
Tumor grade					
Grade 2	−1.95	1.25	−1.55	0.121	−4.40 to 0.51
Grade 3	−1.95	1.11	−1.76	0.079	−4.13 to 0.23

Table 3 Multivariable logistic regression of tumor diameter and grade on positive sentinel node biopsy

Variable	Coefficient (β)	SE	Wald χ^2	<i>p</i> value	95% CI
Tumor diameter	0.05	0.05	1.13	0.259	−0.04 to 0.14
Tumor grade					
Grade 2	−1.73	1.31	−1.32	0.186	−4.29 to 0.83
Grade 3	−1.75	1.21	−1.44	0.149	−4.13 to 0.63

Table 4 Node positivity association with architectural patterns

Architectural patterns	Node negative	Node positive	Total
Cribriform and micropapillary	9	1	10
papillary and micropapillary	3	2	5
Papillary	2	0	2
Micropapillary	2	0	2
Clinging	1	0	1
Cribriform and solid	8	1	9
Cribriform, papillary, and solid	5	0	5
Comedo and solid	2	1	3
Cribriform	2	2	4
Comedo	4	0	4
NOS	8	1	9
Comedo, cribriform, and micropapillary	2	1	3
Papillary, micropapillary, and solid	3	0	3

Using a Fisher's exact test the results indicate there is no statistical relationship between node and architectural pattern categories, $p=0.166$

Table 5 Node positivity association with necrosis ($n=39$)

	Node negative	Node positive	Total
No necrosis	21	5	26
Necrosis	30	4	34

Using a Fisher's exact test the results indicate there is no statistical relationship between necrosis and node categories, $p=1.00$

mammography, and this supports the movement away from axillary evaluation based on tumor size criteria only.

In an analysis from Britain in women identified with pure DCIS by screening mammography, it was noted that high-grade histology and increasing tumor size were more likely to prompt axillary evaluation. Their large national-based registry included over 20,000 women treated over an 8-year period of time, 26% of whom underwent axillary evaluation. The authors found axillary nodal involvement in 0.2% of women presenting with pure DCIS. The statistical analysis indicated that larger tumors were more likely addressed with mastectomy rather than breast conservation, and the larger tumors were more often associated with occult axillary disease. Specifically, patients with tumors larger than 1.6 cm in size were 50% more likely to undergo sentinel node biopsy while those with tumors larger than 4 cm in diameter were 300% more likely to undergo axillary evaluation. With regard to tumor grade, patients with grade 3 lesions were 67% more likely to undergo sentinel node biopsy than lower grade tumors. The authors did not provide specific details on whether they found a cutoff in tumor diameter below which they would not recommend sentinel node mapping, nor did they report the rate of occult lymph node disease based on tumor diameter or grade [11].

A single institutional report from Harvard investigated 109 women with DCIS approached with a sentinel node mapping procedure. They found 3.6% with nodal disease by hematoxylin and eosin (H&E) staining and another 3.6% by immunohistochemistry (IHC) only. The authors failed to identify risk factors associated with occult nodal disease and concluded that rates of nodal involvement were modest and of uncertain significance [12].

In a large series from Memorial Sloan Kettering, 470 women with DCIS underwent sentinel node mapping, 9% of whom had occult nodal involvement; the majority or 84% (36 patients) had nodal disease identified by IHC only. The authors determined that large volume disease (> 5 cm tumor diameter) and tumor necrosis were associated with occult nodal involvement [13].

A large series from Moffitt Cancer Center included 559 women with pure DCIS who underwent a sentinel node mapping; 5% overall had evidence of nodal disease, 70% of whom with disease identified by IHC only. The authors concluded that high-grade tumors were more likely to harbor occult microinvasive disease, warranting sentinel node evaluation. They also surmised that in patients opting for a mastectomy, a sentinel node evaluation should always be performed; once the breast tissue was absent, performance of a sentinel node mapping would no longer be feasible and a formal more morbid axillary dissection would be required (should invasive disease be found) [7].

A French review article evaluated 92 women with pure DCIS managed at a single center who underwent axillary

nodal evaluation. This center then researched the primary tumor looking for evidence of microinvasive disease to explain the nodal spread. Of the women ultimately proven to have pure DCIS (without evidence of invasion on review of the primary tumor site), 10% had axillary nodal disease, all by IHC only. Like the series from Florida [7], this French series recommended sentinel node mapping with extensive pure DCIS in women undergoing a mastectomy, with consideration given to women undergoing breast conservation with high-grade tumors or tumors with a diameter exceeding 5 cm [6].

Ultimately, a Finnish series addressed the clinical impact of sentinel node disease in patients with pure DCIS. In a report of 246 women with pure DCIS, 6% of whom had sentinel node disease, none experienced locoregional failure or distant disease recurrence at a median follow-up of 50 months. This clinical result led the authors to conclude that some women with pure DCIS will harbor occult micrometastatic axillary disease which does not prove morbid or life threatening [14].

Because of the unexpected percentage of patients with micrometastatic regional axillary disease, we evaluated both the presence of necrosis as well as the architectural pattern within the index lesion as potential attributes. Neither tumor architectural pattern nor the presence of necrosis predicted for the presence of occult nodal disease.

Conclusion

Our moderate volume single institutional experience corroborated that found in the literature; although there was a 15% risk of regionally metastatic disease found in the sampled axillary nodes, this was not statistically associated with higher tumor grade or tumor diameter. Our finding was greater than the 5–10% risk of occult regional nodal disease reported by other centers with larger patient numbers. An analysis of necrosis and architectural pattern of the index lesion did not identify a relationship between either and risk of nodal disease. It is possible that our smaller patient numbers or an as-yet unidentified tumor related variable explains the 15% positive nodal disease. Furthermore, and in agreement with the Finnish trial [14], we did not identify any regional axillary recurrences at a median follow-up of 18 months in the sentinel node group and 30 months in the un-evaluated axilla group. Although it was not an institutional policy, a larger number of women undergoing a mastectomy submitted to a sentinel node biopsy (39% vs 4% in the non-sentinel node group). This approach has been accepted as preferable by others in women with a large volume of DCIS who may harbor microinvasive disease [6, 7]. Our experience adds to the surgical perspective that women presenting with pure DCIS do not benefit from a staging

sentinel node mapping based on tumor grade or tumor diameter as risk factors; however, in women with a large tumor volume deemed best managed by a mastectomy, a sentinel node mapping appears practical.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

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