Continuing Education

Sentinel node in melanoma and breast cancer. Current considerations

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\textbf{ABSTRACT}

The main objectives of sentinel node (SN) biopsy are to avoid unnecessary lymphadenectomies and to identify the 20–25% of patients with occult regional metastatic involvement. This technique reduces the associated morbidity from lymphadenectomy and increases the occult lymphatic metastases identification rate by offering the pathologist the lymph nodes with the highest probability of containing metastatic cells. Pre-surgical lymphoscintigraphy is considered a "road map" to guide the surgeon toward the sentinel nodes and to localize unpredictable lymphatic drainage patterns. The SPECT/CT advantages include a better SN detection rate than planar images, the ability to detect SNs in difficult to interpret studies, better SN depiction, especially in sites closer to the injection site and better anatomic localization. These advantages may result in a change in the patient’s clinical management both in melanoma and breast cancer. The correct SN evaluation by pathology implies a tumoral load stratification and further prognostic implication. The use of intraoperative imaging devices allows the surgeon a better surgical approach and precise SN localization. Several studies report the added value of such devices for more sentinel nodes excision and a complete monitoring of the whole procedure. New techniques, by using fluorescent or hybrid tracers, are currently being developed.

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\textbf{Ganglio centinela en melanoma y cáncer de mama. Consideraciones actuales}

\textbf{RÉSUMÉ}

Los principales objetivos de la biopsia del ganglio centinela (GC) es evitar linfadenectomías innecesarias e identificar el 20–25% de pacientes que presentan enfermedad ganglionar regional clínicamente oculta. Esta técnica mínimiza la morbilidad asociada a la linfadenectomía y aumenta también la tasa de identificación de metástasis linfáticas ocultas al ofrecer al patólogo aquel o aquellos ganglios con mayor probabilidad de contener células tumorales procedentes del tumor primario. La linfogammagrafía prequirúrgica se considera como un «mapa de carreteras» para guiar al cirujano hacia los GC y para la localización de patrones de drenaje impredecibles. Las ventajas del SPECT/TC incluyen un índice global de detección del GC superior a las imágenes planares, la capacidad para detectar ganglios centinelas en estudios convencionales difíciles de interpretar, mejor definición de los mismos en localizaciones cercanas a la inyección y una mejor localización anatómica. Estas ventajas pueden provocar un cambio en el manejo clínico-quirúrgico del paciente tanto en melanoma como en cáncer de mama. La correcta evaluación anatomoapalástica del GC supone una estratificación de la carga tumoral y su posterior implicación pronóstica. La utilización de la imagen intraoperatoria permite al cirujano adaptar las marcas previamente hechas a la incisión quirúrgica planeada y confirmar la localización exacta del GC. Diversos estudios han demostrado el valor añadido de la utilización de estos dispositivos, al permitir la resección de GC adicionales y monitorizar el proceso quirúrgico. Nuevas técnicas, utilizando trazadores híbridos o fluorescentes, se están desarrollando en la actualidad.

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Introduction

Sentinel lymph node (SLN) biopsy has been accepted as the method of lymph node staging in breast cancer and melanoma throughout the world. The incidence of melanoma has shown the greatest increase in recent years with 10–14 cases/100,000 inhabitants in Central Europe and 6–10/100,000 inhabitants in Southern Europe. In the USA the incidence has risen to 10–25/10,000 inhabitants, and Australia and New Zealand have the highest incidence with 60 cases/100,000 inhabitants. According to the WHO the global number of new patients with melanoma is of more than 130,000 cases per year and represents 90% of the deaths by cutaneous cancer. Breast cancer is the most frequent among women worldwide. In 2010 approximately 230,000 new cases and 40,000 deaths were estimated to be described and in 2012, 1.7 million new cases were calculated in the world, representing 12% of all the cancers and 25% of the cancers in women.1,2

In both tumors lymph node status is a very important prognostic factor and also facilitates the choice of adequate treatment. Surgical staging was classically based on regional lymph node dissection and histological evaluation of the lymph nodes. However, this procedure has the risk of lymphedema, infections, and alterations in sensitivity and mobility in the zones operated.

SLN biopsy has become the gold standard for the staging of melanoma and breast cancer. This minimally invasive method assesses the regional lymph node status. It is based on the presumption that there is an orderly progression of lymph node infiltration by tumor cells. Thus, if the SLN does not demonstrate metastasis, neither will the remaining lymph nodes of the lymphatic region. The American Joint Committee on Cancer (AJCC) and the International Union Against Cancer include SLN biopsy in their classifications for the staging of these solid tumors.3,4

Despite more than 20 years of establishing the indications for the use of the technique for localizing SLN (based on presurgical lymphoscintigraphy and intraoperative detection by probes and/or staining), each of these tumors continues to have some controversial aspects. Different technical factors such as the type of radiotracer used, the puncture site and the histological processing have a real impact on the yield of SLN biopsy.

The present article attempts to clarify the most important points of discussion related to each tumor and discusses future developments to refine the technique.

Previous lymphoscintigraphy and common criteria

SLN biopsy is a multidisciplinary procedure requiring close cooperation among nuclear physicians, surgeons and pathologists to achieve precise lymph node mapping, adequate resection and correct histological study. To determine which lymph nodes should be considered as a SLN, injection of the radiotracer is required as well as adequate evaluation of the pre- and intraoperative protocol.5

Vital dyes were used in the early years of the technique when presurgical imaging had not yet been incorporated. The procedure was described by Morton et al.6 and involved the search for the SLN in the expected lymphatic drainage area according to the localization of the primary lesion. This method constituted the “open and see (dyes)” paradigm.

The introduction of radiotracers allowed visualization of the physiology of lymphatic drainage using gamma cameras, thereby changing the paradigm of “open and see” to “see (scintigraphy) to open”. Presurgical lymphoscintigraphy is considered the “roadmap” for guiding surgeons toward subsidiary lymph nodes of potential metastasis and is very useful for localizing unpredictable drainage patterns. The value of lymphoscintigraphy lies in different points which are summarized in Table 1.

Radiotracer choice and injection

The radiocolloids which best visualize the lymphatic chains have a particle size of between 5 and 50 nm making it necessary to acquire the image early (dynamic/sequential study). The SLN are seen 2 h after the injection. Median sized particles (50–200 nm) present less migration from the primary lesion but a more prolonged deposition in the SLN. Consequently, images are sometimes necessary 2 h after the administration to clearly visualize the SLN. Large sized radiocolloids (>200 nm) may make migration from the injection zone difficult. It has been suggested that the optimal particle size for SLN detection is between 100 and 200 nm, however, there is no specific consensus regarding the activity to inject. The time between the puncture and the surgery should be adjusted. The dose usually ranges from 5 to 120 MBq according to a one- or two-day protocol. It has been demonstrated that both procedures are equally effective for SLN detection.7

In cases of melanoma lymphoscintigraphy is performed by intradermal injection of a radiotracer around the primary lesion or the scar of the excisional biopsy because of the greater density of lymph ducts on the cutaneous surface compared to deeper layers. It is generally agreed that the radiotracer or dye should be injected at 0.1–1 cm from the tumor margin of the biopsy scar.8,9

The type of radiotracer injection used is the most controversial aspect of the SLN procedure in breast cancer. Superficial (cutaneous-areolar) injections related to the skin as well as deep (peri- or intratumoral) are used. It is important to note that cutaneous areolar techniques are accompanied by a minimum visualization of non-axillary lymph nodes, thereby reflecting the superficial drainage system of the breast. In contrast, deep punctures show non-axillary lymph nodes in 20–40% of the cases, demonstrating separate pathways for the deep and superficial drainage pathways of the breast.10 We can therefore follow the subdermal/intradermal pathway as that established with experience in procedures in melanoma, providing excellent results in axillary staging.

