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Review

Is there an indication for sentinel node biopsy in patients with ductal carcinoma *in situ* of the breast? A review

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ABSTRACT

Ductal carcinoma *in situ* (DCIS) of the breast is defined as a proliferation of malignant epithelial cells within breast ducts without evidence of invasion through the basement membrane. The detection rate of DCIS of the breast has dramatically increased since the mid-1980s as the result of the widespread use of screening mammography. DCIS currently represents about 15–25% of all breast cancers detected in population screening programmes. Although inherently a non-invasive disease, occult invasion with the potential of lymph node metastases may occur. Where performing an axillary lymph node dissection-or-not for DCIS used to be an important dilemma, the same now holds for the sentinel node biopsy. This article reviews the potential role of the sentinel node biopsy (SNB) in patients with DCIS. We conclude that based on the current literature, there is in general no role for a SNB in DCIS. A SNB should only be considered in patients with an excisional biopsy diagnosis of high risk DCIS (grade III with palpable mass or large tumour area by imaging) as well as in patients undergoing mastectomy after a core or excisional biopsy diagnosis of DCIS, although SNB may be contraindicated in many of the latter patients because of lesion size and/or multifocality. Even in these patients the value of a positive SN, containing mostly isolated tumour cells, is questionable.

1. Introduction

Ductal carcinoma *in situ* (DCIS) is defined as a clonal proliferation of malignant epithelial cells limited to the ductal units without evidence of invasion through the basement membrane. DCIS is a heterogeneous group of lesions rather than a single entity that differ with regard to their genetic make-up, histological characteristics, clinical presentation, mammographic features, extent and distribution within the breast, and biological behaviour. Currently available management options include mastectomy, local excision combined with radiation therapy, local excision alone and hormonal therapy.[1–6] The value of staging the axillary lymph nodes is a matter of debate.

Because invasion of the basement membrane by definition does not occur and the epithelial layer and even the intralobular space[7] is devoid of lymphatics and blood vessels, the incidence of metastatic disease to the regional lymph nodes or distant sites should theoretically be zero. However, the breast cancer specific mortality rate for patients with DCIS

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is 1–2%,[8] indicating that some patients had occult distant metastases at the time of surgery that later progressed. Further, about 1% of patients with DCIS have been found to have nodal metastases on axillary lymph node dissection (ALND) in historical series.[9–14] Although this has been considered low enough to abandon ALND as a routine procedure in DCIS because of the significant morbidity associated with the procedure, this indicates that there must be occult invasion in some DCIS cases. In view of the fact that pathology sampling generally involves assessment of less than 0.1% of the specimen volume, this is understandable.[15]

The introduction of lymphatic mapping and sentinel node biopsy (SNB) as an alternative to routine staging by ALND[16] with markedly reduced morbidity and complications has again raised the question if one should stage DCIS by SNB. The SN is conceptually the first lymph node to receive lymphatic drainage from the primary tumour and is thereby at the highest risk to contain metastases.[17–19]

The SN can thereby be selectively targeted by pathologists with serial sectioning and immunohistochemistry (IHC) to efficiently detect micrometastases.[20,21] In patients with infiltrating carcinoma of the breast, the detection rate of metastases to the SN increased by 13–28%[22–25] using this technique. In patients with pure DCIS an increase up to 18% has been found, a comparable but less dramatic trend.[26–45]

There has therefore been discussion whether a SNB is indicated for DCIS. Arguments in favour of performing a SNB in DCIS are (1) microinvasion can be missed in the excision specimen, possibly resulting in understaging when no SNB would be done; (2) in core biopsies showing DCIS, there may be invasion in the following excision specimen, necessitating a second operation for the SN procedure; (3) there are some data suggesting that SNB may be less accurate after previous excisional biopsy, so can better be done upfront; (4) the SNB has few side effects, so the threshold for the procedure may be low. Arguments against a routine SNB procedure are (1) although the complication rate is low, it is not zero; (2) the SNB procedure is expensive; (3) the SNB procedure is not a useful staging procedure in the large majority of DCIS patients; (4) when the SN is not found there is not an easily acceptable alternative for nodal staging.

