Original Article

J Breast Health 2016; 12: 78-82
DOI: 10.5152/tjbh.2016.2929

Sentinel Node Biopsy in Special Histologic Types of Invasive Breast Cancer

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ABSTRACT

Objective: To assess the feasibility of sentinel node biopsy (SNB) in ductal and lobular invasive breast cancer, a group of tumors known as special histologic type (SHT) of breast cancer.

Materials and Methods: Between January 1997 and July 2008, 2253 patients from 6 affiliated hospitals underwent SNB who had early breast cancer and clinically negative axilla. The patients' data were collected in a multicenter database. For lymphatic mapping, all patients received an intralesional dose of radiocolloid Tc-99m (4mCi in 0.4 mL saline), at least two hours before the surgical procedure. SNB was performed by physicians from the same nuclear medicine department in all cases.

Results: Of the 2253 patients in the database, the SN identification rate was 94.5% (no radiotracer migration in 123 patients), and positive sentinel node prevalence was 22%. SHT was reported in 144 patients (6.4%) of the whole series. In this subgroup, migration of radiotracer was unsuccessful in 8 patients (identification rate was 94.4%) and SNs were positive in 7.4%. SN positivity prevalence in these tumors was variable across the subtypes. Higher probability of lymphatic spread seemed to be related to tumor invasiveness (20% of positivity in micropapillary, 15% in cribriform subtypes, and 0% in adenoid-cystic).

Conclusion: Sentinel node biopsy is feasible in special histologic subtypes of breast carcinoma with a good identification rate. Lower migration rates, however, might be associated with special histologic features (colloid subtype). Complete axillary dissection after a positive sentinel node cannot be omitted in patients with SHT breast cancer because they can be associated with further axillary disease; the reported very low incidence of axillary metastases would justify avoiding axillary dissection only in the adenoid-cystic subtype.

Keywords: Sentinel lymph node biopsy, breast cancer, invasiveness

Introduction

Sentinel node biopsy (SNB) is a minimally invasive technique used to stage the axilla in patients with early breast cancer and is the current gold standard for lobular or ductal breast carcinoma (1-3). However, around 10% of breast tumors belong to other histologic subtypes such as tubular, colloid, medullary, papillary carcinoma, and others. This is a heterogeneous group of malignancies known as special histologic types (SHT) of invasive breast cancer, with variable outcomes, as well as with variable rates of axillary metastases (4, 5).

Some authors have advocated that complete axillary dissection (CAD) could be omitted because axillary involvement is uncommon in such tumors. However, the question is whether SNB itself can also be omitted. As the SNB technique keeps improving and consolidating, some authors have shown a higher than expected rate of positive sentinel nodes in this subset (6). This remains an outstanding question for its implication in adjuvant treatment planning. Although SNB morbidity is lower than CAD morbidity, SNB has nevertheless been reported to carry a lymphedema risk of around 10%.

Sentinel node biopsy in these unusual subtypes of breast cancer is poorly studied. The series of these patients are short and there are no data on the technical feasibility in this kind of breast cancer.

The purpose of this study was to assess the feasibility of sentinel node biopsy in special histologic types of invasive breast cancer.

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Received: 29.01.2016
Accepted: 07.03.2016

Material and Methods

This was a retrospective observational study conducted at Germans Trias i Pujol University Hospital, Badalona (Spain). The recruitment period spanned from January 1997 to July 2008. During this period, 2253 patients with early breast cancer and clinically negative axilla (from 6 affiliated hospitals) underwent SNB.

Lymphoscintigraphy was performed 2 hours after intratumoral administration of 2 mCi (74 MBq) of 99mTc radiocolloid. Dual agents for SN detection were not used. Tracer administration was guided by sonography or mammography; hence, the radio-guided occult lesion localization technique was also available. SN detection was performed by physicians from the same nuclear medicine department in all cases.