Alternatively, peritumoral injection has been proposed as possibly the most ideal since the radiotracer is deposited near the tumor and thus reflects the drainage directly from the tumor. Intratumoral injection has also been described to have comparable results to those of the previously mentioned technique, achieving 100% of reproducibility in regard to the drainage pathway and the number

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Table 1

Lymphoscintigraphy aspects of note.

| Identification of the lymph nodes with activity (although not all active lymph nodes are SLN and neither is the SLN necessarily the most active lymph node). |
| Identification of the lymphatic drainage regions. Different active lymph nodes belonging to a lymph node region should be distinguished from multiple active lymph nodes of different regions. |
| Identification of the SLN or the SLN of the secondary lymph nodes. |
| Identification of the essential SLN, including those in-transit (that is, lymph nodes localized between the primary tumor and the region of lymph node drainage) and aberrant (lymph nodes located in zones outside the usual drainage areas). |
| Confirmation of true radiotracer uptake versus false positive findings such as cutaneous folds, lymphatic dilatations and lymphangiomas. |

SLN, sentinel lymph node.
of SLN found, with some variability in the degree of lymph node uptake.\textsuperscript{11}

Other groups have proposed the subareolar/periareolar approach since the lymphatic drainage of the breast flows into the Sappey’s subareolar plexus. This kind of injection has numerous advantages for nuclear physicians: ease of use, does not require collaboration with radiologists, can be applied in non-palpable tumors, avoids the shine-through phenomenon (occult SLN due to proximity to the activity injected into the tumor, usually performed in axilla when the tumor is located in the outer upper quadrant of the breast and less frequent in internal mammary lymph node chain with tumor in internal quadrants) and shows rapid drainage toward the axilla.\textsuperscript{12} Another advantage is its reproducibility in controversial situations such as resolving the performance of a previous surgical biopsy at least for axillary staging.\textsuperscript{13} In areas with precise staging and considering the use of the TNM classification, the injection should be peritumoral or intratumoral (deep) since these sites guarantee an important percentage of visualization of the SLN in extra-axillary localizations. On the other hand, some groups advocate the use of superficial injections for the simplicity and the scarce clinical impact of the percentage of extra-axillary metastatic SLN.\textsuperscript{14}

Image acquisition

After injection the lymphoscintigraphy is carried out to assess the distribution of the radiotracer using a large field of view gamma camera. The use of radioactive flood sources (\textsuperscript{57}Co or \textsuperscript{99m}Tc) or alternative techniques (drawing the body contour with a pointer or the rest of the activity) help to provide a basic anatomical reference.

In most patients the direction of the lymphatic channels is determined by a 10–20 min dynamic study with images acquired every 30–60 s. The dynamic images are initiated immediately after the injection, especially in melanomas.\textsuperscript{8} Although in breast cancer some groups do the same,\textsuperscript{15} more delayed sequential images are usually made. At the end of the dynamic study 180–300 s static planar images of the lymphatic region should be obtained in order to identify the lymph nodes that have arrived to the lymphatic channels and determine which is the SLN. The images should be obtained at different projections to correctly identify the lymph nodes.\textsuperscript{7} This is especially important in the lower extremities when multiple channels may mask the direct passage toward the iliac region or the head and neck where it is difficult to precisely determine the depth or exact location of the SLN (Fig. 1). To detect SLN close to the puncture site it may be useful to mask the injection point with lead material during image acquisition.

Delayed images allow the correct SLN identification and their external marking on the skin. The SLN are usually identified in the first 30 min after injection, although images should be obtained in 2 h due to possible slow lymph flow to other areas. The great variability of cutaneous drainage, especially of the head and neck, chest and abdomen should be taken into account as well as the possibility of detecting lymph nodes which are aberrant or in-transit. Several groups have studied the reproducibility of lymphoscintigraphy achieving similar results in 84–96% of the cases.\textsuperscript{16,17}

SPECT/CT

Planar lymphoscintigraphy provides clear visualization of the SLN, providing information on their number and facilitating the localization on the skin. However, the depth and anatomical relationships of the SLN with the surrounding tissues are not easily obtained. For example, the presence of deep SLN in the neck or other areas is a challenge during surgery, and in certain circumstances they cannot be removed (i.e. deep paravertebral, paraaortic). False negative or false positive results of the SLN can also be obtained in other situations.

With the new generation of multimodality gamma cameras the functional information of the SPECT (tomoscintigraphic study) can be combined with the morphological information of the CT. These devices potentiate the focus of “open to see” by providing images corrected for attenuation and scatter and provide better contrast

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.jpg}
\caption{Lymphoscintigraphic images should be performed in different projections to correctly identify the lymph nodes. This is especially important in the head and neck region where it is difficult to precisely determine the depth or position of the SLN (A and B). In the lower extremities multiple channels may mask the direct pathway toward the iliac region (C and D).}
\end{figure}
Figure 2. Tomoscintigraphic imaging improves SLN identification and solves some of the limitations of planar imaging. Patient with melanoma in the right flank showing paracostal in-transit lymph nodes. Early images (A) and delayed (B). The localization of the SLN with rendering imaging is anatomically situated in the zone of the eighth costal arch (C). The axial image of the CT shows the subcutaneous localization of the lymph node (D).

Table 2
Main advantages of SPECT/CT.

<table>
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<th>Advantage</th>
<th>Details</th>
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<td>Provides an anatomical roadmap. Precise localization improves the treatment of the patient.</td>
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<tr>
<td>Greater sensitivity (additional lesions).</td>
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<tr>
<td>Detection of additional lesions improves the sensitivity of the technique and the precision of staging.</td>
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<tr>
<td>Greater specificity and reduction in false negative findings.</td>
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<tr>
<td>Reduces the false positive results. The physiologic uptake may be elevated in lesions adjacent to the liver, the spleen and kidneys.</td>
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<tr>
<td>Greater specificity improves the reliability of the diagnosis and changes the need for unnecessary treatments.</td>
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<tr>
<td>Erroneous lesions.</td>
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<td>Anatomical evaluation of erroneous areas in planar images or functional definition of inconclusive alterations.</td>
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and resolution. Tomoscintigraphic images improve SLN identification and solve some of the limitations of planar imaging. Fusion with CT images shows the SLN in 2D and 3D (Figs. 2 and 3). The SPECT/CT images are usually acquired after the delayed planar images (from 2 to 4 h postinjection). Table 2 demonstrates the advantages of SPECT/CT studies. Validation of SPECT/CT in tumors with mainly superficial drainage (i.e. melanoma and breast cancer) is based on specific indications such as when the SLN in the axillary region is not observed in the planar images or when the injection masks the subjacent lymph nodes. Likewise, SPECT/CT facilitates recognition of non-lymph node deposits of the radio-tracer and helps to clarify drainage in inconclusive images. With the use of volumetric rendering techniques with 3D viewing, figures can be obtained in defined anatomical detail which facilitate the interpretation of the lymphoscintigraphy and help assess the complex images in the planar study.18,19

Image interpretation

The SLN are identified by visualizing lymphatic channels leading directly toward the SLN from the tumor. Drainage may involve more than one SLN in a lymphatic region and more than one lymph node region and thus, one patient may have multiple SLN.

