Sentinel node biopsy in patients with multifocal and multicentric breast cancer: A 5-year follow-up

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ABSTRACT

Objective: Sentinel lymph node biopsy (SLNB) as a staging procedure in multiple breast cancer is a controversial issue. We have aimed to evaluate the efficacy of sentinel node (SN) detection in patients with multifocal or multicentric breast cancer as well as the safety of its clinical application after a long follow-up.

Material and methods: A prospective descriptive study was performed. Eighty-nine patients diagnosed of multiple breast cancer (73 multifocal; 16 multicentric) underwent SLNB. These patients were compared to those with unifocal neoplasia. Periareolar radiocolloid administration was performed in most of the patients. Evaluation was made at an average of 67.2 months of follow-up (32–126 months).

Results: Scintigraphic and surgical SN localization in patients with multiple breast cancer were 95.5% and 92.1%, respectively. A higher percentage of extra-axillary nodes were observed than in the unifocal group (11.7% vs. 5.4%) as well as a significantly higher number of SN per patient (1.70 vs. 1.57). The rate of SN localization in multicentric cancer was slightly lower than in multifocal cancer (87.5% vs. 93.1%), and the finding of extra-axillary drainages was higher (20% vs. 10%). Number of SN per patient was significantly higher in multicentric breast cancer (2.33 vs. 1.57). No axillary relapses have been demonstrated in the follow-up in multiple breast cancer patients group.

Conclusions: SLNB performed by periareolar injection is a reliable and accurate staging procedure of patients with multiple breast cancer, including those with multicentric processes.

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Biopsia de ganglio centinela en pacientes con cáncer de mama multifocal y multicéntrico: 5 años de seguimiento

RESUMEN

Objetivo: La biopsia selectiva del ganglio centinela (BSGC) como procedimiento de estadificación en el cáncer de mama múltiple es cuestión de controversia. Nuestro objetivo es evaluar la eficiencia de detección del ganglio centinela (GC) en las pacientes con cáncer multifocal o multicéntrico, y la seguridad de su aplicación clínica, tras un seguimiento prolongado.

Material y métodos: Se realizó un estudio prospectivo descriptivo. Se estudiaron 89 pacientes con cáncer múltiple de mama sometidas a BSGC (73 procesos multifocales, 16 multicéntricos), comparándolas con las que presentaron neoplasia unifocal. En la mayor parte de las BSGC se realizó administración periareolar de radiocoloide. Se realizó la evaluación a los 67.2 meses de seguimiento medio (32–126 meses).

Resultados: Las tasas de localización gammagráfica y quirúrgica del GC en las pacientes con cáncer múltiple fueron respectivamente 95.5% y 92.1%, observándose mayor porcentaje de GC extraaxilares que en los procesos unifocales (11.7% frente a 5.4%) y un número de GC por paciente significativamente mayor (1.70 frente a 1.38). La tasa de localización del GC en el cáncer multicéntrico fue ligeramente inferior al multifocal (87.5% frente a 93.1%) y el hallazgo de drenajes extra-axilares más elevado (20% frente a 10%). El número promedio de GC por paciente fue significativamente superior en el cáncer multicéntrico (2.33 frente a 1.57). No se han registrado recurrencias axilares en el seguimiento de las pacientes con cáncer múltiple.

Conclusiones: BSGC mediante inyección periareolar es un procedimiento preciso y fiable de estadificación del cáncer de mama múltiple, incluso multicéntrico.

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Introduction

Lymphatic dissemination is a key prognostic factor in the early diagnosis of breast cancer, being in close relationship with other determinant characteristics of the primary tumor such as the size and histologic grade and molecular typing established according to the expression of oncogenes and hormone receptors, and factors of proliferation, among others.

Selective sentinel lymph node biopsy (SLNB) is the current procedure for the regional lymph node staging of patients with early breast cancer. Since the first recommendations of inclusion for this technique, the spectrum of clinical situations in which lymphatic staging by SLNB is indicated has progressively increased. In this sense, to date, probably the only breast cancer scenario in which SLNB is absolutely contraindicated is the demonstration of positive adenopathies. Nonetheless, the application of SLNB in other clinical situations such as in the case of patients with a history of breast surgery or after primary chemotherapy or with multicentric neo-plasms remains under debate.