After intraoperative SN detection and biopsy, specimens were evaluated for the presence of tumor cells both intraoperatively with a fast variation of the May Grünwald-Giemsa staining technique, and definitively using hematoxylin-eosin staining on serial sections. Whenever hematoxylin-eosin stains were negative, immunocytochemistry using an anti-cytokeratin antibody (CAM 5.2) was performed. In cases of positive sentinel node lymph node, axillary dissection was eligible. Also, complete axillary dissection was mandatory in cases with no SN identification.

Approval was obtained from the Ethics Committee at each institution, and written consent for biopsy was obtained from every participating patient.

Patient data were collected in a multicentre database. The study variables were patient age, tumor-related characteristics including histologic type, diagnostic method, size, location, radiologic presentation and results of SNB technique and axillary involvement if CAD was indicated.

Statistical analysis

A descriptive analysis was performed of all variables. Qualitative variables were described using frequency tables for the different categories, and quantitative variables as the mean and standard deviation (SD). Fisher's exact test was used to compare qualitative variables, and Student's t-test was used for quantitative variables (dichotomy variable). The two-tail concept was used for hypothesis testing with a significance level of 0.05 and 90% power. Statistical analysis was achieved using Statistical Package for Social Sciences version 14.0 (SPSS Inc.; Chicago, IL, USA).

Results

In the 2253 patients in our database, sentinel node identification rate was 94.5% (no radiotracer migration in 123 patients), and positive sentinel node prevalence was 22%. The mean age was 57.9 years (range, 24-90 years) and tumor size was 18.5 mm (range, 1-81 mm).

Special histologic type carcinoma was reported in 144 (6.4%) patients in the whole series. The mean age was 61.4 years (range, 24-86 years) and tumor size was 13.5 mm (range, 1-55 mm). The diagnostic method was fine needle aspiration in 41% of patients and core biopsy in 59%. Table 1 presents the clinico-pathologic characteristics of these patients.

Tubular carcinoma was the most frequent subtype, followed by colloid, medullary, and papillary. Tubular carcinomas presented as small, nonpalpable lesions. Tubular and cribriform tumor subtypes presented more often as microcalcifications. Medullary carcinomas were larger, more often palpable, and presented as nodules. The invasive apocrine subtype was the less frequent.

Different subtypes of breast tumors showed different SNB identification and positivity rates, as well as variable additional axillary lymph node involvement in subsequent CAD (Table 2). Regarding the results of the sentinel detection technique, it was unsuccessful due to no radiotracer migration in 8 patients (94.4% identification rate), 4 of which had a colloid carcinoma.

Overall**,** sentinel nodes were positive in 10 (7.4%) patients. Higher rates of positive SN (over 10%) were observed in the micropapillary and cribriform subtypes, whereas intermediate rates (5-10%) were

Table 1. Clinico-pathologic characteristics of SHT breast cancer patients

	n	Age (y)	Diagnostic method b/f	Tumor size (mm)	Tumor palpability	Location eq/iq	Radiological presentation d/m/n
Tubular	41 (28.5%)	58.6 (10.3)	79/21%	9.2 (6.5)	20%	49/51%	34/13/53%
Colloid	34 (14%)	67.6 (13.4)	48/52%	15.2 (10.3)	74%	47/53%	0/0/100%
Medullary	20 (13.9%)	51.5 (11.6)	19/81%	16.9 (9.6)	80%	50/50%	10/0/90%
Papillary	19 (13.2%)	64.4 (11.8)	56/44%	15.6 (13.1)	63%	47/53%	5/5/90%
Cribriform	8 (5.6%)	64.8 (12.3)	50/50%	10.7 (1-45)	63%	43/57%	13/13/74%
Metaplastic	5 (3.5%)	66.5 (7.3)	50/50%	12.7 (11.1)	75%	75/25%	25/0/75%
Invasive micropapillary	5 (3.5%)	60.8 (8.5)	75/25%	11.0 (6.5)	75%	40/60%	25/0/75%
Neuro-endocrine	5(3.5%)	68.3 (7.5)	100/0%	21.3 (7.2)	100%	50/50%	0/0/100%
Adenoid cystic	5 (3.5%)	61.5 (12.0)	0/100%	19.0 (8.5)	50%	50/50%	0/0/100%
Invasive apocrine	2 (1.4%)	52.0 (11.3)	100/0%	7.0 (8.5)	100%	50/50%	0/0/100%

