Selective biopsy of the sentinel lymph node in patients with breast cancer and previous excisional biopsy: Is there a change in the reliability of the technique according to time from surgery?


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Aim: To assess the influence of time on the reliability of sentinel lymph node biopsy (SLNB) in breast cancer patients with previous excisional biopsy (EB), analyzing both the sentinel lymph node detection and the lymph node recurrence rate.

Materials and methods: Thirty-six patients with cT1/T2 N0 breast cancer and previous EB of the lesion underwent a lymphoscintigraphy after subdermal periareolar administration of radiocolloid, the day before SLNB. Patients were classified into two groups, one including 12 patients with up to 29 days elapsed between EB and SLNB (group A), and another with the remaining 24 in which time between both procedures was of 30 days or more (group B). Scintigraphic and surgical detection of the sentinel lymph node, histological status of the sentinel lymph node and of the axillary lymph node dissection, if performed, and lymphatic recurrences during follow-up, were analyzed.

Results: Sentinel lymph node visualization at the lymphoscintigraphy and surgical detection was 100% in both groups. Histologically, three patients showed macrometastasis in the sentinel lymph node, one from group A and two from group B. None of the patients, not even those with malignancy of the sentinel lymph node, relapsed after a medium follow-up of 49.5 months (24–75).

Conclusion: Time elapsed between EB and SLNB does not influence the reliability of this latter technique as long as a superficial injection of the radiopharmaceutical is performed, proving a very high detection rate of the sentinel lymph node without evidence of lymphatic relapse during follow-up.

Biopsia selectiva del ganglio centinela en pacientes con cáncer de mama y biopsia escisional previa: ¿cambia la fiabilidad de la técnica según el tiempo transcurrido desde la cirugía?

Objetivo: Analizar la influencia del tiempo sobre la fiabilidad de la biopsia selectiva del ganglio centinela (BSGC) en pacientes con cáncer de mama y biopsia escisional (BE) previa, estudiando la tasa de detección del ganglio centinela y de recidivas ganglionares.

Material y métodos: Se incluyeron 36 pacientes con cáncer de mama cT1/T2 N0 y BE de la lesión, a los que se realizó la linfogammagrafía tras la administración periareolar subdérmica de radiocoloide, el día previo a la cirugía para BSGC. Los pacientes se clasificaron en dos grupos: uno incluyó 12 pacientes en los que la BSGC tuvo lugar durante los 29 días posteriores a la BE (grupo A) y otro 24 en que el tiempo transcurrido entre ambas cirugías fue igual o superior a 30 días (grupo B). Se analizaron la detección gammagráfica y quirúrgica del ganglio centinela, la histología del ganglio centinela y de la linfadenectomía axilar realizada, y las recidivas ganglionares durante el seguimiento.

Resultados: La detección gammagráfica y quirúrgica del ganglio centinela fue del 100% en ambos grupos. Histológicamente, tres pacientes presentaron macrometastasis en el ganglio centinela, una del grupo A y dos del B. Ningún paciente, ni siquiera aquellos con afectación metastásica del ganglio centinela, recidió después de un seguimiento medio de 49,5 meses (24–75).
Introduction

Selective sentinel lymph node biopsy (SSNB) in breast cancer is a widely accepted technique for predicting the state of the axillary lymph nodes. Compared to axillary lymph node dissection (ALND), SSNB presents less morbidity. Indeed, in the last years SSNB has been used as a tool for the staging of patients with early stage breast cancer, thereby reducing the number of unnecessary ALND. Different factors have been related to a reduction in the sensitivity of the identification of the sentinel node (SN) and an increase in the false negative (FN) rate. One of these factors is the previous history of excisional biopsy (EB) of the breast lesion, which is believed to alter the pathways of lymphatic drainage. However, different studies have demonstrated that after EB neither factor is significantly different from those of patients undergoing thick needle biopsy or fine needle aspiration puncture, and thus, previous EB is not currently a contraindication to SSNB in breast cancer. Several groups have analyzed the effect of time between EB and SSNB in relation to the detection of the SN. Nonetheless, the ideal time interval and how this interval may influence the rate of lymph node recurrence remains to be established.

The aim of the present study was to analyze how the time between EB and SSNB influences the reliability of the latter in patients with breast cancer and previous EB, taking into account not only the detection of the SN but also lymph node recurrence during follow-up.

Materials and methods

We retrospectively analyzed 36 patients with breast cancer referred for SSNB from July 2007 to October 2011. All the cases were clinical stage T1 or T2 N0 and had undergone previous EB of the primary tumor (Table 1 shows the characteristics of the patients). Patients with a previous history of radiotherapy and/or chemotherapy were excluded from the study.

The patients were classified into two groups based on the time between EB and radioguided surgery for SSNB performed on completion of the excision of the primary tumor. Group A included 12 patients with a mean age of 51 years who underwent SSNB in the first 29 days after EB. Group B included 24 patients with a mean age of 55 years who underwent SSNB 30 days or more after EB. In most Group B patients (20/24, 83%), the range in time between EB and radioguided surgery was between 30 and 60 days (mean 52 days). The time between the two techniques was greater than 60 days in only 4 cases (17%), with a maximum of 105 days in one of these patients.

