Original Article

Presence of intramammary lymph nodes in the preoperative lymphoscintigraphy to locate the sentinel lymph node. Clinical significance

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Abstract

Objective: The routes of lymphatic drainage from a breast cancer are the axilla (the most frequent) and the extra axillary regions. Among the latter, there are the so-called intramammary lymph nodes (IMLN). This study has aimed to assess the incidence of IMLNs in our patients and study the evolution of these cases with IMLN in the lymphoscintigraphy.

Material and methods: Thirty-eight patients (out of 1725) with IMLN in the pre-operative lymphoscintigraphy were assessed. During the surgical procedure, using a gamma probe, IMLNs were located and excised. After their harvesting, a meticulous surgical field scan was performed. When the axillary sentinel node was positive for metastasis, a complete axillary lymphadenectomy was performed. In those where the axillary sentinel node was negative and IMLN was positive (IMLN+), axillary lymphadenectomy was also performed, except for one case.

Results: Thirty-four out of the 38 IMLN were obtained (89.5%), because no lymphatic tissue was found in pathology analysis in three cases (8%) and in one patient (3%) IMLN was not found during surgery. Ten (26%) metastatic IMLN were located and the remaining 24 IMLN cases (63%) were metastasis-free. During the clinical follow-up, one patient with IMLN+ developed hepatic metastases. The remaining 33 patients did not present any recurrence. No follow-up data were available for three patients.

Conclusions: IMLN and axillary sentinel node biopsy are recommended when both are depicted in preoperative lymphoscintigraphy. The axilla treatment will only depend on the axillary sentinel node status. Based on the data from other authors and our own experience, avoiding the axillary lymphadenectomy when a metastatic IMLN without axillary involvement seems reasonable.

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Palabras clave:
Ganglios intramamarios
Linfogammagrafía
Cáncer de mama
Ganglio centinela

Resumen

Presencia de ganglios intramamarios en la linfogammagrafía prequirúrgica para localizar el ganglio centinela. Relevancia clínica

Objetivo: Entre las vías de drenaje linfático de un tumor mamario se encuentran las de la cadena axilar (la más frecuente) y a las regiones extraaxilares. Dentro de éstas últimas existen los denominados ganglios intramamarios (GIM). El objetivo de este estudio fue valorar la incidencia de GIM en nuestra casuística y estudiar la evolución de las pacientes que presentaron GIM en la linfogammagrafía.

Material y métodos: Se han evaluado 38 pacientes (de un total de 1725) que presentaron un GIM en la linfogammagrafía preoperatoria. Durante el acto quirúrgico, utilizando una sonda detectora, se procedió a su localización y exéresis. Posteriormente a su resección y meticuloso rastreo del lecho quirúrgico, se realizó linfadenectomía axilar en los casos en los que el GC axilar fue positivo para metástasis. En aquellas pacientes con GC axilar negativo y GIM positivo (GIM+) se realizó también, con excepción de un caso, linfadenectomía axilar.

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Introduction

The status of the lymph nodes is one of the main prognostic factors in breast cancer and their study is crucial for cancer staging. Nowadays, sentinel lymph node (SLN) biopsy is the gold standard test for regional lymph node staging and has prevented axillary lymphadenectomy and its subsequent morbidity in most early stage breast cancer patients.

Among the potential lymphatic drainage routes of a primary breast tumor there are those of the axillary region (the most frequent) and those that drain to extra-axillary basins (internal mammary region and supraclavicular region). The so-called intramammary lymph nodes (IMLN) are another potential drainage route.

IMLN are lymph nodes found within the breast parenchyma, which are different from those found in the lower axillary region. They are most commonly found in the upper outer quadrant (UOQ), although they may be present in any of the other quadrants. IMLN incidence rate ranges widely from 0.2% to 12% when detected on lymphoscintigraphy. Variability is wider when identified in anatomopathological samples and ranges from 1% to 48%. Percentage of detected metastases in these lymph nodes ranges from 21% to 34%.