The main criteria for the identification of the SLN are visualization of the lymphatic channels, when they appear in the scintigraphic images, the area of lymphatic drainage and the intensity of lymph node uptake.20 In summary, lymph nodes may be classified into 3 categories:

1) Definitive SLN:
- Lymph nodes with their own direct lymphatic drainage: each SLN has its own lymphatic channel from the primary tumor.
- A single lymph node which appears early-delayed in a specific lymphatic region.

2) High probability of being a SLN (despite no visualization of a specific lymphatic channel):
- Lymph nodes which appear between the injection site and the SLN of the region of lymphatic drainage.
- Lymph nodes appearing early and with progressive uptake in the delayed images visualized in other lymphatic sites.

3) Low probability of being a SLN:
- Lymph nodes other than those in criteria 1 and 2 (usually second and third levels in lymphatic progression and with less uptake).

The lymph nodes included in the first two categories are what are conceptually considered the SLN and should be marked on the skin (cutaneous marking) for posterior resection by the surgeon.

Figure 3. Patient with melanoma in the left deltoid region. The planar image (A) shows two areas of drainage (supraclavicular and axillary). The volumetric imaging more precisely localizes the supraclavicular site of the SLN (posterior to the sternocleidomastoid muscle) influencing surgical planning (B).
Non-visualization of the SLN in the case of melanoma is exceptional. If the passage of the radiotracer is not observed from the injection site toward the lymphatic region, a gentle 5-min massage of the region may be useful. If an active SLN is not clearly observed, more delayed images, SPECT/CT or even another injection should be considered.

In breast cancer the main causes of not visualizing the SLN include the “shine-through” phenomenon in the cases of tumors in the tail of the breast, massive metastatic SLN infiltration, fat infiltration of the SLN (with scarce radiotracer uptake due to the substitution of the lymph node tissue by fat and minimum depositing of the radiotracer in the residual cortical lymph node tissue) and advanced age.\(^{21,22}\)

**Surgery**

In addition to the information provided by lymphoscintigraphy, another hallmark of the technique is the ability of the detector probe to guide the dissection and identify the SLN. It is recommended to do the search with the detector probe prior to making the incision. The scan should be slow and systematic and should initiate between the zone of the injection and the area of drainage until an increase in activity is observed. This activity should optimally coincide with the cutaneous markings made in Nuclear Medicine. Great precaution should be taken when the injection area overlies or is within the field of view of the detector probe and thus, if possible, mobilization maneuvers should be made or attempt to direct the gamma probe opposite to the injection site. The ex vivo activity of the SLN should be reported and the remnant surgical bed examined to rule out the presence of other potential SLN. Although the SLN is only viewed in the lymphoscintigraphy, in practice there may be two adjacent lymph nodes seen as one in the images, and therefore, the lymphatic region should always be reevaluated. It is also advisable to intraoperatively palpate the lymphatic region to identify lymph nodes which are possibly enlarged and more consistent, especially if ultrasonography has not been performed previously (although this should currently be mandatory).\(^{7,14}\) Nonetheless many authors consider that lymph node resection should continue up to achieving lymph node activity in the surgical bed <10% of the activity of the most active SLN, although this is not a strict norm.\(^{23}\) Almost all metastatic lymph nodes can be identified following the concept of the SLN and using a strict technique.\(^{24}\)

Vital dye may help to visually confirm the lymphatic vessels from the primary tumor to the SLN. The combination of lymphoscintigraphy and dye and the detector probe presents the highest precision in SLN identification, thereby recommending their use. The vital dye is especially important in cases in which the primary tumor is very near the lymphatic region and the radiotracer activity produces an elevated background which does not allow the detector probe to distinguish the SLN. Isosulfan blue (Lymphazurin) and Patent blue V are the dyes of choice for the SLN. Methylene blue is also used because of its lower cost, lesser risk of anaphylaxis and its similar ability to detect the SLN compared with the other two dyes.\(^{25}\)

**Aspects related to melanoma**

The diagnosis of melanoma is mainly based on the clinical manifestations, and its treatment is largely surgical. The evolution of melanoma often initiates with progression of invasion toward the surrounding skin, the regional lymph nodes and later the remainder of the body. If diagnosed early the probability of lymph node metastasis is lower, and thus, the tumor status of the lymph nodes is the most important prognostic factor in stages I and II patients.\(^{20}\)

Determination of the SLN allows the identification of patients with occult metastasis before it is clinically evident.

Other prognostic factors include tumor thickness (Breslow), the presence of ulceration and the mitotic index. In the 6th version of the AJCC, patients with thin melanomas, Clark level IV–V and/or ulceration were candidates for SLN biopsy. In the new version the Clark level has been omitted and the mitotic index (≥1/mm\(^2\)) has been introduced as a new factor.\(^{3}\)

SLN biopsy is a minimally invasive procedure which should be explained and recommended to patients with the following characteristics:

- a) A risk of presenting occult metastasis which justifies the procedure (>10%).
- b) The prognostic information provided by the SLN biopsy is valuable for the patient and the physician.
- c) The tumoral status of the SLN is useful for decision making concerning lymphoscintigraphy and adjuvant therapies and/or
- d) The information of lymph node staging is necessary for inclusion in clinical trials of benefit to the patient.

Taking this into account, SLN biopsy should be offered to all patients with: melanomas ≥1.0 mm in thickness, clinically negative regional lymph nodes on physical examination, fulfilling the above mentioned criteria and in whom the morbidity and risk are considered acceptable. However, SLN biopsy can also be offered to patients with melanomas <1.0 mm with characteristics which increase the probability of micrometastasis in the regional lymph nodes (presence of ulceration, mitotic index ≥1/mm\(^2\) and/or Clark IV/V invasion, especially in tumors >0.75 mm in thickness). Analysis of the AJCC database demonstrated a significant inverse correlation between the mitotic index and survival. Thus, the greater the mitotic value the shorter the survival.\(^{27}\)

In patients with melanomas from 0.5 to 1.0 mm in thickness and with <1 mitosis/mm\(^2\) the 10-year survival is 93%, 87% being in patient in the same group with >1 mitosis/mm\(^2\).

On the other hand, SLN biopsy may be considered in patients with melanocytic lesions with unknown metastatic potential.\(^{3}\) The guidelines of the NCCN is similar in regard to melanomas with a thickness >1 mm. However, the presence of ≥1 mitosis/mm\(^2\), which upstage IA to IB tumors, is not taken into account for indicating SLN biopsy in melanomas of <1 mm in thickness. SLN biopsy is not recommended in lesions with a thickness <0.75 mm, and in tumors from 0.76 to 1 mm in thickness the performance or not of biopsy should be discussed with the patient since the proportion of metastasis is low (~6%) and its clinical impact is modest.\(^{28}\) In patients with a SLN positive for metastasis regional lymphoscintigraphy is useful to improve local disease control, reduce operative morbidity, reduce the relative risk of recurrence by 26% and improve the survival in cases with lymph node metastases.\(^{29}\) In addition, the information provided by the SLN may be useful for advising patients about inclusion in clinical studies.

