



Preoperative and Intraoperative Lymphatic Mapping for Radioguided Sentinel Lymph Node Biopsy in Breast Cancer

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Contents

9.1	Introduction	186
9.2	The Clinical Problem	186
9.3	Lymphatic Drainage of the Breast	187
9.4	Lymphoscintigraphy: Technical Controversies	189
9.5	Intraoperative SLN Detection in Patients with Breast Cancer	195
9.6	Indications and Controversies for SLN Mapping in Patients with Breast Cancer	196
9.7	Clinical Impact of SLNB in Breast Cancer	200
	Clinical Cases	203
	References	215

Learning Objectives

- To understand the pathophysiologic basis of the sentinel lymph node (SLN) concept in breast cancer
- To acquire basic knowledge on the lymphatic drainage routes in the breast and draining lymph node stations
- To become familiar with the lymphoscintigraphy procedure in breast cancer patients concerning

radiotracer type, injection procedure, and lymphatic mapping acquisition, including the indications and advantages of SPECT/CT

- To understand the differences between superficial and deep tumor-related injections including advantages, limitations, and consequences
- To become familiar with the intraoperative aspects of radioguided SLN localization procedure inside and outside the axilla aided by the use of the hand-held gamma-detecting probe
- To gain knowledge on the advantages of intraoperative usage of portable gamma cameras
- To become familiar with the clinical indications for sentinel lymph node biopsy (SLNB) in breast cancer patients
- To become aware of the benefits and risks of the SLNB procedure in other, controversial clinical situations
- To understand the pros and cons concerning the treatment of the internal mammary chain if involved, related to clinical outcome

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- To understand the advantages and limitations of the SLNB procedure when applied before or after treatment in patients pretreated with chemotherapy and to gain knowledge on how to improve the accuracy of the procedure in these situations
- To become familiar with the management strategies of the axilla, related to the result of the SLN procedure

9.1 Introduction

Axillary lymph node status still is a major prognostic factor in early-stage breast cancer, providing information that is important for tailoring postsurgical treatment [1, 2].

Since imaging techniques have limited sensitivity for detecting metastases in axillary lymph nodes, the axilla must be explored surgically. Histology of all resected nodes at the time of axillary lymph node dissection (ALND) has traditionally been thought to be the most accurate method for assessing metastatic spread of disease to the locoregional lymph nodes. However, the anatomic disruption caused by ALND may result in lymphedema, nerve injury, shoulder dysfunction, and other short-term and long-term complications that may compromise function and quality of life.

SLNB is a less invasive method of assessing nodal involvement [3]. The concept of the SLN is intimately embedded in the notion that, as a consequence of the orderly pattern of lymph flow, metastatic spread of solid tumors through the lymphatic route follows a predictable pattern [4]. According to this concept, early systematic studies in breast cancer patients [5, 6] have suggested that the use of SLNB can be reliably performed in selected patients with early-stage breast cancer by a carefully trained multidisciplinary team (surgeon, pathologist, nuclear physician), thus reducing the need for ALND and avoiding the associated morbidity [6]. While nowadays the SLNB procedure is considered “standard of care” in patients with early-stage breast cancer without cytologically or histologically proven axillary lymph node metastases, controversy remains concerning its use in patients with ductal carcinoma in situ (DCIS), in patients with large or multifocal/multicentric tumors, in recurrent disease, and in the neoadjuvant setting.

With the implementation of SLNB, not only the technique itself but also the histologic processing and SLNB-based management of the axilla have evolved over time, resulting in a paradigm shift in patient management [7, 8]. In contrast to the axilla, the importance of treatment of the internal mammary nodes (IMNs) is still a highly debated issue [9].

Recent guidelines and reviews have updated the field, which encompasses a growing body of literature dealing with several aspects of the procedure, from technical modalities to immediate and long-term clinical implications [9–13].

9.2 The Clinical Problem

ALND has been an integral part of the management of breast cancer since Halsted described the radical mastectomy in the 1890s [14]. This operation was designed to achieve locoregional control in women with large locally advanced tumors metastatic to the axillary lymph nodes. Since then, breast cancer is detected earlier, with smaller tumors and less nodal involvement [15]. Since Halsted’s time, operations on the breast itself have become less radical. Radical mastectomy was replaced by modified radical mastectomy, which in turn has been largely replaced by lumpectomy in patients with early breast cancer. Despite the revolution in surgery on the breast itself, ALND continued largely unchanged until the 1990s, when SLNB was first introduced [16].