According to the American Joint Committee on Cancer metastases found in these nodes have the same impact on cancer staging as those found in the ipsilateral axillary lymph nodes and studies suggest they are a bad prognosis factor. A recent review of the MD Anderson Cancer Center experience led to the conclusion that disease-free survival time and total survival time were significantly shorter in the group with metastases found in the IMLN.

The goal of this study was to consider incidence of IMLN in our casuistry and to assess the evolution of patients with IMLN found in the lymphoscintigraphy.

Material and methods

Patients

All patients included prospectively in the data registry of the Nuclear Medicine Service from January 1999 to November 2013 were reviewed. A total of 1725 breast cancer patients qualified for SLN biopsy. Thirty-eight patients presented internal mammary lymph node drainage.

In 4 patients, the tumor had been resected in a surgery prior to the SLN biopsy. Median clinical follow up was 65 months (range, 7–15 years). There are no available follow-up data of 3 patients.

Lymphoscintigraphy

The day before surgery patients received 111MBq of Tc nanocolloid (Nanocoll® GE Saluggia, Italy), injected intratumorally in most cases. The volume injected ranged from 0.2 to 0.5 ml, depending on the technique chosen. In non-palpable breast lesions, for which ROLL technique is usually chosen, 0.2 ml were injected under ultrasound guidance with a 20- to 22-G needle. On the other hand, in palpable lesions or extensive calcifications 0.5 ml were administered by direct intratumoral injection or, in some cases, subareolar or subdermal injection.

Puncture location was: peritumoral in 3 cases, intratumoral in 26 cases, subdermal in 4 cases and subareolar in 5. After the radiotracer administration, early and late (30 min and 2 h) planar images of the thoracic region were acquired. They last 180 s each in anterior, oblique and lateral projections in order to optimize the location of SNL. SPECT/CT images of the regions of interest were acquired in 8 of the cases (SPECT/CT was available in our Department since June 2007) (Fig. 1). Then, the approximate location of the SNL was marked on the skin of the patient in oblique projection and with the help of a 57Co-penmark, in order to provide reference for intraoperative identification. To retrieve the images a single-head gamma camera with a high-resolution low energy collimator was used (E-Cam, Siemens, Erlangen, Germany). An Infinia Hawk-eye 4 gamma camera (GE, Wauwatosa, WI, USA) was used for the SPECT/CT images. The SPECT/CT images reconstruction was done in a workstation (Xeleris, GE) and subsequent volume-rendering images were generated using Osirix MD software (Pixmeo SARL, Bern, Switzerland).

All lymph nodes directly connected to the tumor and all single lymph nodes shown in early and late imaging of the lymph drainage area of the tumor have been considered SLNs, as well as all groups of two or more lymph nodes appearing between the injection site and the SLN of the lymphatic drainage area or all groups of two or more lymph nodes appearing in early images and showing increased uptake on delayed images.

Surgery

After the induction of anesthesia in the operating room, the SNL was located with a handheld gammaprobe (Navigator, RMD, Watertown, MA, USA) in the anatomic area observed in the preoperative images. In 14 patients in whom a conventional gamma camera showed lymph nodes near the injection site or with faint tracer uptake, the study was completed with a portable gamma camera (Sentinella S102, Oncovision, Valencia, Spain), which produced intraoperative images.

During surgery we considered SLNs those that had previously been identified on lymphoscintigraphy, which frequently coincided with the most active lymph node intraoperatively found with the gammaprobe in the lymphatic drainage chain. After their resection, a very thorough examination of the surgical bed was done and all other nodes with activity higher than 10% of the maximum detected in a SLN were also resected. Axillary lymphadenectomy was performed in all cases with axillary SNL positive for micrometastases and/or micrometastases, except for 2 micrometastases cases. Lymphadenectomy was also performed in all but one cases with negative SNL and positive IMLN.
Fig. 1. Lymphoscintigraphy. Planar image, left anterior oblique projection (A), with a lead shield masking the injection site (B), showing more clearly the intramammary SLN (arrow) and the axillary lymph nodes. 3D reconstruction (C).