**Presurgical ultrasonography versus the sentinel lymph node**

Injection of a radiotracer in the dermis surrounding the primary tumor provides a roadmap guiding to the SLN. One of the main objectives of SLN biopsy is to identify the 20–25% of patients with clinically occult regional lymph node disease. Histopathological analysis of the material obtained by ultrasound-guided fine needle aspiration puncture (FNAP) is potentially interesting for evaluating the presence of lymph node metastasis. According to Voit et al.,\(^{31}\) this procedure may identify up to 65% of the metastasis in the SLN. In expert hands the precision of this procedure allows identification of the SLN in 79% of the cases based on specific patterns (Berlin morphologic criteria). In
a recent study including 1000 patients ultrasound-guided FNAP identified 50% of the positive SLN prior to SLN biopsy.

Nonetheless, this technique is operator-dependent and ultrasonography is not sensitive enough to identify metastasis of <4 mm. In most series, the SLN metastasis measure <1 mm in diameter, thereby suggesting that they cannot be identified by ultrasonography. Negative ultrasonographic evaluations (with or without FNAP) are therefore not a reliable substitute for pathological study of the SLN, although it should be performed as a complementary technique since it reduces the possibility of false negative results and allows identification of the cases which should undergo SLN biopsy.

Localization of head and neck melanoma

Approximately 15–35% of melanomas are presented in the head and neck and are associated with a worse prognosis. Several authors have demonstrated a greater index of recurrence in this zone after having been negative in the lymphatic roadmap, thereby reducing the accuracy of SLN biopsy.33

The complexity of the lymphatic area and the difficulty in achieving correct SLN identification in this zone constitute a challenge for surgeons. Melanomas located in the parietal zone demonstrate a greater trend to aberrant lymphatic drainage and metastasis on the contralateral side. In addition, the scarce distance between the zone of the tumor and the area of drainage and the presence of SLN which are difficult to access or potentially morbilliform (i.e. parotideal, pericarotidic, etc.) restrict the biopsy procedure.44

In a series including 3442 melanomas in the head and neck the SLN was localized in 93% of the cases. However, the false negative rate was >20%, being higher than that observed in other anatomical areas.35 Another study with 246 patients demonstrated that melanomas located in the facial region presented a better prognosis than those in the skull, ears or cervical region, even in thin tumors (Breslow index <1 mm). The presence of ulceration, elevated Clark level (IV/V) and young age were the strongest predictive factors to determine the presence of cervical lymph node metastasis.36

In-transit, aberrant, ectopic lymph nodes

Although a large proportion of melanomas drain into anatomically described lymphatic regions based on the localization of the primary tumor, lymph nodes are sometimes found outside the expected lymph node stations. Any lymph node visualized along the lymphatic channel between the primary localization and a known lymph node station is called an in-transit, interval, aberrant or ectopic lymph node and should be identified as a SLN regardless of its localization.

Lymph nodes in expected zones (Fig. 4) have been described in parascapular intermuscle, and supraclavicular spaces, the par correlation, paravertebral, and retroperitoneal regions, intercostal zones, the internal mammary lymph node chain, epicraniac, popliteal and even in the skull. Lymph nodes have been observed in these areas in 12% of the cases, and the probability of presenting metastasis in these lymph nodes is similar to that of the SLN in areas of classical drainage. With regard to localization of the primary tumor, melanomas in the upper extremities and the trunk are more likely to present in-transit SLN.37 On the other hand, tumors localized in the head and neck and the genital area present a lower rate of in-transit SLN.

The need to preoperatively identify the SLN is as important as identifying and resecting these SLN during surgery. An in-transit SLN may indicate infiltration in the regional lymphatic bed but may also be the only site with metastatic cells. Thus, in most studies the incidence of metastasis in the in-transit SLN is quite similar, ranging from 14 to 22%. Ortín-Pérez et al.38 reported a percentage of 19.5%. In 15 patients histologically identified as having metastasis in the in-transit SLN, 11 also presented infiltration of at least one SLN in the lymphatic region with classical drainage. The remaining 4 patients only showed infiltration in the in-transit SLN. These values reinforce the need to identify and resect in-transit SLN since they may occasionally be the only foci of lymph node metastasis.39,40

Use of SPECT/CT in melanoma

Some SLN are small in size and present scarce activity, sometimes being very difficult to localize through the skin with a gamma probe. Different studies have shown that SPECT/CT has advantages versus conventional planar studies in patients with melanoma (Table 3). These advantages include a greater global SLN detection index than planar images, the capacity to detect SLN in difficult to interpret conventional studies, better definition of the SLN at localizations close to the injection site and better anatomical localization.

The utility of SPECT/CT in patients with melanoma in the head and neck and the trunk has also been described in patients without visualization of the SLN and in patients with aberrant drainage.41,42

In one study including 18 patients the SLN was detected in 100% of the cases using SPECT/CT versus 89% with planar lymphoscintigraphy, with the surgical procedure being modified in 4 patients.34 Kraft et al.34 studied 113 patients in whom SPECT/CT images localized the SLN in 95% of the cases and found SLN which had not been observed in the planar images in 8 patients.

The clinical importance of the added value of SPECT/CT in melanomas was assessed in 63 patients. A change in surgical approach was made in 14 of these patients (22%), thereby indicating the need to use this procedure, especially in cases with ambiguous drainage.45 Alvarez Paez et al.46 observed that hybrid SPECT/CT images provided additional clinically important data in 50% of the cases and detected additional SLN in 23% of the patients with melanoma in the thoracic zones.

Stoffels et al.47 demonstrated that SPECT/CT improved the identification of SLN in the head and neck and in obese patients. Moreover, SPECT/CT was associated with a greater detection of metastasis and improvement in disease-free survival. These authors also described a reduction in the costs associated with the technique (reducing surgical time, hospital stay and greater proportion of local anesthesia).48

Clinical impact of the SLN in melanoma

The indexes of SLN localization in the inguinal and axilla are excellent in most studies, with only 20% of false negatives (1% in the inguinal area and 5% in the axilla). In the head and neck false negative SLN are observed in up to 20%, although the indexes of localization have increased in the last years from 85% to 93% possibly due to the introduction of SPECT/CT and intraoperative imaging. In-transit and aberrant lymph nodes should be resected whenever possible (popliteal, epicraniac, flank, parascapular, etc.). There is still no clear consensus are to whether to resect lymph nodes in the obturator or external iliac zone, despite being technically possible. SLN located deep in the abdomen are not resected, but rather are clinically followed using imaging techniques.

Histological examination of the SLN is done in paraffin sections and with hematoxylin eosin staining. Nonetheless, even expert pathologists may rule out the presence of micrometastasis in up to 12–15% of the cases with these techniques. Immunohistochecmical staining allows the diagnosis of micrometastasis or even isolated tumor cells (ITC). Some immunohistochecmical markers are sensitive but not specific for staining of melanoma cells.
Figure 4. Lymph nodes in unexpected sites. In-transit lymph nodes have been described in the epitroclear (A), and humeral zones (B), and intercostal, paravertebral and even paraaortic zones (C)–(E).

(i.e. S100, tyrosinase); therefore, the definitive diagnosis should at least include detection with a specific marker (i.e. HMB-45, melan-A, MART 1) if conventional staining with hematoxylin-eosin is not diagnostic. The use of both strategies increases the sensitivity. The literature has shown that even small deposits of metastatic cells are associated with a worse prognosis in patients with negative SLN. ITC (especially in subcapsular sinuses) have adverse biological significance in melanoma but not in breast cancer. The staging committee of the AJCC concluded that there is no definitive evidence to define a minimum threshold of tumor load for defining the stage of lymph node metastasis. However, recent studies indicate that lymph node dissection does not have an effect on the global survival after a positive SLN with scarce tumor load (<0.1 mm in diameter). It has therefore been suggested that lymph node dissection can safely be omitted in these cases.