The finding of multiple unilateral breast cancer is increasingly more frequent since the introduction of magnetic resonance (MR) imaging in the routine protocol of presurgical diagnosis, with an incidence of 7–15.4% in patients with breast cancer undergoing SLNB. The presence of more than one synchronous breast lesion does not per se contraindicate the performance of SLNB, although this indication presents a better level of evidence in the case of multifocality (several tumors in the same quadrant) than in multicentricity (several tumors in different quadrants). Tumor multiplicity implies prognostic impairment. In this context, the percentage of positive sentinel lymph nodes (SLN) in these patients is greater (25–61%) with a significant association having been described with the incidence of macrometastasis and with the finding of an elevated number of affected lymph nodes.

In multiple breast cancer the presence of different independent pathways of lymphatic drainage which are tributaries of each tumor is frequent, particularly if these tumors are separated in the breast. Very high rates of positivity of non-SLN have been described, and the appearance of false negative results in validation studies is quite elevated (7–33%), which, in the clinical phase, translates into an increase of demonstrated axillary recurrence of up to 1.6–2.2%. For these reasons some groups have questioned the systematic application of the SLNB technique in patients with multiple unilateral synchronous breast cancer. In any case, in the absence of randomized trials to this respect, the performance of SLNB in patients with more than one synchronous breast lesion should be made with caution in regard to both the route of radiotracer administration and the safety of the application of the procedure itself. With respect to the first, protocols of multiple injection in the area of each tumor or a single areolar injection have been proposed, and in relation to safety the registry of lymph node recurrence is the most relevant parameter to determine the reliability of the technique in these patients.

The aim of this study was, on one hand, to evaluate the efficiency of the SLNB technique in patients with multiple breast cancer, particularly in multicentric processes, determining the suitability of the periareolar administration in these patients. On the other hand, we verified the safety of its clinical application, performing a prolonged follow-up of the patients and consequently establishing the indication of this staging procedure in multiple breast cancer.

Material and methods

We included 89 patients diagnosed with multiple unilateral synchronous breast cancer who underwent SLNB for lymph node staging. These patients represent 14.8% of the 600 SLNB procedures carried out from February 2003 (when the clinical application began) to December 2010 in 591 patients with early breast cancer (bilateral in 9 cases) presenting T1–T2 tumors (or Tis with risk of microinvasion or indication of mastectomy), with clinical and ultrasonographic indications established according to the expression of oncogenes and hormone receptors, and factors of proliferation, among others.

For the intraoperative detection of the SLN we used a Europrobe™ (Eurad, Strasbourg, France). A SLN was considered as any lymph node previously visualized in the scintigraphy and which presented a significant intraoperative count. Any other lymph node registering activity > 10% of the SLN, as well as any other suspicious palpable lymph node was resected. Dyes were not used for the surgical detection of the SLN.

The patients provided written informed consent to participate in the study.

Surgery was only performed in the internal mammary chain in one patient presenting only drainage in this lymphatic territory.
Table 1
Patients included in the study.