Pathology

The preoperative study of all resected SLNs was done through serial sectioning every 2 mm, imprint cytology and hematoxylin-eosin staining. Negative SLNs were immunohistochemically examined with CAM 5.2 cytokeratin marker,\textsuperscript{13} for its high sensitivity (100% to metastases) and specificity. Metastases were divided in three groups: macrometastases, tumor nest >2 mm; micrometastases, between 0.2 and 2 mm; and isolated tumor cells (ITC), <0.2 mm. Since September of 2012 SLNs are studied with OSNA technique. All lymph nodes of the axillary lymphadenectomy were studied using standard hematoxylin-eosin staining.

Results

From 1999 to 2013 our center performed a total of 1725 lymphoscintigraphies in women diagnosed with breast cancer, identifying 38 cases of IMLN (2.2%). In 8 cases (21%), SPECT/CT was used together with the planar images, which allowed anatomical location of the previously visualized tracer deposits.

The median age at diagnosis was 57 years (IQR 13). Histological diagnosis for primary tumoral lesion was ductal carcinoma in situ in 5 cases, invasive ductal carcinoma in 27, lobular infiltrating carcinoma in 3 cases and other diagnosis in another 3. Tables 1 and 2 show tumor locations and clinical pathological characteristics of the patients.

Table 1

<table>
<thead>
<tr>
<th>Location of the tumor</th>
<th>Num. of cases: 38</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQU\textsuperscript{a}</td>
<td>5</td>
</tr>
<tr>
<td>UOQ\textsuperscript{b}</td>
<td>11</td>
</tr>
<tr>
<td>OQU\textsuperscript{c}</td>
<td>2</td>
</tr>
<tr>
<td>Retroareolar</td>
<td>1</td>
</tr>
<tr>
<td>UIQ\textsuperscript{d}</td>
<td>4</td>
</tr>
<tr>
<td>LOQ\textsuperscript{e}</td>
<td>2</td>
</tr>
<tr>
<td>LIQ\textsuperscript{f}</td>
<td>2</td>
</tr>
<tr>
<td>UQ\textsuperscript{g}</td>
<td>3</td>
</tr>
<tr>
<td>Bilateral\textsuperscript{h}</td>
<td>2</td>
</tr>
<tr>
<td>LOQ + UQ</td>
<td>1</td>
</tr>
<tr>
<td>OQU + LOQ</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
</tr>
</tbody>
</table>

Average size of primary tumors was 15 mm (5–40 mm); 28 cases (74%) were T1 and 10 cases (26%) were T2. Conservative surgery was performed in 30 patients (79%) and mastectomy in the other 8 (21%).

In 4 patients (11%) IMLN was not finally identified; in one case, because the IMLN was not found during surgery and in the other 3 cases because no lymphatic tissue was found in the samples sent for anatomo pathological study. Among the rest of the cases, 24 (63%)

Table 2

Clinical-pathological characteristics of patients with surgical detection of IMLN (num. = 34).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>+IMLN (Num. = 10)</th>
<th>−IMLN (Num. = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>55.9</td>
<td>57.1</td>
</tr>
<tr>
<td>Range</td>
<td>(29–74)</td>
<td>(41–74)</td>
</tr>
<tr>
<td>Size of the tumor (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>16.1</td>
<td>15.6</td>
</tr>
<tr>
<td>Range</td>
<td>(8–29)</td>
<td>(5–40)</td>
</tr>
<tr>
<td>Histological type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In situ</td>
<td>0</td>
<td>4 (16.7%)</td>
</tr>
<tr>
<td>Invasive ductal</td>
<td>9(90%)</td>
<td>16(66.7%)</td>
</tr>
<tr>
<td>Invasive lobular</td>
<td>0</td>
<td>3 (12.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>1(10%)</td>
<td>1 (4.1%)</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2(20%)</td>
<td>2 (8.3%)</td>
</tr>
<tr>
<td>No</td>
<td>7(70%)</td>
<td>17(70.8%)</td>
</tr>
<tr>
<td>Not available</td>
<td>1(10%)</td>
<td>5 (20.8%)</td>
</tr>
<tr>
<td>Hormone receptors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER−/PR−</td>
<td>4(40%)</td>
<td>13 (54.2%)</td>
</tr>
<tr>
<td>ER+/PR−</td>
<td>3(30%)</td>
<td>5 (20.8%)</td>
</tr>
<tr>
<td>ER−/PR+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ER−/PR−</td>
<td>2(20%)</td>
<td>3 (12.5%)</td>
</tr>
<tr>
<td>Not available</td>
<td>1(10%)</td>
<td>3 (12.5%)</td>
</tr>
<tr>
<td>Axillary involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLN−</td>
<td>5(50%)</td>
<td>17 (70.8%)</td>
</tr>
<tr>
<td>SLN+</td>
<td>4(40%)</td>
<td>4 (16.7%)</td>
</tr>
<tr>
<td>Isolated tumor cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1(10%)</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Micrometastasis</td>
<td>2(20%)</td>
<td>2(20%)</td>
</tr>
<tr>
<td>Macrometastasis</td>
<td>1(20%)</td>
<td>2(20%)</td>
</tr>
<tr>
<td>No SLN</td>
<td>1(10%)\textsuperscript{a}</td>
<td>3 (12.5%)\textsuperscript{a}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Not visualized in lymphoscintigraphy.