Accurate lymph node staging is essential for both prognosis and treatment in patients with breast cancer. Axillary nodal status is the most important predictor of overall survival, and control of the axilla remains essential to patient well-being. Axillary dissection, however, is associated with a number of significant morbidities and complications such as seroma, infection, decreased range of motion, axillary web syndrome, shoulder pain, paresthesias, and lymphedema [17].

The SLNB procedure was introduced as a means of accurately identifying axillary metastases by removing only a few lymph nodes, usually one or two, and avoiding the complications and morbidity of ALND. The rate and severity of complications such as lymphedema and sensory loss are markedly less after SLNB compared to ALND (2% versus 13% and 12% versus 44%, respectively), while patients are dealing with less adverse effects in terms of range of motion, quality of life, and resumption of normal activities of daily life after surgery [8, 18].

Numerous prospective single-institutional and multicenter randomized controlled studies have shown the accuracy and safety of SLNB in early breast cancer [6, 19, 20]. With the increasing use of neoadjuvant chemotherapeutic agents in order to preserve the breast in patients with locally advanced cancer, a new, highly debated issue is the appropriate timing of the SLNB, pre- or post-neoadjuvant chemotherapy [21].

SLNB has radically changed the management of the axilla for patients with early breast cancer. After more than a century, axillary management has finally changed to a less morbid and less radical approach. Patients have far fewer complications after SLNB alone than they do after ALND,

and quality of life and time missed from the activities of daily living are markedly improved with this less radical operation.

Key Learning Points

- Axillary nodal status is the most important predictor of overall survival.
- Accurate lymph node staging is essential for both prognosis and treatment in patients with breast cancer.
- Axillary lymph node dissection is associated with significant morbidity and complications.
- The SLNB procedure can accurately identify axillary metastases while avoiding the complications and morbidity of axillary dissection.
- SLNB has radically altered the management of the axilla for patients with early breast cancer with fewer complications and better quality of life than ALND.

9.3 Lymphatic Drainage of the Breast

9.3.1 Lymphatic System of the Breast

Anatomical knowledge of the breast lymphatics is primarily derived from the work of Sappey in the 1850s. Sappey identified two groups of lymphatic vessels with extensive interconnections: one group draining the superficial aspect of the breast, primarily the skin and subcutaneous tissue, while a deep lymphatic vessel group draining the gland itself to a subareolar

plexus, which in turn drains to the axilla [22]. Subsequent and more contemporary studies of breast lymphatics involved not only postmortem injections, but also metastatic routes and, more recently, lymphangiography and lymphoscintigraphy. Suami and coworkers investigated the lymph drainage of the breast in cadavers and found no evidence of a centripetal lymphatic pathway to a subareolar plexus; instead, their study showed that different areas of the breast frequently drained to different lymph nodes [23]. This finding has been supported by clinical studies involving lymphoscintigraphy using tumor-related injections (see below) [24–26].

9.3.2 Draining Lymph Node Stations

The breast drains to lymph nodes at different sites. Most of the breast lymph drains to the axilla. A subareolar plexus-related injection will not identify sites of metastases outside the axilla. In fact, a subareolar plexus-related injection rarely identifies lymphatic drainage to the internal mammary, parasternal, or intramammary lymph nodes. Posterior to the breast parenchyma itself is a second plexus in the retromammary space, which drains not only to the axilla, but also to the internal mammary chain as well as to the intercostal and diaphragmatic lymph nodes. Drainage to the internal mammary basin occurs in 20% of patients after intratumoral or peritumoral radiocolloid injection. Other unusually located SLNs are also seen in a non-negligible fraction of patients: intramammary (pre-pectoral) in 6%, inter-pectoral in 2%, and infraclavicular (axilla level III) in 3% [27]. There is overlap of drainage areas and extensive anastomoses of the lymphatics of the breast [28]. In each quadrant, a breast cancer may drain to SLNs in various locations [24] (Fig. 9.1). When drainage to the internal mammary chain occurs, most

Fig. 9.1 Lymphatic drainage from the untreated breast. *On the left*, drainage from tumors in the quadrants outer upper (blue), outer lower (yellow), inner upper (red), inner lower (green), and central (black) to the axilla and internal mammary chain according to data from Estourgie et al. [24]. *On the right*, drainage to non-axillary SLNs according to data from Tanis et al. [81]