<table>
<thead>
<tr>
<th></th>
<th>Multiple cancer</th>
<th>Unifocal cancer</th>
<th>p (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 40</td>
<td>56.5</td>
<td>60.1</td>
<td>0.0153 (0.675 6.3439)</td>
</tr>
<tr>
<td>40–60</td>
<td>47 (52.8)</td>
<td>223 (44.4)</td>
<td></td>
</tr>
<tr>
<td>60–80</td>
<td>30 (33.7)</td>
<td>229 (45.6)</td>
<td></td>
</tr>
<tr>
<td>≥ 80</td>
<td>5 (5.6)</td>
<td>32 (6.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Mean tumor size (cm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tis</td>
<td>1.81</td>
<td>1.56</td>
<td>0.0382 (0.014 0.474)</td>
</tr>
<tr>
<td>T1a (≤ 5 mm)</td>
<td>16 (18)</td>
<td>30 (5.8)</td>
<td></td>
</tr>
<tr>
<td>T1b (&gt;5 ≤ 10 mm)</td>
<td>15 (16.8)</td>
<td>148 (29)</td>
<td></td>
</tr>
<tr>
<td>T1c (&gt;10 ≤ 20 mm)</td>
<td>33 (37.1)</td>
<td>243 (47.5)</td>
<td></td>
</tr>
<tr>
<td>T2 (&gt;2 ≤ 5 cm)</td>
<td>25 (28)</td>
<td>79 (15.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Lymph nodes</strong></td>
<td>62 (69.7)</td>
<td>428 (83.8)</td>
<td></td>
</tr>
<tr>
<td>Microcalcifications</td>
<td>24 (27)</td>
<td>38 (7.4)</td>
<td>&lt;0.0001 (–0.248 –0.034)</td>
</tr>
<tr>
<td>Distortion/opacity</td>
<td>3 (3.3)</td>
<td>45 (8.8)</td>
<td>&lt;0.0001 (0.094 0.297)</td>
</tr>
<tr>
<td>Palpable</td>
<td>44 (49.4)</td>
<td>285 (55.8)</td>
<td></td>
</tr>
<tr>
<td>Non-palpable</td>
<td>45 (50.6)</td>
<td>226 (44.2)</td>
<td>0.2994 (–0.182 0.056)</td>
</tr>
<tr>
<td>Conservative surgery</td>
<td>22 (24.7)</td>
<td>443 (86.7)</td>
<td>&lt;0.0001 (–0.721 –0.519)</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>67 (75.3)</td>
<td>68 (13.3)</td>
<td>&lt;0.0001 (0.519 0.721)</td>
</tr>
<tr>
<td><strong>Periareolar injection</strong></td>
<td></td>
<td>391 (76.5)</td>
<td>0.2151 (–0.026 0.159)</td>
</tr>
<tr>
<td>Combined injection*</td>
<td>11 (12.4)</td>
<td>67 (13.1)</td>
<td></td>
</tr>
<tr>
<td>Deep injection**</td>
<td>4 (4.5)</td>
<td>53 (10.4)</td>
<td></td>
</tr>
<tr>
<td>Pure IDC</td>
<td>32 (36)</td>
<td>380 (74.4)</td>
<td>&lt;0.0001 (–0.497 –0.271)</td>
</tr>
<tr>
<td>IDC + DCIS</td>
<td>32 (36)</td>
<td>51 (9.9)</td>
<td>&lt;0.0001 (0.150 0.369)</td>
</tr>
<tr>
<td>DCIS (of risk)</td>
<td>16 (18)</td>
<td>30 (5.9)</td>
<td>0.0003 (0.032 0.210)</td>
</tr>
<tr>
<td>ILC (± CLIS)</td>
<td>8 (8.9)</td>
<td>46 (9)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>1 (1.1)</td>
<td>4 (0.8)</td>
<td></td>
</tr>
</tbody>
</table>

IDC: invasive ductal carcinoma; ILC: invasive lobulillar carcinoma; CLIS carcinoma lobulillar in situ; DCIS: carcinoma ductal in situ (high grade, extensive, risk of microinvasion).

* Unifocal cancer group: 511 Sentinel lymph node biopsies, 502 patients (9 bilateral).

** Combined injection: periareolar and deep; deep injection: intratumoral or peritumoral. p significant < 0.05.

without axillary migration. In the remaining patients presenting axillary and extra-axillary lymphatic migration only the axilla underwent intervention. Surgery of the other extra-axillary lymphatic chains was not performed.

Intraoperative analysis of the SLN resected was performed. The SLN were first bisectioned longitudinally (2 mm), studying each side of the sections by scrape cytology and hematoxylin-eosin (H–E) staining. The SLN were then frozen in 5 micra sections each 100 and studied by levels. In each level 3 slices were stained with H–E, reserving one for immunohistochemistry (wide spectrum AE1–AE3 cytokeratins) which was deferred when the H–E study was negative. According to conventional criteria, macrometastases were considered as those greater than 2 mm, micrometastases were those from 2 to 0.2 mm or more than 200 tumor cells and isolated tumor cells (ITC) were considered the tumor groups of less than 0.2 mm and 200 cells.