The final analysis of the Multicenter Selective Lymphadenectomy Trial (MSLT-I) has recently been published. This study began in 1994 to evaluate the controversial therapeutic benefits of SLN biopsy in melanoma and has demonstrated the importance of this technique for staging and as a prognostic factor in melanomas of >1.20 mm in thickness. In summary, staging based on SLN biopsy in melanoma with intermediate or thick Breslow index provides relevant prognostic information and identifies patients with metastasis who may benefit from immediate lymph node dissection. This option increases the disease-free survival in all patients and specific survival in patients with lymph node metastasis of melanomas of intermediate thickness.

Table 3
Clinical impact of SPECT/CT in melanoma.

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Characteristics</th>
<th>% visualization</th>
<th>SPECT/CT results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ishiara, 2006</td>
<td>26</td>
<td>17 patients with MM</td>
<td>SPECT/CT identified 100 versus 85% (dye)</td>
<td>Shorter surgical time attributable to SPECT/CT</td>
</tr>
<tr>
<td>Covarelli, 2007</td>
<td>23</td>
<td>Only head and neck</td>
<td>SPECT/CT identified 100 versus 82% (planar images)</td>
<td>Change in surgical approach in 35% of the cases.</td>
</tr>
<tr>
<td>Van der Ploeg, 2009</td>
<td>85</td>
<td>All with MM</td>
<td>SPECT/CT 100 versus 99% (planar images)</td>
<td>Additional SLN in 16% of the cases.</td>
</tr>
<tr>
<td>Vermeerden, 2011</td>
<td>38</td>
<td>Only head and neck</td>
<td>SPECT/CT in 100% versus 95% (planar images)</td>
<td>Change in surgical approach in 55% of the cases.</td>
</tr>
<tr>
<td>Klode, 2011</td>
<td>48</td>
<td>Head and neck</td>
<td>NA</td>
<td>Change in surgical approach in 27% of the cases.</td>
</tr>
<tr>
<td>Veenstra, 2012</td>
<td>35</td>
<td>Extremities trunk</td>
<td>100% identification (planar SPECT/CT)</td>
<td>Change in surgical approach in 29% of the cases. Additional SLN in 20% of the cases.</td>
</tr>
<tr>
<td>Stoffels, 2012</td>
<td>149</td>
<td>All regions</td>
<td>100% identification (SPECT/CT and planar images)</td>
<td>False negatives with SPECT/CT = 6.8%. 23% in historic cohort. Disease-free survival at 4 years 93.9% with SPECT/CT versus 79.2% historic cohort. Modification in SN localization in 22% of the cases versus planar images.</td>
</tr>
<tr>
<td>Martinez, 2014</td>
<td>63</td>
<td>All regions</td>
<td>SPECT/CT in 100% versus 98% (planar images)</td>
<td></td>
</tr>
</tbody>
</table>

SLN, sentinel lymph node; MM, malignant melanoma; NA, not available.
However, there is no agreement among the scientific community and although the value for staging of SLN biopsy is recognized, its therapeutic effect remains under debate. The prognostic information of the SLN in melanomas of greater thickness is still limited. Hopefully, in the future, information from SLN biopsy will provide an effective adjuvant treatment in patients who are SLN positive for metastasis. The efficacy of the role of lymph node dissection in patients with metastatic SLN is uncertain and it is currently under evaluation in the randomized MSLT-II study which has been designed to assess the role of lymph node dissection in early melanomas. The patients are randomized to undergo observation or lymph node dissection. Serial ultrasonography is used to detect small metastatic deposits which may remain undetected on follow up visits.

Aspects related to breast cancer

Breast cancer surgery has been modified according to the current medical advances and greater knowledge of the disease. The concept of the SLN in breast cancer was validated in the EORTC-2000 Manual considering it as a staging procedure analogous to axillary lymph node dissection. The 2002 Consensus Conference in Philadelphia confirmed the efficacy of selective SLN biopsy in early breast cancer. Over the years the indications have varied from use in earlier stages and very specific situations up to a certain liberalization of the indications.

In the last update of the Consensus of the Spanish Society of Senology and Breast Disease (SESPM) (2013) the following were considered to be contraindications or exclusion criteria for performing SLN biopsy:

1. Preoperative confirmation of lymph node involvement using imaging tests (ultrasonography) and, at least, cytology of suspicious adenopathies with a diagnosis compatible with metastasis of carcinoma.
2. Inflammatory carcinoma.
3. Previous axillary radiotherapy at a dose of 50 Gy.

Accepted indications are:

1. T1, T2 and T3 infiltrating carcinomas, with clinical, ultrasonographic and pathological negative axilla.
2. Intraductal carcinoma with the indication of mastectomy. May be considered in cases of high risk of microinfiltration.
3. In male breast cancer the indications are the same as in females.

According to the Consensus, the following are not criteria contraindicating SLN biopsy:

1. Previous excisional biopsy, in the absence of exclusion criteria. SLN biopsy is usually recommended in the first month after excisional biopsy; however, this concept was “liberalized” in the last guidelines.
2. Previous breast augmentation or reduction surgery.
4. Conservative surgery with previous SLN biopsy for carcinoma: there is no evidence to contraindicate a new SLN biopsy, although individual evaluation is necessary in each case based on the dose of irradiation received in the axilla.
5. Pregnant women or those who are breastfeeding 24 h before withdrawal of lactation. It is recommended to use the lowest dose possible of radiotracer and on the same day of surgery. In these cases, the use of any vital dye is contraindicated.

Previous axillary evaluation. Role of ultrasonography

In the regional evaluation axillary status may be studied by clinical examination, magnetic resonance, PET-CT (specificity of more than 95% but with low sensitivity) and ultrasonography (high sensitivity, simple, inexpensive).

Ultrasonography is an adequate method in non-palpable axillary lymph nodes, presenting a sensitivity of 56–72% and a specificity of between 70% and 90%. Different morphologic ultrasonographic criteria indicate suspicion of lymph node infiltration: loss of hilum, cortical thickening and rounded appearance of the lymph node. However, up to 30% of the patients with lymph nodes of normal morphology present metastasis.

The technique most frequently used in axillary evaluation is FNAP. At present, different groups advocate the use of thick needle biopsy.

Using thick needle biopsy, Britton et al. obtained a sensitivity of 53% (60% micrometastasis and 26% micrometastasis) for the detection of metastasis. In a study including more than 100 patients, thick needle biopsy presented a false negative rate of 30%.

Despite the great inter-observer variability with the ultrasonographic technique it is currently an essential tool to presurgically assess the axilla and avoid unnecessary SLN biopsies.

SPECT/CT in breast cancer

The axilla is the main area of lymphatic drainage from breast cancer. Although the SLN are preferentially localized at Berg level I, direct drainage to levels II and III may be observed. Drainage to the internal mammary lymph node chain (IMLNC) may also be found as well as in the supraclavicular and intramammary regions and/or the Rotter’s space (interpectoral).

In a study including 134 patients, SPECT/CT demonstrated added value in 48 patients (42%), with the detection of additional SLN or modification of the foreseen surgical incision. Nineteen of the SLN were localized in an intramammary and interpectoral zone, and metastatic SLN which had not been seen in the planar study were detected in 4 cases. Another series with 41 patients demonstrated the exact anatomical localization of the SLN in the axilla, differentiating their position in the Berg levels. In overweight or obese patients SPECT/CT localized the SLN which were not visualized in the planar images in 29 out of 49 patients (59%).