The day prior to radioguided surgery lymphoscintigraphy (LS) was performed in all the patients 2 h after 4 subdermal periareolar injections of 111 MBq (3 mCi) 99mTc-albumin nanocolloid (Nanocol®) at a volume of 0.4 ml. Planar images of the chest were obtained in anterior, oblique or lateral of the affected side. A 57Co flood source was used to draw the anatomical contour. A gamma camera with a high resolution, low energy collimators and dual energy acquisition window centered in the photopeaks of 140 keV of 99mTc (10%) and 122 keV of 57Co (5%) was used with an acquisition time of 300 s/image. Foci of increased uptake were localized on the skin with a 57Co pencil and marked with a waterproof marker. Lymphatic drainage was not initially demonstrated in 2 patients, and they therefore underwent subdermal reinjection with 18.5 MBq (0.5 mCi) at a volume of 0.2 ml in a single injection in the quadrant in which the EB had been performed, and new images were obtained at 1 h.

Surgical localization of the SN was made from 18 to 24 h after the injection of the radiocolloid using a gamma detector probe (Euro-probe; BriTec, Sheffield, UK). A SN was considered to have a greater radioactive count and activity 10% greater than that of the most active lymph node. During surgery, the lymph nodes resected were peroperatively analyzed (cytological marking and staining with Diff Quick (QCA, Amposta, Spain) until December 2010, and OSNA method thereafter), leading to ALND in the same intervention if macrometastases were shown or in another procedure (in the following 4 weeks) if these were observed in the posterior analysis.

The parameters studied included scintigraphic and surgical detection of the SN, the histological grade of SN and the ALND in patients with macrometastasis in the SN as well as the lymph node recurrences during up to 6 years (24–75 months) of follow-up.

Results

Presurgical LS showed at least one axillary SN in all the patients as well as in the 2 patients (5.5%) in Group B who were re-injected. In another 2 cases in Group B the SN also showed extra-axillary drainage: to the internal mammary lymph node chain in one and to the supraclavicular region in the other, ipsilateral to the affected breast in both cases. The extra-axillary lymph nodes were not
resected during surgery due to low focal detection of the radioactivity which did not ensure correct localization of the lymph node.

At least one SN was detected and resected in all the patients in the two groups. A total of 81 lymph nodes were obtained, 79 of which were classified as SN.

Histological analysis of all the SN showed metastatic involvement in 5 lymph nodes of 3 patients: one from Group A and two from Group B.

- The patient in Group A presented two foci of malignancy in the breast, one with histological findings of infiltrating ductal carcinoma and the other with infiltrating lobular carcinoma. During surgery a SN was obtained showing a metastasis of 3 mm. This patient had a history of contralateral breast cancer 8 years previously, treated with mastectomy and ALND, and thus did not undergo ALND on this occasion. She received radiotherapy in the breast and axilla as well as chemotherapy.

- One of the patients in Group B had an in situ pleomorphic lobular carcinoma, with microcalcifications and two foci of microinfiltration. Two SN were resected in this patient: one with micrometastasis and the other with isolated malignant cells, and thus, according to our hospital protocol ALND was not performed. The patient was treated with radiotherapy, adjuvant chemotherapy and hormone therapy (for presenting positive estrogenic receptors).

- The remaining patients in Group B presented infiltrating ductal carcinoma. Two SN were obtained, both with macrometastasis. ALND was performed in the same surgical procedure with no evidence of malignant cells in the 16 additional lymph nodes.

Neither of the two lymph nodes resected and classified as non-sentinel showed metastatic involvement.

After a mean follow-up of 48.5 months (24–75), none of the patients in either group, those with metastatic involvement of the SN or those who did not undergo ALND, presented regional or distant recurrence (Table 2).

**Discussion**

The performance of SSNB after EB has been controversial for some time. Several studies at the end of the 1990s concluded that this type of biopsy had a negative influence on SSNB, reducing the probability of detecting drainage in the LS and localizing the SN during surgery. Nonetheless, later publications demonstrated that the type of biopsy did not affect either the detection of the SN or the global rate of FN, suggesting that the previous results could have been due to injection of the radiotracer into the biopsy cavity.

Once it had been clarified that EB did not contraindicate posterior SSNB we decided to study the influence of the time between the two procedures on the detection of the SN and especially on the rate of lymph node recurrence. It is commonly considered that SSNB should be performed as soon as possible after EB in order to prevent the negative influence of tissue remodeling on the identification of the true SN. Nonetheless, it is not always possible to meet this requisite and the time between the two interventions is often greater than desired. This may facilitate the identification of lymph nodes belonging to new drainage pathways which do not demonstrate the real state of lymphatic drainage of the diseased breast and thus, increase the number of FN axilla. On the other hand, it has been hypothesized that an SSNB performed too early after EB may have a negative influence due to postsurgical inflammation. Haigh et al. did not find significant differences in the rate of SN detection in 284 procedures performed after different types of biopsies carried out at different time intervals prior to SSNB (<2 weeks and >8 weeks). They obtained a FN rate of 3.2%, all in patients in whom the SSNB had been performed within the first 4 weeks after EB. However, they did not study the rate of FN in the different intervals as they did with the detection of SN. Blanco et al. compared 22 patients with previous EB (15–60 days before SSNB), with 16 patients with a remote history of breast surgery (more than one year previously) not always because of malignancy, and found a similar rate of SN identification between the two groups, with 5.2% of recurrence (one patient in each group) after a mean follow-up of 36 months. In the study by Heuts et al., 88 patients underwent SSNB after EB, followed by ALND for the study of the FN. The SN detection rate was 99%, with no evidence of FN in the corresponding ALND. In this case the interval of time between the two procedures, which varied from 10 to 85 days (mean of 19), was not taken into account.