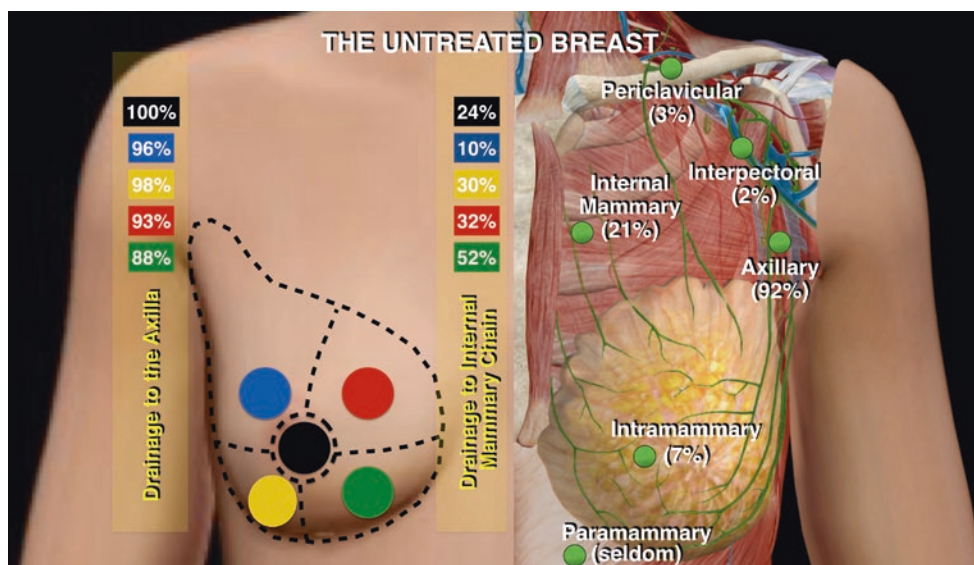
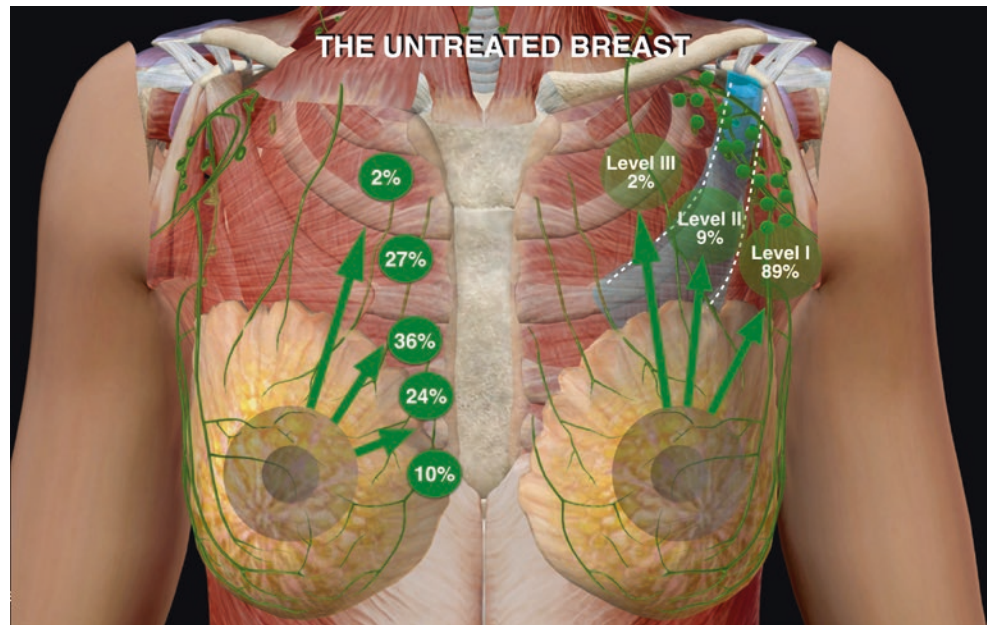


Fig. 9.2 Lymphatic drainage from malignant tumors in the untreated breast. *On the right*, drainage to the internal mammary chain according to data from Estourgie et al. [24] showing most frequent drainage to SLNs in the second, third, and fourth intercostal spaces. *On the left*, drainage to the axilla according to data from Uren et al. [29] with level I (89%) and II as the most frequent SLN sites



SLNs are found in the second, third, and fourth intercostal spaces (Fig. 9.2).

There are three groups of axillary nodes, arbitrarily defined by their anatomic relationship to the pectoralis major and minor muscles. These nodes are caudal to the axillary vein. Level I lymph nodes extend from the lateral edge of the pectoralis major muscle to the lateral edge of the pectoralis minor muscle. Level II lymph nodes are those directly posterior to the pectoralis minor muscle, and level III are the lymph nodes medial to the medial border of the pectoralis minor muscle and extending to the Halsted's ligament at the chest wall. There are very few lymph nodes in level III.