In the following, we will review the validity of these arguments in view of the current literature. The following terminology will be used for SN metastatic load: macrometastases are >2 mm, micrometastases are larger than 0.2 mm and maximally 2 mm in size, and isolated tumour cells (ITCs) are smaller than or equal to 0.2 mm.

2. (Micro)invasion can be missed in excision specimens

Historical data before the era of the SN report a low rate of axillary metastases detected by ALND in DCIS cases using conventional pathological analysis. Leonard and Swain[46] reviewed the literature and reported a 1.4% positive ALND rate in 1621 patients with DCIS. The significance of these metastases with regard to local control and prognosis is a matter of debate.

In SN studies, a 0–18% risk of SN involvement has been reported in patients with pure DCIS (Table 1). In the largest

Table 1 – Overview of studies on the sentinel node (SN) biopsy in patients with a final diagnosis of DCIS of the breast

First author	Year	# Patients with DCIS	# Patients with positive SN (%)	#SN positive patients undergoing ALND	# Patients with ALND metastases (%)
Klauber De More and colleagues[26]	2000	72[a]	5 (7%)	Unknown[b]	Unknown
Kelly and colleagues[27]	2003	41	1 (2%)	1	0
Farkas and colleagues[28]	2003	46	0 (0%)	0	
Trisal and colleagues[29]	2004	15	0 (0%)	0	
Buttarelli and colleagues[30]	2004	41	3 (7%)	4	0
Zavagno and colleagues[31]	2005	102	1 (1%)	0	0
Mittendorf and colleagues[32]	2005	34	6 (18%)	2	0
Giard and colleagues[33]	2005	55	1 (2%)	0	
Yen and colleagues[34]	2005	99	3 (3%)	1	0
Schrenk and colleagues[35]	2005	29	0 (0%)	0	
Wilkie and colleagues[36]	2005	559	27 (5%)	Unknown	Unknown
Camp and colleagues[37]	2005	25	1 (4%)	0	
Veronesi and colleagues[38]	2005	508	9 (2%)	8	0
Torok and colleagues[39]	2006	40	2 (5%)	0	
Cserni and colleagues[40]	2006	36	4 (11%)	4	0
Katz and colleagues[41]	2006	110	8 (7%)	2	0
Mabry and colleagues[42]	2006	171	10 (6%)	0	
Sakr and colleagues[43]	2006	39	4 (10%)	4	0
Leidenius and colleagues[44]	2006	74	5 (7%)	3	0
Fraile and colleagues[45]	2006	92	1 (1%)	0	
UMC Utrecht (unpublished)	2006	8	0 (0%)	0	0
Total		2196	91 (4%)	29	0

a Three patients with stromal or lymphovascular invasion and one patient with contralateral breast cancer excluded. It is not mentioned if the one patient with an additional ALND metastasis had invasiveness on retrospection.
b Six patients had ALND and one of them had one additional node involved. They did not mention if these patients had pure DCIS or stromal/lymphovascular invasion.

study on SNB for DCIS published to date, Wilkie and colleagues[36] reported a SN positivity rate of 5% in 559 patients after excluding those patients upstaged to invasive carcinoma upon definitive surgical resection. Seventy percent of these SN metastases were only detected by IHC. They found that the combined findings of a high histological grade, presence of a mass by mammography and microinvasion predicted patients at a higher risk for invasive carcinoma. They therefore propose that the SN procedure should be considered in patients with such high risk indicators. In their series, however, 79% of the patients met these criteria. They comment that the presence of micrometastases in SNs of patients with DCIS does not mandate an ALND but did not mention if these DCIS patients with metastatic SN underwent an ALND and if further metastases were found.

In the second largest study, Veronesi and colleagues[38] reported a 2% rate of SN metastases out of 508 patient with a final diagnosis of DCIS. Only tumour size and the high grade seemed to be relevant in predicting the risk of SN metastases. In 56% only micrometastases were detected. The SN was the only affected node in the eight patients who underwent subsequent ALND. Seven out of the nine patients with a metastatic SN had undergone a previous breast biopsy. After 46 months of follow-up, no loco-regional or systemic events were observed in the nine SN positive patients.