y: years, mean (SD); mm: millimeters, mean (SD); b/f: core biopsy/fine needle aspiration; eq/iq: external quadrants/internal or retroareolar quadrants; d/m/n: distortion/microcalcifications/nodule

found in tubular, colloid, and medullary subtypes. Papillary, adenoid cystic, and apocrine subtypes did not present with positive sentinel nodes. Metaplastic or neuroendocrine cases did not occur in our series. CAD following a positive sentinel node was positive in 4 patients, one in a tubular subtype, and 3 in colloid subtypes.

Of the 8 cases with no SN identification, no axillary involvement was found after CAD. Therefore, final axillary invasion was observed in 10 patients, among whom those with micropapillary and cribriform subtypes showed the highest rates of axillary involvement with 20% and 12.5%, respectively. Table 3 presents the clinico-pathologic characteristics of patients with SHT breast cancer with and without axillary infiltration. Patients with axillary invasion were younger (p=0.006) and had slightly larger tumors (non significant) than patients with no axillary involvement.

Discussion and Conclusion

Our results show that SNB is feasible in patients with SHT of breast carcinoma with good identification rates. However, this was a heterogeneous group and technical discrepancies and variable results can be expected.

Table 2. Results of SNB and CAD in the different SHT breast cancer

	n	No migration	SN+	SN+CAD+	CAD+/CAD
Tubular	41	2 (1.4%)	4 (9.7%)	1	4/6
Colloid	34	4 (2.7%)	3 (8.8%)	3	3/7
Medullary	20	1(1.4%)	1(5%)	0	1/2
Papillary	19	0	0		-
Cribriform	8	0	1(12.5%)	0	1/1
Metaplastic	5	1(1.4%)	0		0/1
Invasive micropapillary	5	0	1 (20%)	0	1/1
Neuroendocrine	5	0	0		-
Adenoid cystic	5	0	0		-
Invasive apocrine	2	0	0		-
TOTAL	144	8 (5.6%)	10 (7.4%)		

SN+: positive sentinel node; SN+CAD+: axillary dissection with additional positive lymph node after; SNB: CAD+/CAD: patients with lymph node involvement after a complete axillary dissection

Table 4 summarizes a few interesting aspects of gross and microscopic pathology, rates of axillary invasion, including SNB results when available and prognostic data collected from the literature. Indeed, scant information can be drawn from the literature because most studies that focused on the feasibility of SNB addressed invasive ductal and lobular cancer and rarely discuss results of SHT breast tumors (7-9). Most papers refer to these 'others' with inadequate detail. As an example, Chagpa et al. (8, 10, 11) assessed clinico-pathologic factors associated with SNB feasibility. They concluded that histologic subtype was not a significant factor for SN false negative rate, which was 9.4% for 'other subtypes' (not ductal nor lobular) ahead of ductal/lobular carcinoma (7.8%). Wong et al. (6) pointed out more specific data, as they described more extensive results on SN feasibility with SN identification rates near 100% in tubular and papillary subtypes and slightly less (92%) in colloid and medullary subtypes.

As in ductal or lobular carcinoma, in well-defined, circumscribed or solid SHT tumors, good SN identification rates can be achieved. Conversely, problems may be expected in soft tumors such as the colloid subtype. Colloid breast tumors usually present as a soft gelatinous mass due to its abundant extracellular mucinous secretion. There seems to be a minimum increase in interstitial pressure required for tracer migration in SNB.