Within level I, there are a number of nodal groups. The external mammary lymph node group runs parallel and along the lateral thoracic artery, draining primarily the lateral breast. The lateral axillary vein group is located posteriorly along the anterior border of the latissimus dorsi and contains the largest amount of nodal tissue. The subscapular nodal group runs parallel to the scapular vessels and drains the lower posterior neck, posterior trunk, and posterior shoulder as well as the breast. The axillary vein group medial and posterior to the axillary vein receives drainage primarily from the upper extremity and not the breast. Axillary dissections for breast cancer should not routinely remove tissue posterior or superior to the axillary vein.

Level II nodes may receive lymphatic drainage directly from the breast, but also drainage from afferent vessels of level I nodes. Level III lymph nodes are the most medial nodal group in the axilla, which not only drain the other axillary nodal groups, but also merge with lymphatic vessels

from the subclavicular group and form the subclavian trunk. Rotter's lymph nodes are located between the pectoralis major and minor muscles. Some lymphatics from the retro-mammary plexus penetrate the pectoralis major muscle and travel along the thoracoacromial vessel, terminating directly in level III. Superior and medial aspects of the breast may also drain directly to level III. However, isolated nodal metastases are rarely seen in level III nodes without extensive involvement of the level I and level II lymph nodes. For this reason, most surgeons perform a level I and level II axillary dissection without removing level III, unless palpable lymph nodes are encountered or there is extensive nodal disease in the first two levels. SLNs are encountered primarily in level I, less so in level II, and rarely in level III [29] (Fig. 9.2). Good exposure of level III lymph nodes often requires partial or full transection of the pectoralis minor muscle.

Lymph nodes of the internal mammary chain (IMNs) primarily drain the postero-central and posteromedial aspects of the breast. Usually nodal metastases are seen in the internal mammary chain only when there are concomitant axillary metastases. Only about 3–5% of the patients have nodal metastases identified in the internal mammary SLN without axillary involvement.

The ipsilateral supraclavicular nodal metastases are no longer considered stage IV disease in the American Joint Commission on Cancer (AJCC) Staging System, because of the direct drainage of the upper inner portion of the breast to the supraclavicular nodes. Involvement of these lymph nodes results in classification of these patients as AJCC nodal stage N3. IMN metastases result in classification as N1, N2, or N3 [30].

Key Learning Points

- There is no evidence of a centripetal lymphatic pathway to a subareolar plexus as proposed by Sappey; instead, most of the lymph from the breast flows toward the nodal basins with a direct course.
- There are three groups of axillary lymph nodes, defined by their anatomic relationship to the pectoralis major and minor muscles: levels I, II, and III.
- SLNs are encountered primarily in level I, less so in level II, and rarely in level III.
- Drainage to the internal mammary basin occurs in 20% of patients after intratumoral or peritumoral radiocolloid injection with 3–5% of the patients having nodal metastases identified in the internal mammary SLN without axillary involvement.
- Ipsilateral supraclavicular nodal metastases are no longer considered stage IV disease in the AJCC Staging System, because of the direct drainage of the upper inner portion of the breast to the supraclavicular nodes.

and Canada, where it is widely used for SLN procedures [31].

It is generally considered that a radiocolloid with most of the particles ranging in size between 100 and 200 nm represents a practical compromise between fast and efficient lymphatic drainage from the site of interstitial injection and satisfactory retention in the SLN. The activity of the radio-tracer depends on the timing of surgery relative to lymphoscintigraphy, with an approximate amount of 37–111 MBq (1–3 mCi).

A novel radiopharmaceutical has been approved in 2013 for lymphatic mapping, ^{99m}Tc-tilmanocept (Lymphoseek®) [32]; Lymphoseek® accumulates in lymphatic tissue by binding to a receptor on the surface of macrophage cells within LNs. Due to its properties, Lymphoseek® has faster clearance from the injection site, prolonged retention in SLNs, and a smaller amount of excised lymphatic nodes than ^{99m}Tc-sulfur colloid [32–34]. Although Lymphoseek® appears to have all the desired properties for SLN mapping, the low yield of excised lymph nodes could become an unfavorable factor in this new era in which the approach toward management of limited metastatic SLN disease in the axilla has changed (see below).

9.4 Lymphoscintigraphy: Technical Controversies

Although SLNB is widely employed in patients with breast cancer, several technical issues remain unresolved. The main areas of controversy concern the radiopharmaceuticals to be used, the site and mode of radiocolloid injection, and the use of preoperative imaging with or without SPECT/CT imaging.