Zavagno and colleagues[31] evaluated 102 patient with pure DCIS who underwent SNB. Only one patient was SN positive. The primary tumour was a small (diameter 1.6 cm) micropapillary intermediate-grade DCIS and the SN harboured a micrometastasis. A pathologic review of the surgical specimen confirmed that no microinvasion could be detected.

Katz and collageas[41] selected 109 patient with DCIS (one patient with bilateral DCIS underwent 2 SN procedures) and reported a 7% rate of SN metastases. Half of these patients had a positive SN by haematoxylin and eosin staining and the other half only by IHC. Two of these patients underwent ALND and had no additional nodes involved.

Mabry and colleagues[42] reported a SN positivity rate of 6% in 171 patients with pure DCIS. These patients were identified for SNB using the following criteria as guidelines: DCIS extensive enough to require mastectomy, large DCIS (>4 cm), palpable DCIS or DCIS located in the upper outer quadrant of the breast. All of these 10 patients with involved SN had ITC detected by IHC. Two of these patients developed local recurrence in the breast; one was a recurrence of DCIS and one was an invasive cancer. None of these patients developed distant disease or axillary recurrence, none received chemotherapy or died.

In our own unpublished series of eight DCIS patients, none had a positive SN.

2.1. *False positive SNB caused by displaced epithelial cells*

One issue that needs to be addressed here is the fact that epithelial cells may possibly be displaced by manipulating the breast during the biopsy procedure and taken to the SN. Moore and colleagues[47] reported a series of 4016 consecutive breast cancer patients in which the frequency of IHC-positive SN was increased after instrumentation of the tumour site, and was increased approximately proportionate to the degree of manipulation. If this is the case, this obviously leads to falsely classifying DCIS patients as having occult microinvasion and a positive lymph node, and possibly incorrectly setting the associated indication for ALND and adjuvant therapy. These results have however been doubted by King and colleagues.[48] In their series of 163 prophylactic mastectomies with SNB, occult carcinoma was identified in 13 (8%) specimens. Two of these had positive SNs. Of the remaining 150 cases, 89% underwent IHC of the SNs. Of these, 43 (33%) had one or more prior biopsies in their 'cancer-free' breast. A total of 310 SNs were examined by IHC, and only 1 (0.8%) patient without occult carcinoma had an IHC-positive SN. This patient had Stage IIIC carcinoma of the contralateral breast. IHC-positive SNs were not identified in any of the 43 patients with a history of prior biopsy. They therefore concluded that IHC-positive cells in SNs are rare in the absence of cancer and are not the result of previous breast instrumentation. In view of these contradictory results, we regard displacement as a possible cause of false positive SNB at present as controversial.

In summary (Table 1), in total 2196 patients with pure DCIS have to date been mapped by a SN procedure which resulted in nodal positivity in 91 (4%). These metastatic nodal cells are proof that microinvasion has been missed. Most of these cases were however detected by IHC alone, and none of the SN positive patients undergoing ALND had non-SN involvement. This indicates that SN metastases in case of DCIS may have little impact on local control and prognosis.

3. Invasion can be missed in core biopsies due to sampling error

DCIS is a diagnosis which can only be established by appropriate tissue sampling and careful microscopic examination to exclude invasion. Many authors reported that a substantial proportion (9–52%) of patients with a core or vacuum assisted biopsy diagnosis of DCIS were upstaged to infiltrating ductal carcinoma (IDC) at examination of the resection specimen.[49–67] Table 2 gives the breakdown of these different studies. Young age, a palpable mass or nodular density on the mammogram, large lesion size, Paget disease or nipple discharge were associated with a higher risk of (micro) invasive disease. Histopathological characteristics associated with invasion underestimation are high grade and comedo type DCIS, and periductal inflammation.[62,66] These patients typically undergo a SN procedure in a second surgical session. Although this procedure may be reliable after excisional biopsy, a one stop approach is nearly always more convenient for the patients.