Axillary lymph node dissection (ALND) was performed whenever the SLN was positive except in 4 of the cases presenting micrometastasis and 2 with ITC and in all those not identified intraoperatively.

The Fisher’s exact test was used for the statistical analysis of the categorical variables and the Student’s t test was used to compare the means of the continuous variables. A p value < 0.05 was considered statistically significant. The confidence intervals (95%) of the difference between the proportions of the categorical variables and between the means of the continuous variables are expressed. The EPIDAT 3.0 statistical program was used for the statistical analyses.

Results

The most relevant characteristics of the patients included with concomitant breast tumor multiplicity are shown in Table 1, as is the comparison with the 511 procedures performed in the 502 patients presenting unifocal neoplasm (9 cases with bilateral cancer). The group of patients with multiple cancer were significantly

Fig. 1. Schema of the procedures of injection used. (A) Subdermal periareolar injection (4 cardinal points): main method. (B) Deep intratumoral or peritumoral injection into each of the coexistent tumoral lesions. (C) Combined injection using both procedures simultaneously.
younger and had a much higher percentage of microcalcifications as the form of mammographic presentation and a greater mean tumor size, with most of these patients undergoing mastectomy. With regard to the histological profile, this group included 16 cases of multiple in situ carcinoma (18%) and 73 of multiple invasive cancer. Lymphoscintigraphy identified the SLN in 85 of the 89 patients with multiple breast cancer (95.5%) while the percentage of detection in the patients with unifocal cancer was 94.3% (Table 2). An average of 1.70 SLN was observed per patient in the multiple cancer group, being 1.38 in the remaining study population (p = 0.0005). The SLN was observed in the extra-axillary territory in 10 of the 85 cases localized, representing 11.7% of the total SLNB procedures performed in multiple carcinoma versus 5.4% of extra-axillary drainages identified in the remaining patients.

During the intervention the SLN was successfully resected in 82 patients with multiple breast cancer, representing an intraoperative detection rate of 92.1% versus 90.2% achieved in the remainder of the population. Multiple lymph node metastases were found on pathological analysis of the axillary lymph nodes in 10% of the patients with multicentric breast cancer, is still under debate since the safety and efficacy of its application presents a lower level of evidence than in the remaining patients.1,11 Tumor multiplicity implies an unfavorable prognosis associated, among other factors, with an elevated risk of lymphatic dissemination.10,12–14,19 In these patients the probability of erroneous identification of the SLN is greater, leading to a high incidence of false negative results16–18,21 and thus, a greater rate of axillary recurrence.6,19

We identified 14.8% of patients with multiple neoplasm in the first 8 years of the clinical application of SLNB in breast cancer, being a similar percentage to that reported by other authors.9–10,23

In our series the efficiency of the localization of the SLN in patients presenting tumor multiplicity was 95.5% in the preoperative scintigraphy and 92.1% in the surgical intervention, with no significant differences between multiple invasive or in situ processes. Axillary lymph node infiltration may have blocked the

**Table 2**

Results in patients with multiple tumors.

<table>
<thead>
<tr>
<th></th>
<th>Multiple cancer</th>
<th>Unifocal cancer</th>
<th>p (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sc.SLN localization</td>
<td>85 (95.5)</td>
<td>482 (94.3)</td>
<td>0.8043 (−0.042 0.066)</td>
</tr>
<tr>
<td>SLN/patient</td>
<td>1.70</td>
<td>1.38</td>
<td>0.0005 (0.140 0.499)</td>
</tr>
<tr>
<td>Extra-axillary SLN</td>
<td>10 (11.7)</td>
<td>26 (5.4)</td>
<td>0.0487 (−0.015 0.142)</td>
</tr>
<tr>
<td>S. localization SLN</td>
<td>82 (92.1)</td>
<td>461 (90.2)</td>
<td>0.6968 (−0.049 0.087)</td>
</tr>
<tr>
<td>SLN (+)</td>
<td>22 (26.8)</td>
<td>105 (22.7)</td>
<td>0.4788 (−0.070 0.151)</td>
</tr>
<tr>
<td>Rate of disease</td>
<td>4 (4.5)</td>
<td>41 (8)</td>
<td>0.3805 (−0.091 0.020)</td>
</tr>
</tbody>
</table>

Sc: scintigraphic, S: surgical; SLN: sentinel lymph node.