9.4.1 Radiopharmaceuticals

Three types of radiocolloid preparations are commonly used for lymphoscintigraphy and intraoperative identification of the SLN with a handheld γ -probe. ^{99m}Tc-sulfur colloid is the most commonly used agent in the United States, either unfiltered (particle size about 15–5000 nm) or filtered (particle size depending on the filter employed, usually 220 nm). Most European investigators use a ^{99m}Tc-nanocolloidal preparation of human serum albumin with particles ranging in size between 4 and about 100 nm (95% of the particles being <80 nm). At present, this radiopharmaceutical offers the best range of particle size, approaching the ideal range, and offers the additional benefits of instant labeling at room temperature and stability both in vitro and in vivo. ^{99m}Tc-antimony trisulfide (3–30 nm) is commercially available in Australia

9.4.2 Radiocolloid Injection for SLN Mapping in Patients with Breast Cancer

No consensus exists on the optimal injection approach. Widely applied techniques include tumor-related injections (intratumoral or peritumoral) and superficial injections (intradermal, subdermal, subareolar, and periareolar) (Fig. 9.3).

Direct intratumoral injection has originally represented a natural extension of the technique developed earlier with vital blue dye [35]. For intratumoral and peritumoral administration, the radiocolloid is injected into the tumor or in a site immediately adjacent to the tumor, in the space with a supposedly normal lymphatic system that is the only possible drainage pathway for fluids, particles, and cells leaving the tumor through the extravascular route. Although in most centers such intra- or peritumoral injections are directed simply by palpation, it is advisable to inject the tracer under sonographic guidance (or stereotactic devices).

The likelihood of visualizing a lymphatic duct and a draining lymph node increases when the radiocolloid is injected in the skin overlying the mammary gland (subdermal/intradermal injection) [36]. Therefore, axillary SLNs can be efficiently visualized as early as 20–30 min after intradermal injection of radiocolloid (versus 30–40 min for the peritumoral and 40–60 min for the intratumoral routes of

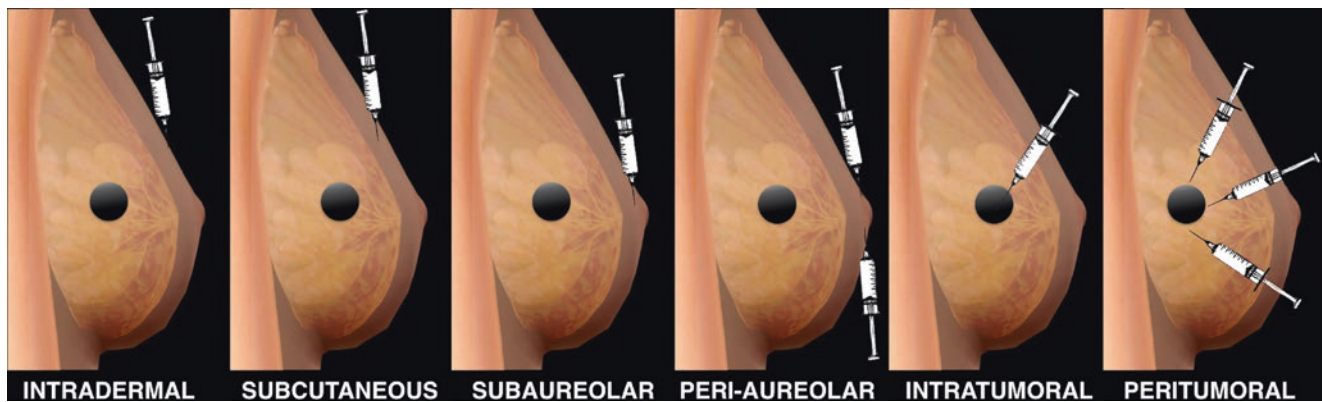


Fig. 9.3 Radiotracer administration modalities for SLN mapping illustrating superficial (first four images) and deep (last two images) injection options

administration), thus making the entire lymphoscintigraphic procedure highly practicable.

Finally, periareolar/subareolar radiocolloid injection [37] is based on the presence of a lymphatic plexus around each lobule of the mammary gland that follows the path of the galactophore ducts, converging to the areola to form the Sappey subareolar plexus, which is part of the general subcutaneous plexus.

As mentioned above, any drainage pattern from any quadrant of the breast can occur, and most of the lymph from the breast flows toward the nodal basins with a direct course, not necessarily passing through the subareolar plexus [23, 24, 28]. These variations in lymphatic drainage of the breast have important implications for the performance of lymphoscintigraphy (Fig. 9.4). Superficial injections will result in primarily axillary nodal drainage. Injection at the level of the tumor in the breast or more posteriorly can identify internal mammary, supraclavicular, or even intramammary SLNs.