Despite being of low dose, the CT component of the multimodal equipment may help to morphologically characterize the lymph nodes suggesting characteristics of suspicion. Finally, in a recent review of 11 studies, the role of SPECT/CT was evaluated and its precision in the localization of the SLN was of note in difficult cases and in the absence of drainage in the planar image.

Isolated tumor cells and micrometastasis

ITC are defined as cellular clusters of no greater than 0.2 mm in size, not confluent or adjacent, with less than 200 cells in a simple histologic sample of the lymph node. They are detectable by immunohistochemical study or conventional staining. Lymph node micrometastasis is defined as lesions greater than 0.2 mm and/or more than 200 isolated cells but not greater than 2 mm in diameter.

The incidence of ITC is of around 20%, and 9% are detected only by immunohistochemical study. According to the TNM classification they are considered N0. Lymph nodes with ITC are excluded from the total count of positive lymph nodes in the pN classification but should be included in the total number of lymph
nodes evaluated. The ITC probably have a negative influence on the global prognosis. However, axillary lymph node dissection in these patients does not demonstrate an improvement in loco control or survival. Five to 10% of patients with ITC also have macrometastasis.64

In the MIROR study patients with ITC without axillary lymph node dissection showed 2% of regional recurrences at 5 years with no significant differences in patients undergoing lymph node dissection (0.9%). In micrometastasis regional recurrence at 5 years was 5.6%, being significantly reduced with axillary lymph node dissection (1.1%). This study demonstrated that systemic adjuvant treatment improved disease-free survival in women with initial stages of cancer and micrometastasis or ITC.61

The NSABP B-32 study reviewed all the SLN samples negative by hematoxylin-eosin, with immunohistochemistry and found 15.9% of occult metastases. However, the difference in overall survival at 5 years was 1.2% and was not considered a significant benefit in systematic immunohistochemical studies.62

In the 23-01 study of the International Breast Cancer Study Group, Galimberti et al.63 compared axillary lymph node dissection or not in patients with T1 and T2 tumors and clinically negative lymph nodes with micrometastasis in the SLN. After a follow up of 60 months and an overall survival of 98% at 5 years, locoregional recurrence was 0.2% in the lymph node dissection group and 1.1% in the group without lymph node dissection. According to these results axillary lymph node dissection is not necessary in lesions of less than 5 cm. Thus, in the last consensus of Saint Gallen endorsed by different scientific societies, lymph node dissection is not recommended when the SLN presents ITC or micrometastasis.64

**Macrometastasis in the sentinel lymph node**

Studies of the SLN have demonstrated a low percentage of positive non-SLN when the SLN identified had metastasis, suggesting that perhaps not all SLN positive patients should undergo lymph node dissection.

The ACOSOG Z0011 study has had a great impact and has led to discussion regarding the need for axillary lymph node dissection despite the presence of macrometastasis in the SLN. This multicenter study includes T1 and T2 patients with invasive breast cancer with clinically negative axilla and who have undergone conservative breast treatment. In the SLN biopsy 1 or 2 positive lymph nodes were identified in the hematoxylin-eosin study and the patients were randomized to lymph node dissection or no axillary lymph node treatment. All the patients received systemic adjuvant treatment and radiotherapy of the breast and axilla. Patients with 2 or more positive lymph nodes and those receiving neoadjuvant treatment were excluded. No significant differences were observed between the two groups in overall survival, disease-free survival and locoregional recurrence at 6.3 years of follow up. The absolute difference in the overall 5-year survival between the two treatment groups was 0.7%, favoring the group with only SLN. The authors concluded that axillary lymph node dissection does not provide additional benefits in terms of local control, disease-free survival or overall survival.65

The great regional control obtained in the Z0011 study was due to multifactorial causes (tumors in early stages, irradiation of the whole breast, routine use of chemotherapy and low tumoral load of metastasis), thereby justifying the doubts of other groups regarding the inclusion of a greater proportion of elderly patients with positive estrogenic receptors and the scarce number of patients with more aggressive tumors (16%) in this study.

In relation to surgical axillary lymph node staging for stages I, IIA, IIB and IIIA (T2N1M0), the NCCN-2014 guidelines state that if the SLN biopsy is negative additional surgery should not be performed. If the SLN is positive in T1 or T2 cases with 1 or 2 positive SLN further axillary surgery is not necessary, implementing conservative treatment plus adjuvant radiotherapy and if neoadjuvant systemic treatment has not been performed. Patients who should undergo lymph node dissection include: those receiving neoadjuvant therapy (ACOSOG Z1071 study), those with a metastatic SLN and are treated with mastectomy, patients presenting 3 or more positive SLN, those showing significant extra-lymph node extension, those not receiving systemic treatment or total breast irradiation and patients with clinically palpable lymph nodes.65

The ACOSOG Z0011 study has had great repercussion in the media and may condition future treatments. Following critical analysis some authors have described some weak points and limitations in the randomization of the two groups and even biases which may affect the final conclusions. Thus, not all the scientific societies agree with the Z0011 approach and the debate remains ongoing. However, this option may be used in patients with low risk and receive systemic therapy and radiotherapy.64

Controversies aside, the ACOSOG Z0011 criteria have progressively been applied in clinical practice. Their implementation has had an impact on the decrease in the number of lymph node dissection performed and, consequently, a reduction in the number of intraoperative SLN studies. In a recent study Caudle et al. reported a reduction in the rate of lymph node dissection from 85 to 24% in one year among SLN positive patients. The rate of intraoperative SLN studies also fell from 69 to 26% during the same period. Not having to await intraoperative results also leads to a reduction in the surgical time.67

Some institutions have even evaluated the economic impact all this may represent. In their study Camp et al.68 concluded that not performing lymph node dissection according to the ACOSOG Z0011 criteria has led to a 64% reduction in hospital stay and a reduction of 18% in perioperative economic costs. The survey carried out by the American Society of Breast Surgeons revealed that surgical practices have changed. However, caution should be taken since lymph node dissection has even been omitted in other scenarios not precisely studied in the Z0011. New studies are therefore necessary to evaluate the omission of axillary dissection in patients undergoing mastectomy or in those treated with neoadjuvant therapies (ACOSOG Z1071).

The SOUNa study is currently in its recruitment phase. This study will presurgically evaluate the axilla by ultrasonography and randomize patients without suspicious lymph nodes and tumors of less than 2 cm to undergo either biopsy of SLN versus observation without axillary surgery. A future without axillary surgery is foreseen even without SLN biopsy in patients with initial breast cancer and presumed load tumoral load in the axilla.69

**Internal mammary lymph node chain**

The presence of metastasis in the internal mammary lymph node chain (IMLNC) is associated with a worse prognosis. Locoregional treatment of IMLNC infiltration should consider the EORTC 22922/10925 protocol which has shown benefits in overall and disease-free survival with parasternal irradiation. Nonetheless, this treatment is not free of risk to the lung and heart.70

Although, as in the axilla, the lymph nodes of the IMLNC are among the first steps of drainage in breast cancer, the importance of their treatment remains under debate. The use of SLN biopsy and the possibility of detecting drainage toward the IMLNC by lymphoscintigraphy have renewed the interest in this region. However, the contribution of SLN biopsy of the IMLNC and the repercussion
of its treatment are not clear. Lymphoscintigraphy has shown that a significant proportion of breast tumors present primary drainage to the IMLNC (30% in the cases of medial tumors and 15% in lateral tumors). The prevalence of drainage toward the IMLNC is determined by the method of radiotracer injection used. Deep punctures present a much greater percentage of drainage toward the IMLNC than superficial punctures. The addition of SPECT/CT may increase the identification of drainage toward the IMLNC and reduce the possible false negative of SLN biopsy. Up to 20% of cases present metastasis in studies performing SLN biopsy in the IMLNC. The risk of infiltration of this SLN is greater if the tumor site is medial and the axillary lymph nodes present metastasis.