\textsuperscript{b} One was not visualized in lymphoscintigraphy. Two were considered secondary lymph nodes and were not resected.
were negative and 10 (26%) presented metastatic involvement, 3 micrometastases and 7 macrometastases.

Among the 10 patients with IMLN metastases (IMLN+), 9 cases presented invasive ductal carcinomas and 1 case presented invasive papillary carcinoma. Seven patients (70%) underwent a tumorectomy and 3 (30%) a mastectomy. It was observed that in 4 of the cases, IMLN+ was associated with axillary SLN invasion and they were all but one treated with axillary lymphadenectomy. This patient only presented isolated tumor cells (ITCs). Among those 3 patients, the first one presented 3 out of the 9 resected lymph nodes positive for metastases; the second one showed one out of 10 lymph nodes positive and in the last one, none of the 7 lymph nodes excised were positive. Four patients with negative axillary SLN were treated with axillary lymphadenectomy and no additional positive lymph nodes were found. No lymphadenectomy was performed to a fifth patient with negative axillary SLN, who has presented no evidence of relapse so far. The remaining patient with IMLN+ presented micrometastasis with no associated axillary SLN; however, lymphadenectomy was performed with no evidence of metastases in any of the 11 resected lymph nodes.

The median follow-up was 65 months (range 7 months to 15 years). There is no data available on 3 patients. One of the patients with IMLN+ and associated axillary invasion developed hepatic metastases.

Four out of the 24 patients with negative IMLN showed positive axillary SLN (2 micrometastases and 2 macrometastases). Axillary lymphadenectomy was performed in the 2 macrometastases. So far, there is no evidence of relapse in this group of patients with negative IMLN.

A higher proportion of lymphovascular invasion in the primary tumor was observed in those cases with IMLN+ versus those cases with negative IMLN (2 out of 10 versus 2 out of 24), as well as a higher proportion of associated axillary invasion (4 out of 10 versus 4 out of 24).

Discussion

IMLNs represent a potential route of breast cancer spread to regional lymph nodes outside the axilla.9,11,13 The first publications about these lymph nodes date from the 80s. In 1983 Egan and McSweeney5 found 45 IMLNs (28%) in 158 mastectomy samples and observed that presence of IMLN+ in stage I patients was related to a worse prognosis, while the evolution was not found to be unfavorable in stage II patients. Since then, several groups have studied clinical meaning and also prevalence of IMLN, which is especially difficult to assess due to the low detection rate and the wide variety of diagnosis methods used.7,14

In 1999, Rull et al.15 described the detection of an IMLN with selective SLN biopsy for the first time in a clinical case. There are few studies about identification of these lymph nodes exclusively with lymphoscintigraphy. Their prevalence in reviewed articles ranges from 0.2% (22 out of 9632)16 to 12% (18 out of 159).17 In our case, prevalence was 2.2% (38 out of 1725), a very similar figure to that obtained by other groups.18 Intra et al.17 point out that such disparity in the prevalence figures may correspond to the use of different injection techniques, injection volumes and radiopharmaceuticals.