Although some have suggested that the site of injection does not necessarily affect the accuracy of axillary SLN detection [38], conflicting results have been published. Noushi and coworkers found a high level of discordance in the localization of SLNs after performing both lymphoscintigraphy using a superficial injection and repeated lymphatic mapping after a tumor-related injection in the same patient. The discordance rate in the axilla and internal mammary chain was 21% and 39%, respectively; the overall discordance rate in this study of 39 patients was quite high, 59% [26]. A second clinical study investigated whether lymphoscintigraphy after intralesional injection in two separate tumors in the same breast of patients with multifocal/multicentric disease yielded additional SLNs compared to intralesional injection of only the largest tumor; they found a high incidence of additional SLNs draining from tumors other than the largest one, mainly in

the axilla [25], which is in line with the investigations by Noushi and coworkers. However, in only 2 out of 50 patients studied, metastatic disease was found in the additional SLNs only, so the clinical implication of these discrepancies is not yet clear.

As mentioned before, the peritumoral, intraparenchymal route of radiocolloid injection results in a high rate of visualization of SLNs in the internal mammary chain, an occurrence reported in an average 20% of the patients, with a maximum of about 30% [39]. Although the long-term clinical impact of identifying pathways of lymphatic drainage to the internal mammary chain in patients with early breast cancer is still unclear (see further below), this finding is a definite plus of the peritumoral administration route when one compares its merits with those of the superficial injection technique. On the contrary, advantages of the superficial injection technique are represented by its high practicability with minimum training, small volume administered as a single injection, fast visualization of lymphatic drainage pathways, and a high SLN detection rate.

Choosing the optimal approach depends on the aim of the lymphatic mapping in the individual patient [28]; in patients at low risk for lymph node metastases, especially with small and/or superficially located tumors in the upper lateral quadrant of the breast in whom the purpose is to spare an unnecessary ALND, a superficial injection technique may be adequate. On the contrary, in high-risk patients with large or multifocal tumors or tumors located deep or medio-caudally in the mammary gland, in whom the purpose of lymphatic mapping is to determine the stage as accurately as possible and to identify also SLNs outside the axilla, a tumor-related injection technique may be more appropriate. Another reasonable approach is to combine both injection techniques (deep and superficial), which may improve SLN detection and decrease false-negative findings.

