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 intrallesional 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.
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
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

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

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

<table>
<thead>
<tr>
<th>Gross pathology</th>
<th>Microscopic pathology</th>
<th>Axillary metastasis</th>
<th>Prognostic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubular</td>
<td>Firm-to hard tumor(4)</td>
<td>Proliferation of small glands to tubules; stroma formed of dense collagenous tissue, with variable elastic tissue(4)</td>
<td>SNB Id:97%(34/35)(6) SN+:17% (6/35) Ax met:9% (17% in mixed types(4)</td>
</tr>
<tr>
<td>Colloid</td>
<td>Soft and gelatinous(6) to firm-to-hard depending on the relative proportions of tumor and fibrous stroma</td>
<td>Accumulation of abundant extracellular mucinous secretion around clusters of tumor cells(4)</td>
<td>SNB Id:92%(77/78)(6) SN+:6%(5/84)</td>
</tr>
<tr>
<td>Medullary</td>
<td>Well-defined contour, firm but(6) softer than the average breast carcinoma</td>
<td>Intense lymphoplasmacytic(6) reaction, poorly different. nuclear grade and a tendency to form broad sheets</td>
<td>SNB Id:92%(22/24)(6) SN+:21%(5/24)</td>
</tr>
<tr>
<td>Papillary</td>
<td>Well-circumscribed or encapsulated. Composed of soft to moderately firm fleshy tissue(4)</td>
<td>Frond-Forming or papillary growth pattern(6)</td>
<td>SNB Id:100%(14/14) SN+:7%(1/14) (Ax.met:31%</td>
</tr>
<tr>
<td>Metaplastic</td>
<td>Hard nodular and well circumscribed(4)</td>
<td>Squamous metaplasia(4)</td>
<td>Ax.met: 25%(6) Ax.met:20-25%(3)</td>
</tr>
<tr>
<td>Micropapillary</td>
<td>Lobulated outline node(4)</td>
<td>Vascular invasion. Hollow aggregates of malignant cells that lie within artifactual stromal spaces(6).</td>
<td>Increased proportion of axillary lymph node metastases(6).</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>Solid(13), Infiltrating expansive tumors.</td>
<td>Morphologic features similar to neuroendocrine tumors of GI and lung (&gt;50% cells express NE markers)(13)</td>
<td>Increased tendency to metastasize to the lymph nodes, and the liver(13).</td>
</tr>
<tr>
<td>Adenoid Cystic</td>
<td>Well defined margins, circumscribed; hyaline stroma and cylinders of tumor cells(4).</td>
<td>Mixture of glandular and stromal or basement membrane material(4)</td>
<td>Mixture rarely ever metastasizes to the axillary nodes. Ax.met:0%(3)</td>
</tr>
<tr>
<td>Apocrine</td>
<td>Usually presents as a mass(6).</td>
<td>Presence of apocrine differentiation(6)</td>
<td>Not specified. (9) ‘good histologic subtype’</td>
</tr>
</tbody>
</table>

...
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.; Analysis and/or Interpretation - M.S., E.J., M.R.; Literature Review - M.S., M.F.; Writing - M.S.; Critical Review - M.F., J.M.G., P.

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