Our study has shown that SN positivity prevalence in SHT breast is variable, but probably lower than in ductal/lobular breast cancer. Increased probability of lymphatic spread seems to be related to tumor invasiveness (as with micropapillary and cribriform subtypes). Histologic features to be considered are vascular invasion, intense lymphoplasmocytic reaction, and poorly-differentiated nuclear grade in specific subtypes. Consequently, axillary involvement and positive SNB seem related to microscopic lymph vascular invasion, which has been shown to be high (>10%) in micropapillary and cribriform tumors, and also in neuroendocrine subtypes (not seen in our series) (12, 13). These subtypes are known for their unfavorable prognosis.

The term of 'favorable histologic subtype' was first used by Page and by Simpson and included tubular, colloid (mucinous) papillary, medullary, adenoid-cystic and secretory tumors (14, 15). These cancers have a low rate of lymph node metastases compared with infiltrating ductal or lobular cancers.

Nevertheless, these tumors may spread to axillary nodes (range 5%-10%) as shown in our study in tubular, colloid, and medullary subtypes, and also in the papillary subtype (not seen in our series). This group represents approximately 60% of SHT tumors, and have been better studied probably because they fall in the larger group. Wong et al. (6) used the term 'favorable subtype' to describe SN involve-

Table 3. Clinico-pathologic characteristics of SHT breast cancer patients with and without axillary infiltration

	n	Age (y)	Diagnostic method b/f	Tumor size (mm)	Tumor palpability	Location eq/iq	Radiologic d/m/n
Patients with axillary infiltration	10	49.4 (11.3)	57/43%	17.0 (8.7)	50%	56/44%	20/10/70%
Patients without axillary infiltration	134	62.3 (11.9)	59/41%	13.2 (9.8)	59%	48/52%	13/5/82%
		p=0.001	ns	ns	ns	ns	ns

y: years, mean (SD); mm: millimeters, mean (SD); b/f: core biopsy/fine needle aspiration; eq/iq: external quadrants/internal or retroareolar quadrants; d/m/n: distortion/microcalcifications/nodule; ns: no significant difference

Table 4. Gross and microscopic pathology, axillary invasion including SNB results when available, and prognostic data from literature

	Gross pathology	Microscopic pathology	Axillary metastasis	Prognostic
Tubular	Firm-to hard tumor[4]	Proliferation of small glands to tubules; stroma formed of dense collagenous tissue, with variable elastic tissue[4]	SNB Id:97%(34/35)[6] SN+:17% (6/35) Ax met:9% (17% in mixed types[4]	Favorable in pure tubular carcinoma[4]
Colloid	Soft and gelatinous[4] to firm-to-hard depending on the relative proportions of tumor and fibrous stroma	Accumulation of abundant extracellular mucinous secretion around clusters of tumor cells[4]	SNB Id:92%(77/78)[6] SN+6%(5/84)	Favorable prognosis with low frequency of ax.met.[4]
Medullary	Well-defined contour, firm but[4] softer than the average breast carcinoma	Intense lymphoplasmacytic[4] reaction, poorly different. nuclear grade and a tendency to form broad sheets	SNB Id:92%(22/24)[6] SN+:21%(5/24) Low frequency of ax.met.[4]	Favorable prognosis, not ever in mixed types(4).
Papillary	Well-circumscribed or encapsulated. Composed of soft to moderately firm fleshy tissue[4]	Frond-forming or papillary growth pattern[4]	SNB[6] Id:100%(14/14) SN+:7%(1/14) [4]Ax.met:31%	Limited data but considered of good prognosis[4]
Cribriform	Invade the stroma. Distinctive holes in between cells, making it look like Swiss cheese[12].	Usually low grade, meaning that its cells look and behave somewhat like normal, healthy breast cells[12].	Ax .met:14-40%[12]	Favorable prognosis, not ever in mixed types[12].
Metaplastic	Hard nodular and well circumscribed[4]	Squamous metaplasia[4]	Ax.met: 25%[4] Ax.met:20-25%[5]	Not favorable prognosis (4)
Micropapillary	Lobulated outline node[4]	Vascular invasion. Hollow aggregates of malignant cells that lie within artifactual stromal spaces[4].	Increased proportion of axillary lymph node metastases[4].	Not independent significance for survival in multivariate analysis[4]
Neuroendocrine	Solid[13]. Infiltrating expansive tumors.	Morphologic features similar to neuroendocrine tumors of GI and lung (>50% cells express NE markers)[13]	Increased tendency to metastasize to the lymph nodes, and the liver[13].	Considered malignant and treated aggressively, usually with surgical removal[13]. However, tend to be very slow growing.
Adenoid Cystic	Well defined margins, circumscribed; hyaline stroma and cylinders of tumor cells[4].	Mixture of glandular and stromal or basement membrane material[4]	[5]It rarely ever metastasizes to the axillary nodes. Ax.met=0%[5]	Less aggressive[5]
Apocrine	Usually presents as a mass[4].	Presence of apocrine differentiation[4]	Not specified. [9] 'good histologic subtype'	Less aggressive[5]