4. There are some data suggesting that SNB may be less accurate after excisional biopsy so can better be done upfront

In case patients are upgraded to invasive cancer after a diagnosis of DCIS on core biopsy, they require a re-operation with lymph node evaluation if lymph node sampling is not done upfront. It has been suggested that SNB for breast cancer may be less accurate after excisional biopsy of the primary tumour compared with core needle biopsy,[68–71] possibly caused by lymphatic disruption and inflammatory changes. Krag and colleagues[70] reported a greater than sevenfold increase

Table 2 – Overview of studies revealing invasion in the resection specimen after a core or vacuum assisted biopsy of DCIS

First author	Year	# Patients	# Patients with invasion in subsequent resection specimen (%)
Jackman and colleagues[49]	1994	43	8 (19%)
Liberman and colleagues[50]	1995	15	3 (20%)
Acheson and colleagues[51]	1997	54	10 (19%)
Burbank and colleagues[52]	1997	87	9 (10%)
Fuhrman and colleagues[53]	1998	84	30 (36%)
Won and colleagues[54]	1999	40	10 (25%)
Burak and colleagues[55]	2000	89	10 (11%)
Darling and colleagues[56]	2000	289	40 (13%)
Lee and colleagues[57]	2000	59	17 (29%)
Cox and colleagues[58]	2001	224	23 (10%)
Brem and colleagues[59]	2001	34	3 (9%)
Jackman and colleagues[60]	2001	1326	183 (14%)
King and colleagues[61]	2001	140	36 (26%)
Renshaw and colleagues[62]	2002	91	17 (19%)
Verkooijen and colleagues[63]	2002	190	32 (17%)
Pandelidis and colleagues[64]	2003	91	12 (13%)
Crowe and colleagues[65]	2003	33	17 (52%)
Hoorntje and colleagues[66]	2003	255	41 (16%)
Goyal and colleagues[67]	2006	587	220 (38%)
Total		3731	721 (19%)

in failed SN identification after excisional biopsy. Borgstein and colleagues[68] also showed a significantly higher lymphatic mapping failure after excision biopsy. Feldman and colleagues[71] reported that in patients with a prior excisional biopsy, the group with a false negative SN had a larger mean maximal biopsy dimension than the true positive group. These early studies however used peritumoural injection by single of dual agent, while dermal injection might be superior.[72,73]. Further, the results of these studies have been contradicted by other authors.[74–79] In the largest study published to date (2206 patients), Wong and colleagues[77] determined the impact of the type of breast biopsy (needle versus excisional) or definitive surgical procedure (lumpectomy versus mastectomy) on the accuracy of the SNB. They reported a significantly improved SN identification rate using dermal versus peritumoural injection techniques for radioactive colloid after either excisional needle biopsy. There was no statistically significant differences in SN identification rate or false-negative rate between patients undergoing excisional versus needle biopsy. This study did not capture values for primary excision volume but the excision volume likely increased with increasing tumour size. Their data indicate that the SN identification and false-negative rates are not clearly worse for larger tumours. Also Haigh and colleagues[76] and Miner and colleagues[75] found no statistical differences after previous biopsy. Haigh and colleagues concluded that the volume of the excisional biopsy did not affect the SN identification rate. The median volume of breast tissue removed was 23 ml.

Vijayakumar and colleagues[80] recently reviewed the literature of variables affecting the accuracy and false-negative rate of SNB procedures in early breast cancer. They concluded that the type of diagnostic biopsy and the type of initial surgery are minor factors determining the accuracy of SN localisation. The success rate depends, above all, on a good injection technique. After reviewing the literature they believe that a dual-agent mapping with a combination of two injection methods (intradermal/subdermal) and interstitial (intratumoural) has a higher success rate.

These studies however only included patients with invasive breast cancer. The SN was identified more frequently in patients with a palpable mass. The identification rate in patients with DCIS might therefore be less, because most of the DCIS lesions are not palpable. Chagpar and colleagues[81] however concluded that intradermal and/or subareolar dual-agent injection can improve SN identification rates regardless of tumour palpability. The experience with radioguided occult lesion localisation (ROLL) in combination with SNB performing intradermal/subcutaneous agent injection also allows high success rates in localising SNs.[82,83] Therefore, proper SN identification protocols probably allow successful finding of the SN in most DCIS cases.