In our case, we established a limit of 30 days according to the recommendations of the Spanish Society of Breast Pathology, which considers that this is the period in which, under normal conditions, the inflammation secondary to surgical biopsy is resolved and the drainage pathways have not yet reorganized. Our results agree with those mentioned previously with no differences observed in the detection of the SN between the two groups of patients. Two patients in Group B had to be re-injected because of the inability to visualize drainage in the LS 2 h after the injection of the radiotracer. The time between EB and SSNB in these two patients was of 56 days and 49 days. Although we first believed that the lack of drainage was probably due to the time since the EB, in both cases scintigraphic visualization was achieved after reinjection. Moreover, it seems that this rate of non-visualization (6%) after ordinary radiotracer injection did not differ from that obtained previously by our group in patients without a history of EB. A total of 3 SN which did not show metastatic involvement were dissected in these 2 patients. After 75 and 31 months of follow-up, both remain disease free. With regard to the two cases presenting extra-axillary drainage, the time between EB and SSNB was 34 days in the patient with drainage to the internal breast chain and 70 days in the patient with a supraclavicular lymph node. This rate of extra-axillary drainage (5.5%) is lower than that obtained by Blanco et al. and is similar to that described by Arıcan et al. As mentioned previously, dissection of the extra-axillary lymph nodes was not possible in either of the two cases, although the axillary SN obtained did not demonstrate malignancy. Moreover neither patient has presented recurrence at 64 months and 36 months of follow-up, respectively.

Although some studies have reported a high rate of FN (greater than 5%) in SSNB after EB, others have described statistically

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**Table 2**

Results of the SSNB and the axillary recurrences during follow up.

<table>
<thead>
<tr>
<th>Group</th>
<th>Scintigraphic detection of the SN</th>
<th>Surgical detection of the SN</th>
<th>Metastasis in the SN</th>
<th>Histology of ALND</th>
<th>Follow up (months)</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>100%</td>
<td>100%</td>
<td>One patient (8.3%)</td>
<td>Not performed</td>
<td>66</td>
<td>0%</td>
</tr>
<tr>
<td>B</td>
<td>100%</td>
<td>100%</td>
<td>Two patients (8.3%)</td>
<td>One patient not performed</td>
<td>30</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Notes:**
- SSNB: selective sentinel node biopsy
- SN: sentinel node
- ALND: axillary lymph node dissection

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significant differences in the global rate of FN after EB compared to other biopsy methods. In a recent meta-analysis by Javan et al., the rate of FN in patients with EB was slightly higher to that of patients without EB with statistically significant odds ratios and attributable risk. However, the difference was so small that they did not consider it to be clinically relevant. These authors did not study whether this higher rate of FN was related to a longer time interval between the two procedures. Since the global rate of FN in our group could not be calculated because ALND was not routinely performed, evaluation of the potential FN (determined in our population with lymph node recurrence) is ongoing with periodical controls in all the patients (every 4–6 months during the first 3 years and once a year thereafter). To date no recurrence has been observed in any patient after a mean follow-up of 49.5 months and a maximum of 6 years, independently of the time between EB and SSNB. This suggests that SSNB after EB is also a safe procedure in regard to the rate of lymph node recurrence. In addition, it should be taken into account that most axillary recurrences appear during the first two years after surgery and all of our patients in both groups have already surpassed this time of follow up.

This high detection rate and the absence of lymph node recurrence, regardless of the time between EB and SSNB, suggests that despite the probable alteration of the lymphatic drainage pathways after EB, drainage possibly continues to the true SN. Nevertheless, considering the structure of lymphatic drainage of the breast, a subdermal periareolar injection may reach the subcutaneous lymphatic and regional lymph nodes through the subareolar plexus, despite the performance of EB at any breast localization and the potential modification of the drainage pathways thereafter, making this a highly reliable and reproducible technique. We therefore believe that the type of injection may be the main point of all the procedures to take into account, overcoming the effect that time may have on the alteration of the lymphatic pathways after EB.

Conclusions

Although the small number of patients included represents a limitation in the present study, with the results obtained it can be concluded that the use of SSNB after breast EB is a safe, reliable technique regardless of the time between the two procedures and has no risks for the patient outcome since lymph node recurrence was not observed. The type of radiotracer injection may play a fundamental role since it may influence the pathways of lymphatic drainage, thereby recommending the use of a subcutaneous injection.

Conflict of interests

The authors declare no conflict of interest.