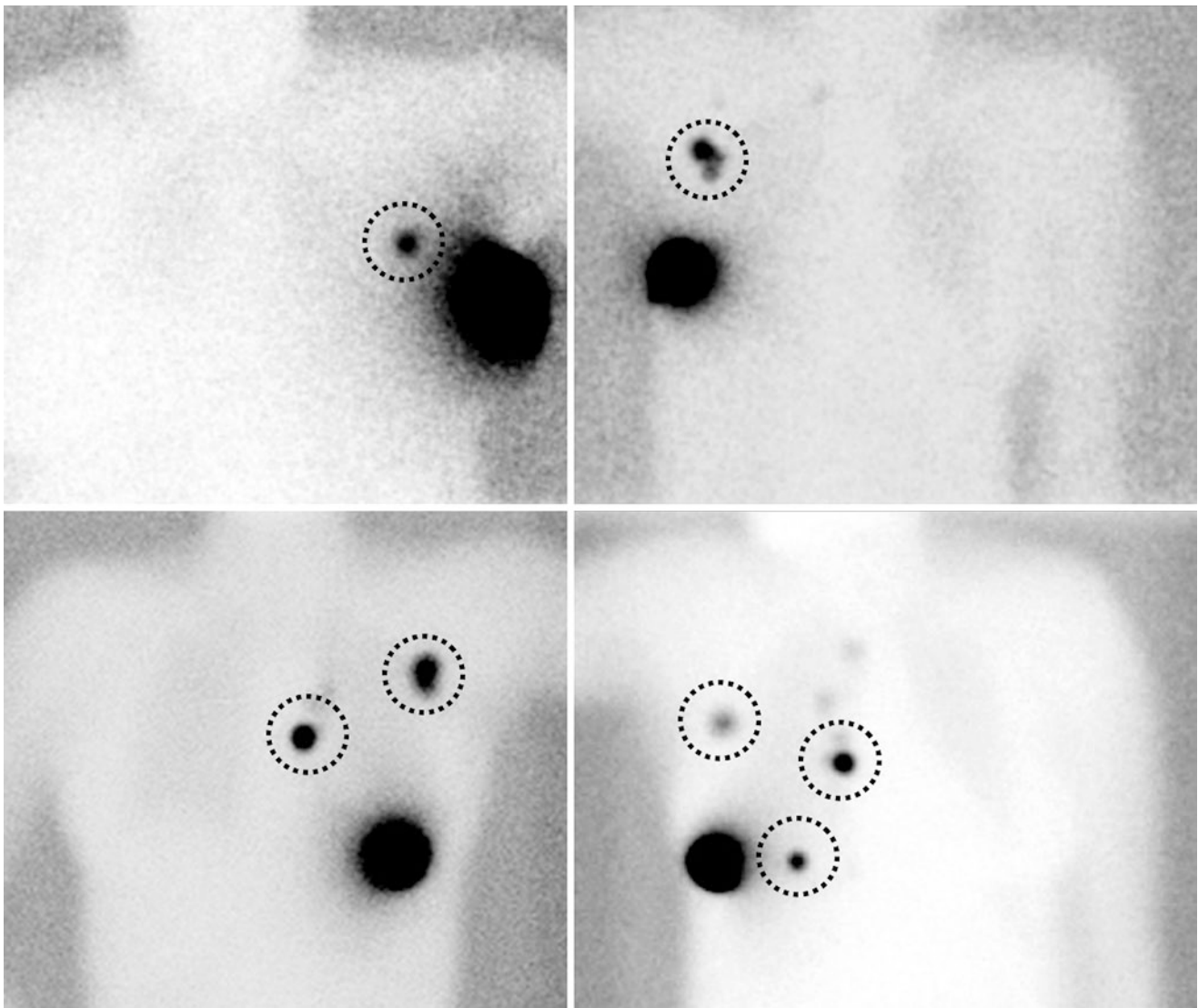


Fig. 9.4 Patterns of radiocolloid migration from untreated breast cancer to SLNs (circles) with a single axillary lymph node (*left above*), two axillary nodes (*right above*), single nodes in axilla and internal mam-

mary chain (*left bottom*), and single axillary, internal mammary, and intramammary SLNs (*right bottom*)

9.4.3 Preoperative Imaging for SLN Mapping in Patients with Breast Cancer

The addition of a radiotracer to the lymphatic mapping procedure with blue dye has transformed lymphoscintigraphy into a visual roadmap for surgeons. This preoperative imaging is essential to determine which lymph nodes should be considered as a SLN and to identify unpredictable lymph drainage patterns leading to SLNs in unusual drainage areas, improving the accuracy and reducing morbidity relative to γ -probing alone [40].

There is general consensus on how to perform lymphoscintigraphic acquisitions for SLN identification. The energy setting of the gamma camera should be centered on the 140 keV emission peak of ^{99m}Tc , with a $\pm 5\%$ window. The

use of a low-energy (ultra-)high-resolution collimator and an acquisition matrix of 256×256 pixels is highly recommended. Large-field-of-view gamma cameras are useful to depict the lymphoscintigraphic pattern of the entire lymphatic basin in a single image.

Planar static images are acquired 15–30 min and 2–4 h after injection, and if necessary in case of non-visualization after 18–24 h as well. At each acquisition time point at least two or three images are acquired: anterior, lateral, and 45° anterior oblique. The use of radioactive flood sources (^{57}Co or ^{99m}Tc) helps to provide a basic anatomical reference, especially when SPECT/CT is not performed or available (Fig. 9.5). A final, integral phase of lymphoscintigraphy is to mark the exact position of the



Fig. 9.5 Incorporation of anatomical aspects to preoperative SLN mapping in breast cancer. A ^{57}Co flat source, placed under the patient's trunk, provides body contour information (upper row) whereas SPECT/CT incorporates more specific anatomical landmarks (lower row)

SLNs using indelible ink, either with the aid of a radioactive point source or preferably using the probe (or both) for counting the axilla externally, focusing on the spot(s) visualized by lymphoscintigraphy. In this topographic localization phase, the arm should be abducted at about 90° , approximately in the same position as on the operating table during surgery, to identify accurate topographic coordinates that the surgeon can use during the surgical procedure. Marking the skin projection of the SLN and having the images available may assist the surgeon in reducing the operating time to locate the SLN, thus keeping the surgical incision to a minimum (Fig. 9.6).

9.4.4 Contribution of SPECT/CT Imaging for SLN Mapping in Patients with Breast Cancer

With the new generation of large-field gamma cameras, hybrid SPECT/CT has been incorporated in the SLN procedure. The functional information provided by SPECT can be combined with the morphological information provided by CT by employing such hybrid imaging in a single session. The fused SPECT/CT images depict the SLNs (visualized by lymphoscintigraphy) in an anatomical landscape, thus providing additional helpful roadmaps for surgeons. In recent years, SPECT/CT has been used in breast cancer patients with unusual or complex drainage, for example in patients with lymphatic drainage outside the axilla [41]. SPECT/CT