In patients treated with mastectomy, ALND (or lymph node sampling as done by some in the UK) is the only remaining option for lymph node evaluation, as the ability to perform SNB is lost if the breast is removed and invasive carcinoma is identified. In those patients with a very low probability of axillary metastases (e.g. DCIS with micro-invasion, pT1a tumours and a subset of pure tubular carcinomas), a wait and see policy may even be considered.[84,85]

5. The SNB has few side effects

The SNB is a minimally invasive procedure that has indeed significantly lower morbidity than conventional ALND.[86–91] However, even SNB is not without short and long-term treatment related morbidity. Rietman and colleagues[92] reported a significant short-term treatment related upper limb morbidity after SNB, which included pain, reduced range of motion, strength of shoulder abductors and elbow flexors, and thereby in perceived disability in activities of daily life (ADL). There was no significant difference in short-term treatment related upper limb morbidity between SNB and ALND. Two years after surgery however these patients showed less treatment related upper limb morbidity, perceived disability in ADL and worsening of quality of life after SNB compared with ALND,[93] indicating that at least the long-term morbidity of the SNB approach is lower. Other studies reported wound infections, seromas, haematomas, paresthesias and even lymph oedema to occur in a small number of patients after SNB.[94–96] Anaphylactic reactions to the vital blue dye used for SLN biopsy have also been reported.[97,98]

6. The SN procedure is expensive

The SN procedure is an expensive procedure due to lymphoscintigraphy, surgical equipment such as gamma detectors and relatively high costs of pathological examination.[99] In patients with invasive carcinoma that are in about 30–40% SN positive,[100,101] costs of the SN procedure will to a large extent

or maybe even completely be compensated for by the shorter operation time and hospital stay in comparison with the ALND (9-day median for ALND versus 3 days for SN procedure), and the lower long-term morbidity.[102,103] However, the percentage of tumour positive SNs is low in patients with pure DCIS. Routinely performing a SNB in this group of patients may therefore not be cost effective.

Cox and colleagues[58] analysed the direct costs of routinely adding lymphatic mapping in patients with DCIS and DCIS with microinvasion. A policy of routine mapping resulted in nearly half of the increased costs of mapping being offset by savings from avoiding re-operations. The end result was an increase in direct costs of $384 per patient. They found this additional amount of money a small price to pay for detecting metastases, which would otherwise have remained unknown. This study however had a high rate of SN metastases.

7. The SNB procedure is not a useful staging procedure in the large majority of DCIS patients

The SNB with intensive pathological workup by serial IHC that allows to detect small clusters and isolated tumour cells[15] has dramatically increased the identification of metastases in patients with DCIS. The prognostic and therapeutic significance of these metastases is however controversial.

Dowlatshahi and colleagues[104] reviewed the literature on women with infiltrating carcinoma who had negative lymph nodes at conventional workup but with micrometastases by serial sections with H&E or IHC. With the exception of one study, all investigations with more than 100 patients and long-term follow-up showed that micrometastatic disease was associated with a statistically significant decrease in disease-free or overall survival.[105–107]

One can hypothesise that micrometastases also may confer a survival disadvantage in women with DCIS. However, recent studies[108–111] reported that positive nodes by IHC do not seem to affect survival in patients with pure DCIS. Lara and colleagues[109] reported the result of occult axillary metastasis in 102 patients with DCIS and negative axillary nodes between 1974 and 1992. Axillary nodes were re-examined with cytokeratin stains. Micrometastases were identified in 13% of patients. At a follow up of 10–28 years, the overall disease recurrence rate was 12%, but axillary micrometastases had not been detected in any of the patients who had a recurrence. Tamhane and colleagues[108] identified 26 patients with pure DCIS who underwent biopsy procedure before mastectomy and who had lymph nodes identified in the mastectomy specimen. No patient had positive lymph nodes by H&E staining, but 6 of 26 had lymph nodes positive by IHC. No patient had received systemic therapy or radiation therapy. At a median follow-up of 5 years, all patients were alive without evidence of local recurrence or metastasis.

Broekhuizen and colleagues[111] examined the axillary lymph nodes with IHC from patients treated with DCIS or DCIS with microinvasion at their institution between 1989 and 1998. In those patients with DCIS ($n = 71$), the incidence of lymph node positivity increased from 1.4% with routine staining to 11% with IHC. None of the patients with positive lymph nodes died during follow-up (mean 102 months).