The success of resection of the SLN of the IMLNC varies from 45 to 100%. Lymphoscintigraphy sometimes shows several parasternal uptakes leading to doubts as to which is the true SLN. In the case of a single visible lymphatic channel, this may sequentially drain to a group of lymph nodes in the IMLNC and only the first should be considered as the SLN (Fig. 5). However, this problem may be solved by performing a sequential study. The shine-through phenomenon may also be a problem for correct visualization of the SLN in tumors in the inner quadrants and may thereby cause false negative cases. SPECT/CT and the possibility of performing intraoperative images may help in this regard.18

Metastasis in the IMLNC has prognostic significance. However, although evaluation of the IMLNC should be indicated, routine use of this procedure has not, as yet, been implemented. Resection of the lymph nodes of the IMLNC may be difficult and require another incision in conservative treatments in addition to the risk of pneumothorax and bleeding. Eight to 10% of axilla negative cases present metastasis in the IMLNC.

Treatment of patients with metastasis in the IMLNC is not completely established and it remains unclear whether the additional information provided by staging of the IMLNC improves the clinical results after standard histopathological study of the axilla.71

Different authors have argued that the information provided by SLN biopsy of the IMLNC changes the treatment approach only in a very small number of patients. Other authors consider that this biopsy may provide additional prognostic information which may modify systemic adjuvant therapy and/or locoregional radiotherapy. This conclusion is based on some retrospective studies which have demonstrated that tumors located in the inner quadrants have a worse prognosis than those in outer quadrants.

This worse prognosis is considered to be due to the underestimation of the metastasis of the IMLNC. In a study including 604 patients, 100 with drainage to the IMLNC without resection of these lymph nodes, both the overall and the disease-free survival were lower in patients with drainage to the IMLNC than in those without. In addition, patients with metastatic axillary SLN and drainage to the IMLNC showed a 3.3-fold higher risk of death compared to those with a positive axillary SLN but without drainage to the IMLNC.72

The prevalence of metastasis in patients with SLN biopsy of the IMLNC ranges from 8% to 27%. From 1% to 8% of the patients have metastasis exclusively in the SLN of the IMLNC.

All these results suggest that drainage to the IMLNC and biopsy of the SLN in the IMLNC may have an impact on surgical treatment and chemo- and radiotherapy. However, this impact may be lower since many patients receive systemic treatment based on biological factors of the tumor and not on lymph node status.73 Evidence that patients with tumors in the inner quadrants have a worse prognosis indicates possible underestimation of the parasternal lymph nodes and thus, knowledge of the SLN in the IMLNC, especially in these patients may have clinical impact for the use of systemic and/or radiotherapy.74

**Intramammary lymph nodes**

The detection of intramammary SLN in the lymphoscintigraphy ranges between 0.7% and 14%. These differences may be explained by the radiotracer injection technique used. The SLN may be presented with axillary lymph nodes or not.

According to the AJCC, metastatic infiltration of these lymph nodes has the same value in staging as that of the ipsilateral axillary lymph nodes, and some studies have suggested that they are a factor of bad prognosis. A recent review of the experience of the MD Anderson Cancer Center concluded that disease-free and overall survival were significantly shorter in the group with intramammary lymph node metastasis.75

Despite the use of planar images and SPECT/CT, the localization of intramammary lymph nodes during surgery may sometimes be a challenge. Combined use of the gamma detector probe and intra-surgical images increases the detection of lymph nodes close to the injection site which present faint uptake or are not stained by the dye if this is used.76

In the presence of an intramammary lymph node, the therapeutic approach to axillary lymph node management is controversial, particularly if the node is metastatic. One possibility is combined detection of the axillary SLN and intramammary lymph node (also SLN). Most authors agree that biopsy of both and treatment of axilla lymph nodes depends on axillary SLN status.

Another possible scenario generating great debate involves the appearance of a positive intramammary lymph node and a negative axillary SLN. In regard to performing axillary lymph node dissection some authors support high values of axillary infiltration when a positive intramammary lymph node is present (around 70%) even when the axillary SLN is negative.77 The detection of an isolated intramammary lymph node is another controversial situation. Andrés et al.78 recommend a new injection of the radiotracer and/or dye as well as the use of a gamma detector probe during surgery to detect axillary drainage. Axillary lymph node dissection is recommended if axillary drainage is still not localized due to possible metastatic blockage.

**SLN biopsy and primary systemic treatment**

The performance of SLN biopsy prior to or after primary systemic treatment remains controversial, with many advantages and disadvantages in each case.

SLN biopsy prior to chemotherapy provides greater safety of the staging and provides more information to the radiotherapist regarding lymph node infiltration but requires two surgical procedures and may delay the initiation of treatment. Biopsy after primary chemotherapy allows evaluation of lymph node response and thereby provides greater information of the results of treatment but the initial status may be understaged.

To determine the most adequate time to perform SLN biopsy patients should be selected according to the possible benefits to be obtained in each particular case. Thus, patients receiving primary systemic therapy should undergo an ultrasonographic study (with FNAP if suspected). In cases with clinically and ultrasonographically negative lymph nodes, SLN biopsy may be indicated before or after systemic treatment. Persistence of negative findings after treatment avoids the use of axillary lymph node dissection. At present, SLN biopsy is done after systemic treatment together with the breast surgery since this avoids one surgical procedure. There is also controversy as to the cases in which the lymph node is initially positive. SLN biopsy should be deferred until after systemic therapy and posterior ultrasonographic assessment. The ASCO
Figure 5. Patient with breast tumor in the inner quadrants of the left breast. Drainage toward axillary region and IMLNC. Multiple parasternal lymph nodes. The early (A) and the delayed image (B) provide doubts as to the possible SLN. The image generated in the SPECT/CT clarifies the position and indicates the first drainage lymph node (C). The axial slice corresponding to the CT shows the parasternal lymph node (D).

consensus still does not accept this possibility while the SESPM does but under special conditions.

The guidelines of the NCCN-2014 consider that SLN biopsy should be done prior to neoadjuvant systemic treatment, and axillary lymph node dissection may be omitted in cases with a negative SLN requiring mastectomy and in patients receiving conservative breast treatment. The guidelines of the NCCN-2014 consider that SLN biopsy should be done prior to neoadjuvant systemic treatment, and axillary lymph node dissection may be omitted in cases with a negative SLN requiring mastectomy and in patients receiving conservative breast treatment. According to the 2013 Consensus of SLN of the SESPM, SLN biopsy may be performed in patients with initial clinically/ultrasonographically negative axilla (cN0) both prior to and after primary systemic treatment. Biopsy may be performed after primary systemic treatment in early cN1/N2, clinically and ultrasonographically axilla negative patients after neoadjuvant therapy (CyN0) to avoid axillary lymph node dissection if the SLN is negative. Nonetheless, recent series (see below) have reported controversial results due to the high false negative rate secondary to primary systemic treatment.