ment in patients with tubular, papillary, colloid, pure medullary and DCIS with microinvasion carcinomas and found rates of 17%, 7%, 6%, 21%, and 8%, respectively. Capdet et al. (9) described tubular, colloid, and apocrine subtypes as 'good histologic types' with a positive SN rate of 12.5%.

More recently, Martin et al. (7) mentioned the 'other' histologic subtypes, including medullary and mucinous subtypes, and found a positive SN rate of 17% for tumors smaller than 1 cm. Tumor size might be an easy parameter to use if SNB is to be considered. In our study, patients with axillary involvement had larger tumors those without. Interestingly, younger age was significantly associated with axillary invasion.

Data obtained from Mendez et al. (16) also supported individualized use of SNB in patients with favorable histologic breast cancer, taking into account the overall 4% incidence of lymph-node metastases. However, the authors found that specific subtypes such as medullary or papillary cancers presented with positive SN rates of 16.6% and 12.5%, respectively. On the other hand, some SHT breast cancer such as the adenoid-cystic subtype, do not usually spread to axillary lymph nodes, and behave as a low-aggressiveness tumors with better prognosis (5, 16).

Clear-cut pathologic definition of these tumor subtypes is important, because favorable subtypes are less likely to spread to lymph nodes and distant sites. Also, efforts to distinguish 'pure' from 'mixed' cancers are needed, as differences in lymph-node involvement have been described. Favorable subtypes are considered 'pure' if they have characteristic histologic features in at least 90% of the tumor. However, wide variations have been reported in the pathologic diagnoses of these lesions. We also have to keep in mind that such a definition might be achieved only in the final pathology report.

Finally, to decide on SNB in these patients, we must consider other related factors such as size, hormone receptors, nuclear grade, and lymphovascular invasion, and especially whether adjuvant treatment should be modified according to SNB results.

To conclude, we believe that taking into account its feasibility and the rates of axillary involvement, SNB must be considered in patients with SHT breast cancer just as with ductal or lobular carcinoma. However, lower migration rates might be associated with special histologic features (colloid subtype). Moreover, subsequent CAD after a positive sentinel node cannot be omitted in patients with SHT breast cancer because they can be associated with further axillary disease as shown in our own study. Avoiding axillary dissection would only be justified in the adenoid-cystic subtype because of its very low reported incidence of axillary metastases.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.S., M.R.; Design - M.S., M.R., M.F.; Supervision - M.S., M.F.; Materials - E.C.; Data Collection and/or Processing - M.S., M.R, J.M.G., P.P.; Analysis and/or Interpretation - M.S., F.J., M.R.; Literature Review - M.S., M.F.; Writing - M.S.; Critical Review - M.F., J.M.G., P.P.

Acknowledgement: The authors wish to express their gratitude to those patients that generously consented to participate in our investigation. Also, we want to acknowledge the local researchers that have allowed collecting primary data.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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