El-Tamer and colleagues[110] described a series of 302 patients with DCIS and >8 lymph nodes dissected that were found to be negative by H&E. Six percent were positive by IHC after reexamination. Seventy-three patients were excluded, for a final study population of 229. Among the 216 patients with negative IHC, 18 (8%) died compared to 1 out of 13 (8%) with positive IHC results. At a median follow-up of 125 months, there was no statistically significant difference between these groups. Only two deaths were related to breast cancer, and these were in the group that tested IHC negative. It can therefore be hypothesised that these cells never develop into clinically evident tumours.

Further, the value of the SN procedure in patients with DCIS will depend on the percentage of patients with positive SN, and the percentage of patients thereof with second echelon metastases requiring an ALND. These figures being 4.6% and (probably) close to 0%, respectively, one can conclude that only a small fraction of DCIS patients will benefit from the procedure and that routine SNB in patients with a final diagnosis of DCIS is thereby indeed not a useful staging procedure in the majority of patients.

8. When no SN is found there is no easily acceptable alternative in nodal staging

The SNB procedure in patients with invasive breast cancer is performed as an alternative to conventional ALND. When the SN cannot be found, as a consequence full ALND will have to be performed. Although the SN identification rate in breast cancer has raised since the improvement of the injection procedures and surgical experience to 90–95%, this still means that 5–10% of these patients will undergo a full ALND to evaluate axillary nodal involvement. One can argue that performing an ALND in patients with DCIS would be consequent in case the SN cannot be found and there was a preoperative indication to stage the lymph nodes. However, there may be reason to act differently in DCIS patients since ALND would be an obvious overtreatment in most cases. Since some studies report that non-palpable tumours (such as most DCIS lesions) have a higher SN identification failure rate, this might be a significant problem.

9. Discussion and conclusions

The status of the regional lymph node remains the most powerful predictor of survival in patients with invasive breast cancer and serves to guide further treatment decisions. In patients with a final diagnosis of pure DCIS, however, there is no consensus about both the prognostic and therapeutic significance of these positive lymph nodes. Based on the literature, there may be three possible scenarios.

(1) Do not offer lymphatic mapping and SNB to any DCIS patients. DCIS has an indolent course. The incidence of nodal positivity is low and the prognostic and therapeutic significance of lymph node metastases in patients with a final diagnosis of DCIS is unclear, and 'isolated tumour cells' may not be true metastases but displaced cells. At this time there are no proven benefits

of the SNB with regard to disease-free or overall survival or local control in patients with DCIS. Although the side effects of the SNB are minor compared to ALND, they are not neglectable and there are significant costs. The SNB is not a useful staging procedure for most DCIS patients since most are SNB negative, and the procedure could jeopardise a successive re-SNB procedure in case of invasive recurrence.

(2) Selective approach applying SNB in patients with high risk DCIS. This would concern DCIS patients with micro-invasion, high grade or large lesions, or having a palpable mass or diffuse microcalcifications by mammography. Although it may be argued that even a core biopsy diagnosis of high risk DCIS would justify upfront SNB in view of the high 'underestimate' rate, there is insufficient proof that a delayed SNB procedure after excisional biopsy is suboptimal. Furthermore, patients undergoing a mastectomy for a core or excisional biopsy diagnosis of DCIS should all be offered upfront SNB since lymphatic mapping can no longer be performed following mastectomy. ALND would be the only remaining unattractive option for lymph node evaluation in case invasive carcinoma is yet identified.

(3) Set up a large randomised trial to evaluate the usefulness of lymphatic mapping and SNB in DCIS patients after long-term follow-up on local control and survival. This approach might define subgroups of patients with DCIS for whom the risk of occult invasive disease and axillary lymph node metastases is sufficiently high to recommend a SNB.

Although the third option would be quite important, it is not realistic that such a trial will ever see the light of day in view of the very large numbers of required patients, and we believe that the second approach is at this moment to be preferred.

10. Conclusions

Based on the current literature, we advise a selective approach of the SNB to patients with an excisional biopsy diagnosis of high risk DCIS as well as to patients undergoing mastectomy for a core or excisional biopsy diagnosis of DCIS.

Conflict of interest statement

None declared.

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