Unifocal cancer group: 511 sentinel lymph node biopsies, 502 patients (9 bilateral).

The mean number of SLN per patient was 2.33 in the multicentric and 1.57 in the multifocal processes (p = 0.0077). Drainage outside the axilla was observed in 20% of the patients with multicentric tumors and in 10% of the multifocal tumors while the percentage of affected SLN was 35.7 and 25%, respectively.

To date, no axillary recurrence has been reported in the group of patients with multiple cancers after 67.2 months of mean follow-up (32–126 months). The appearance of breast cancer-related disease has been reported in 4 of the 89 patients with multiple neoplasm (3 corresponding to multifocal and one to multicentric cancer), representing a rate of disease of 4.5% (Table 2). These 4 patients presented distant disease (one with local recurrence) and to date 3 have died.

The rate of events currently related to the breast cancer described in the group of patients with unifocal neoplasm is 8% (41/502), with axillary recurrence in 3 of the 406 patients with benign SLN (rate: 0.7%).

**Discussion**

At present, SLNB is the procedure of choice for lymphatic staging of early breast cancer.1,2 Although the efficacy and reliability of this technique has been widely demonstrated, some aspects remain controversial, as do certain criteria of inclusion.3,4 Thus, for example, the indication of SLNB in multiple breast cancer, particularly multicentric breast cancer, is still under debate since the safety of its application presents a lower level of evidence than in the remaining patients.1,11

Tumor multiplicity implies an unfavorable prognosis associated, among other factors, with an elevated risk of lymphatic dissemination.10,12–14,19 In these patients the probability of erroneous identification of the SLN is greater, leading to a high incidence of false negative results16–18,21 and thus, a greater rate of axillary recurrence.6,19

We identified 14.8% of patients with multiple neoplasm in the first 8 years of the clinical application of SLNB in breast cancer, being a similar percentage to that reported by other authors.9–10,23

In our series the efficiency of the localization of the SLN in patients presenting tumor multiplicity was 95.5% in the preoperative scintigraphy and 92.1% in the surgical intervention, with no significant differences between multiple invasive or in situ processes. Axillary lymph node infiltration may have blocked the

**Table 3**

Results in multifocal and multicentric tumors.

<table>
<thead>
<tr>
<th></th>
<th>MC 16 (%)</th>
<th>MF 73 (%)</th>
<th>p (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sc localization SLN</td>
<td>15 (93.7)</td>
<td>70 (95.8)</td>
<td>0.5542 (−0.187 0.144)</td>
</tr>
<tr>
<td>SLN/patient</td>
<td>2.33</td>
<td>1.57</td>
<td>0.0077 (0.206 1.317)</td>
</tr>
<tr>
<td>Extra-axillary SLN</td>
<td>3 (20)</td>
<td>7 (10)</td>
<td>0.3715 (−0.155 0.335)</td>
</tr>
<tr>
<td>S. localization SLN</td>
<td>14 (87.5)</td>
<td>68 (93.1)</td>
<td>0.0647 (−0.267 0.154)</td>
</tr>
<tr>
<td>SLN (+)</td>
<td>5 (35.7)</td>
<td>17 (25)</td>
<td>0.5901 (−0.207 0.421)</td>
</tr>
<tr>
<td>Rate of disease</td>
<td>1 (6.2)</td>
<td>3 (4.1)</td>
<td>0.5542 (−0.144 0.187)</td>
</tr>
</tbody>
</table>

MC: multicentric; MF: multifocal; Sc: scintigraphic; SLN: sentinel lymph node. S: surgical.

p significant < 0.05.
migration of the radiocolloid in almost half of the cases not localized.