In the SENTINA study SLN biopsy was performed in 1022 patients prior to neoadjuvant chemotherapy, with the SLN being detected in 99%. A second SLN procedure was performed in patients who had positive SLN before chemotherapy to determine whether the second procedure might be useful to identify the subgroup of patients in whom the positive lymph node became negative after treatment. Nonetheless, detection was achieved in 60% and the false negative rate was 51%. The SLN was detected in 80% of women with suspicious lymph nodes before neoadjuvant therapy and a normal lymph node status thereafter, with a false negative rate of 14%.

The ACOSOG Z1071 study reported similar results. In both studies the false negative rate was less than 10% only if 3 SLN were localized. This means that the percentages of SLN localization after primary systemic therapy are less favorable than in patients who first undergo surgical treatment, making axillary lymph node dissection necessary in these cases.

The recommendations of the ASCO 2014 indicate that SLN biopsy may be done prior to or after systemic therapy but the false negative rate is higher after treatment and thus, this procedure is less precise after neoadjuvant chemotherapy.

New possibilities for radioguided surgery

Despite satisfactory results in localizing the SLN with previous lymphoscintigraphy (and SPECT/CT), precise localization for surgical planning may sometimes be difficult. The gamma detector probe provides a clear perspective of the activity in the surgical field, with identification rates of 99% in melanoma and 95% in breast cancer. Nonetheless, the technique can be further improved. The combination of dye and probe has prevailed for many years as the standard technique during surgery. However, dye is less effective in areas of aberrant drainage and in deep lymph nodes (head and neck region or in IMLNC the percentage of identification of the SLN is around 85%).

The technological advances in portable devices and the possibility of using new radiotracers (i.e. fluorescent) have led to the gradual transformation of the “see to open” approach to the new “see, open and see again” paradigm. The combination of SPECT/CT with portable imaging devices reinforces the reliability of the detector probe, especially in complex drainage regions and areas in which the SLN is very close to the injection site. The properties of these gamma cameras allow optimal surgical use and increase the sensitivity and precision in small spaces.

The use of portable gamma cameras allows the surgeon to adapt the previously made marks to the surgical incision and confirms the exact localization of the SLN since the position of the patients may be different. This is especially important in the cervical region in which lateralization of the neck may involve marked changes in the position of the SLN as well as the IMLNC in order to precisely select the intercostal space in which the SLN is located. Different studies
Figure 6. Intraoperative image. (A) Patient with drainage in the IMLNC. (B) Image obtained with the portable gamma camera demonstrates the drainage and intraoperatively allows a change in the incision site. (C) Patient with frontal melanoma showing drainage toward the preauricular region and left malar regions. (D) SPECT/CT image and intraoperative image (fused with optical image) showing the anatomical surroundings in real time and favoring lymph node identification (E).

have demonstrated the added value of the use of these devices in that they allow resection of additional SLN, some of which are positive for metastasis. In this way the false negative rate is reduced while the SLN identification rate is increased and ensures that none are left in the surgical field. New perspectives in radioguided surgery may be opened by the fusion of the scintigraphic images with an optical image (Fig. 6).

Freehand SPECT is another device designed for intrasurgical navigation. This method combines the acoustic signals with a 3D image to localize the SLN in the operating room. It has a spatial localization system and two scanning devices which are attached to the detector probe and the patient. The localization system consists in an optical camera and an infrared-based localization device. Virtual 3D images are generated and shown on the screen by exhaustive scanning in the area of interest with the detector probe. These images may be seen in real time and provide information about the depth at which the SLN is found or the tissue to be resected. Specific training in the use of the technique is required for data acquisition and for making several readings during surgery which, in the case of gamma cameras, lengthens the operation time. Nevertheless, in both cases the results may refine the conventional technique. The use of freehand SPECT is currently demonstrating excellent results in melanoma and breast cancer.

Another field which is undergoing expansion is the use of fluorescent agents for making a lymphatic roadmap and localization of the SLN. The use of indocyanine green (ICG) as a radiotracer has been evaluated in recent years. Similar to other vital dyes, ICG is constituted by particles which rapidly migrate through the lymphatic system with a relatively short detection time and the need for very strict temporal planning in surgery in order to identify the SLN. Moreover, high doses of ICG are needed and the penetrability of the fluorescence in tissues is scarce (1–2 mm). Therefore visualization and detection of the lymphatic channels and SLN in patients with great adipose panniculum are difficult. Taking this into account a hybrid compound has been developed combining the radiotracer classically used in Europe for lymphoscintigraphy ($^{99m}$Tc-albumin nanocolloid) with ICG. A recent study demonstrated its stability and reproducibility versus the classical radiotracer. Indeed, it was shown to detect fluorescent SLN up to 23 h after administration of the hybrid compound, thereby increasing the useful time for planning surgery. The combination of the properties of the two radiotracers (tissular penetrability of the radiotracer and high resolution of the fluorescent image) implies greater accuracy in the detection of the SLN in complex drainage areas.

It should not be forgotten that each technique has its own devices and these will be combined and adapted in future multimodal devices to provide all the potential of intraoperative imaging and thereby achieve greater reliability in the surgical procedures.

Key points

1. SLN biopsy has become the gold standard for the staging of melanoma and breast cancer. This minimally invasive method evaluates regional lymph node status. It is based on the presumption of orderly progression of lymph node infiltration by the tumor cells so that if the SLN does not show metastasis neither will the remaining lymph nodes in the lymphatic region.

2. Presurgical lymphoscintigraphy is considered the roadmap to guide the surgeon to subsidiary lymph nodes with potential metastasis and is very useful for the localization of unpredictable drainage patterns.

3. In melanoma lymphoscintigraphy is performed by intradermal injection of the radiotracer. In breast cancer superficial (cutaneous-areolar) and deep (peri/intratumoral) injections are made. The superficial punctures barely present extra-axillary drainage while deep punctures show non-axillary lymph nodes in 20–40% of the cases.
9. Wong SL, Balch CM, Hurley P, Agarwala SS, Akhurst TJ, Cochran, et al. Sentinel node biopsy should be offered to patients with melanomas of ≥1.0 mm in thickness and regional lymph nodes which are clinically negative on physical examination. It can also be offered to patients with melanomas of <1.0 mm in thickness showing characteristics which increase the probability of micrometastasis in the regional lymph nodes (presence of ulceration, mitotic index >1/mm² and/or invasion at Clark level IV/V, especially if the tumor is 0.75 mm in thickness).

6. The current indications of SLN biopsy in breast cancer are centered on T1, T2 and T3 infiltrating carcinomas provided that the axilla is clinically, ultrasonographically and pathologically negative. It is also indicated in intraductal carcinoma with mastectomy (can be considered in cases of high risk of microinfiltration).

7. Axillary lymph node dissection is currently not recommended in patients with breast cancer and the presence of micrometastasis in the SLN.

8. The risk of infiltration of the SLN in the IMLNC is greater in cases with medially located breast tumors and with axillary lymph node metastasis. Metastasis in the IMLNC has prognostic significance. However, despite being indicated, routine application of IMLNC is not currently carried out.

9. SLN biopsy prior to chemotherapy provides greater safety in staging but requires two surgeons and may delay the initiation of treatment. After chemotherapy lymph node response may be assessed, obtaining more information on the results of the treatment, although the initial status may be understaged.

10. The use of portable gamma cameras allows the surgeon to adapt the previously made marks to the planned surgical incision site and confirms the exact localization of the SLN and its resection. Likewise, the addition and combination of new radiotracers (fluorescent agents) provides greater detection of the SLN in areas with complex drainage.

Conflict of interest

The authors have no conflicts of interest to declare.

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