It is well known that SLN identification results vary depending on the radiotracer injection technique; thus, intratumoral administration provides the highest percentage of detection of extra-axillary lymph nodes, including IMLNs, followed by peritumoral administration.17 Uren et al.13 located 56% of extra-axillary lymph nodes using peritumoral injections. In our center, the main radiotracer injection techniques used are intratumoral or peritumoral. In 29 (76.3%) out of the 38 cases with IMLN the injections performed were deep and only in 9 cases (23.7%) were the injections superficial (subdermal/subareolar). Additionally, it is important to take into account that previous tumor resection may also increase detection rate of extra-axillary drainage.18

The intense activity generated by radiotracers in the injection site and its proximity to IMLN complicate their location.15,19 SPECT/CT, due to its better contrast and resolution images, has been of great help in this sense. It enables identification of lymph nodes that cannot be seen in planar images and, in those near the injection site, it enables distinction between radiotracer contamination and real lymph nodes. Moreover, it improves the location of anatomical sites of tracer uptake, helping in the surgical approach.20,21 In any case, in our own experience, as well as in the experience of Van der Ploeg et al.21 it is concluded that SPECT/CT does not replace lymphoscintigraphy but rather complements it and it should always be used in problematic cases (lymph nodes in head, neck, trunk, extra-axillary and deep). Sometimes, in spite of having planar and SPECT/CT images, identification of IMLNs during surgery is really a challenge. Combined use of a gamma probe and real-time images obtained with a portable gamma camera (Fig. 2) enables to increase detection rate of those lymph nodes located near the injection site and also lymph nodes with low-grade tracer uptake or not-blue stained (when blue dye is used).22

The 7th edition of the AJCC states that IMLN must be considered to be an axillary lymph node when there is metastatic involvement and, therefore, it must be treated as a N123 (if the metastasis is >0.2 mm), even if the axilla is negative. The figures of IMLN obtained in the reviewed publications range from 21%5 to 34%.10 In our case, 10 out of 38 (26%) IMLNs were positive, a similar ratio to that obtained by Intra et al.17 However, as Andrés et al.14 correctly

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**Fig. 2.** Planar lymphoscintigraphy image that shows an intramammary lymph node (arrow) and axillary lymph nodes (A). Fusion image obtained with a portable gamma camera in a short distance (1 cm) from the skin of the patient. The image allowed us to distinguish the activity derived from the injection site and from the intramammary lymph node (arrow), as well as tracer deposits in the axillary region (C).
point out, if we consider all the patients, this percentage decreases remarkably; in our case it drops from 26% to 6.6%.

Certain factors such as histological degree, stage, lymphovascular invasion rate and tumor-cell invasion in the axilla are associated with metastatic involvement of the IMLNs.5,11,24,25 According to the study of Guth et al.,11 patients with IMLN+ presented more aggressive cancers, including the highest rates of lymphovascular invasion (55% vs. 11%) and axillary lymphatic involvement (75% vs. 54%), and they were multifocal more frequently (50% vs. 11%). Thus, the presence of metastatic IMLN would be related to decreased total survival time and disease-free survival time.5,24,25 In our case, none of the patients with ductal carcinoma in situ presented IMLN+ (16.7% IMLN without metastases vs. 0% IMLN+). Higher percentages of lymphovascular invasion were observed in cases with IMLN+ (20% vs. 8.3%) and they presented axillary invasion more frequently (40% vs. 16.7%). It is important to remark that our data are not comparable with those obtained in other studies, in which most of their cases were not detected by lymphoscintigraphy and the sizes of their primary tumors were bigger than those in our study (0.5–4 cm). Hence Guth et al.11 include cases with a size range from 1.2 to 10 cm and Hogan et al.9 from 0.4 to 10 cm.