These rates of SLN detection in multiple cancer are even greater than those obtained in unifocal cancer, being similar to those described by other groups,7–9,13–15 and are probably related to various factors affecting the detection of the SLN.

Firstly, although tumor multiplicity implies a worst prognosis of breast cancer, the patients with multiple neoplasms included in the present study presented a relatively low lymph node tumor burden suggesting their “profile” of aggressiveness was not high and therefore did not have an unfavorable effect on the detection process, contrary to what was expected.25 On the other hand, the percentage of positive SLN was only slightly higher than that in the remaining patients (non-statistically significant difference) and lower than that described in other series.7,13–15,19 This is unusual8,9,19 and is even more so on taking into account that the mean size of the multiple tumors was significantly greater than that of the unifocal lesions. This data is directly related to the fact that a relevant number of multiple cases corresponded to in situ processes, being otherwise unable to metastasize. On the other hand, the positive SLN was the only lymph node affected in the axilla in a percentage of patients which was practically identical to that of the unifocal group.7 The finding of other affected axillary lymph nodes was only related to the size of the metastasis of the SLN.

Secondly, the mean age of the women presenting multiple breast cancer was significantly lower than that of the remaining study population. Migration of the radiocolloid is better in younger women and thus, the detection of the SLN is higher.26

Lastly, in most patients with multiple cancer, administration of the radiocolloid is subdermal periareolar. This method of injection is usually applied by our group,3 providing elevated rates of SLN identification,23,24 similar to those described in unifocal cancer and has been proposed as the procedure of choice in multifocal breast cancer.19 This method has other advantages as proposed by Bézu et al.,25 in patients in whom the diagnosis of multilocality is made from the mastectomy piece following surgery and the SLNB. In these cases axillary representativeness of the whole breast is guaranteed in the SLN resected only if the injection is areolar, while if the injection is performed in the only tumor diagnosed preoperatively, lymph node staging would be incomplete and a new procedure of SLNB after mastectomy would not be viable.

However, other authors,9 including Brouwer et al.,22 have proposed multiple intratumoral injections and even of each tumor as a protocol to identify specific drainage. In contrast, Holl et al.25 reported a direct association between peritumoral injection and the percentage of false negative results (26%), being much greater than the 5.6% obtained with subareolar injection. The disparity of these results probably depends on rigorous administration of the radiotracer and representative of the whole breast.25,29

It therefore seems that the application of SLNB to multicentric breast cancer is acceptable, although it implies some unfavorable factors which must be taken into account,13,20 the efficacy of the identification of the SLN is slightly lower, the number of SLN per patient is higher, often with extra-axillary localization and with a greater risk of tumoral lymph node involvement.

To date, axillary recurrence has not been reported in the patients with multiple, whether multifocal or multicentric, breast cancer indicating the safety of the technique in both groups as suggested by other authors.18 The minimum follow-up was of 32 months, which was considerably lengthy considering that most recurrences in breast cancer appear in the first 2–3 years. In this context it should be taken into account that in one of the 60 patients in whom the SLN was benign, one “suspicious” adenopathy was resected which was malignant, and the ALND performed probably avoided future axillary recurrence.

The rate of disease observed, to date, in the patients with multiple cancer is lower, albeit not significantly, than that of the remaining study population (4.5% vs. 8%), which is clearly consistent with the profile of good prognosis of the patients with multiple cancer included (elevated proportion of in situ processes, low percentage of positive lymph nodes and affected axillas). This aspect has been previously described and probably constitutes the main limitation of this study on comparing the 2 study groups.

Conclusions

The presence of tumoral multiplicity did not represent a detriment to the efficacy of SLNB in breast cancer, with the rate of SLN detection in these patients being elevated and with no relevant differences compared to patients with a single lesion.

The periareolar injection seems adequate in multiple breast cancer and suggests that it represents the drainage of each of the tumors since the average SLN per patient and the finding of extra-axillary drainages were significantly higher than in the population with unifocal cancer.

The indication of SLNB is also correct and safe in the cases of multicentric breast cancer.
Conflicts of interest

The authors have no conflicts of interest to declare.

References