Therapeutic attitude toward axillary approach when there is IMLN is controversial, especially if it is metastatic. There are several situations that we may face in the daily practice. One of them is the joint detection of axillary SLN and IMLN. The reviewed publications suggest performing a biopsy of both and an axillary treatment that would depend on the status of the axillary SLN.7,11,26,27 The appearance of IMLN+ and negative axillary SLN is also a possible situation that has created a lot of controversy. Based on the high figures of axillary invasion when there is IMLN+ some authors (Shen17,18, Nassar25 80%, Guth11 72%, Vijan10 69% y Hogan9 67%) recommend axillary lymphadenectomy even when the axillary SLN is negative. Hogan et al.9 present the case of a patient with IMLN+ and negative axillary SLN that did not undergo axillary lymphadenectomy and that after a 19-month follow-up developed axillary recurrence. On the contrary, there are other authors that do not recommend axillary lymphadenectomy when axillary SLN is negative in spite of the presence of IMLN+, arguing that the axillary approach should only be based on the SLN results of the axillary lymphatic region.7,13,26,27 Intra et al.7 detected 6 IMLN+ and none of them presented axillary metastatic invasion. Two of these patients underwent axillary lymphadenectomy and all the extracted lymph nodes were negative. Díaz et al.27 include 23 patients with IMLN+ and negative axillary SLN that underwent lymphadenectomies, without detection of any false-negative case. Pluguese et al.13 present 14 patients with IMLN+ and negative axilla, out of which 7 underwent axillary lymphadenectomies, with no signs of recurrence or death in 75 months. Finally, in the study carried out by Cox et al.26 a lower rate of recurrence and death was observed in patients with isolated IMLNs+ than in those with isolated positive axillary SLNs, which led to the conclusion that the first would have a better prognosis. Some authors13 consider IMLN and axillary SLN to be independent drainage routes and therefore IMLN biopsy would only be prescribed in order to improve staging. Our data supports these last results. Out of the 10 patients with IMLN+, 5 presented negative axillary SLN; 4 of them underwent axillary lymphadenectomies, in which none of the resected lymph nodes showed metastasis. The fifth patient in this group did not undergo axillary lymphadenectomy and there has been no sign of recurrence in 60 months.

Another possible situation subject to controversy would be the detection of an isolated IMLN. Andrés et al.14 recommend to try to find axillary drainage with a new radiotracers and/or blue dye injection, as well as the use of a gamma sensitive probe during surgery. If axillary drainage is still not found, they recommend axillary lymphadenectomy due to the possibility of a metastatic lymphatic blockage. Other groups recommend level I axillary dissection in patients with isolated IMLN+.26 Intra et al.7 recommend to individualize each case. Among our patients we only found one in this situation, who presented IMLN with 0.3 mm micrometastasis. A lymphadenectomy was performed anyway, where all 11 extracted lymph nodes were negative.

The most recent NCCN guidelines28 take into consideration the study reported by Giuliano et al.29 in the axillary approach to stage I and II breast cancers. That study recommends not to perform axillary lymphadenectomy in patients with SLN biopsy positive for metastasis (maximum two positive lymph nodes) with T1-T2 tumors, which are to be treated with tumorectomy, total radiotherapy and chemotherapy, since they observed that there was no improvement regarding locoregional recurrence and there were no differences in the total survival time and disease-free time data. According to that study, complications derived from lymphadenectomies are avoided in this way with no decrease in survival rate. However, there is no conclusion regarding presence of IMLN. It may be reasonable, in this context, to recommend individualization of each case when there is an isolated IMLN and when there is IMLN+ and positive axillary SLN.

Conclusions

Even though there are several studies about IMLNs, the diversity of diagnosis methods and the scarce number of patients assessed lead to no consensus about clinical meaning and the best approach, especially when they present metastatic involvement.

In spite of the size of our sample, we observed that presence of IMLN+ does not entail axillary invasion. IMLN and axillary SLN biopsy is recommended when both are depicted in lymphoscintigraphy and treatment over the axilla should depend only on the axillary SLN status. According to several authors and our own experience, it seems reasonable to avoid axillary lymphadenectomy when a metastatic IMLN without axillary involvement is found.

Conflict of interest

The authors declare no conflict of interest.

References