imaging can also visualize SLNs within the axilla when no nodes are visualized by planar imaging (including lateral images after breast displacement or with hanging breast) or if high activity at the injection site masks adjacent lymph nodes (Fig. 9.7). SPECT/CT also helps to identify SLNs in case of inconclusive planar images and especially when SLNs appear to be located in uncommon sites (Fig. 9.8). Table 9.1 gives an overview of the overall advantages of SPECT/CT versus planar imaging during lymphoscintigraphy in breast cancer [41–43]. SPECT/CT is principally oriented to the anatomical localization of SLNs, by acquiring a low-dose CT. For SLN localization, the CT component of SPECT/CT must provide optimal anatomical information. For superficial areas such as the axilla, 5 mm slices are recommended. The CT component is also used to correct the SPECT signal for tissue attenuation and scattering. After these corrections, SPECT is fused with CT [41].

A gray scale is used to display the anatomic information in the background image (CT), whereas a color scale is used to depict lymphoscintigraphic mapping in the foreground image (SPECT). Multiplanar reconstruction (MPR) enables two-dimensional display of fusion images in relation to CT and SPECT. The use of cross-reference lines allows the navigation between axial, coronal, and sagittal views. At the same time, this procedure enables to correlate radioactive SLNs seen on fused SPECT/CT images with lymph nodes seen on the CT portion. This information may be helpful for the intraoperative procedure, as well as for post-excision control using portable gamma cameras or

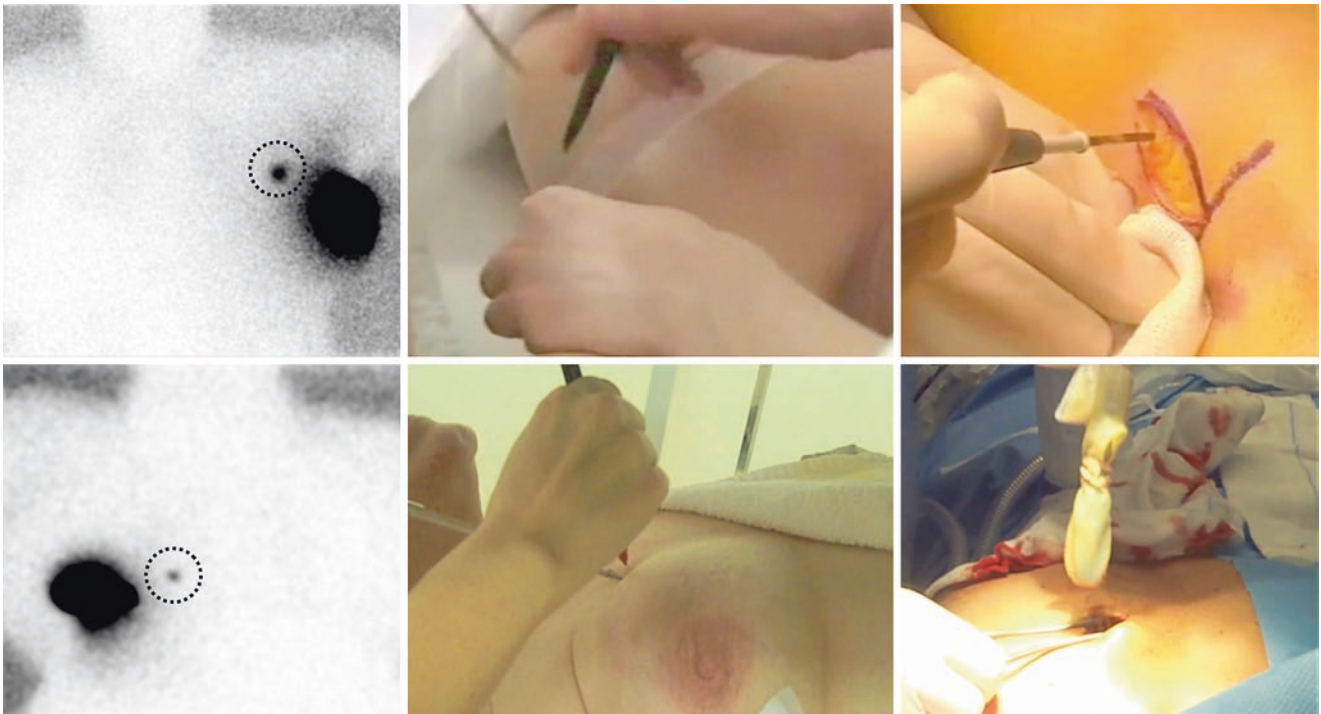


Fig. 9.6 Importance of cutaneous marking during preoperative imaging to guide skin incision in the operating room for SLNs (circles) in the left axilla (upper row) and right internal mammary chain (lower row)

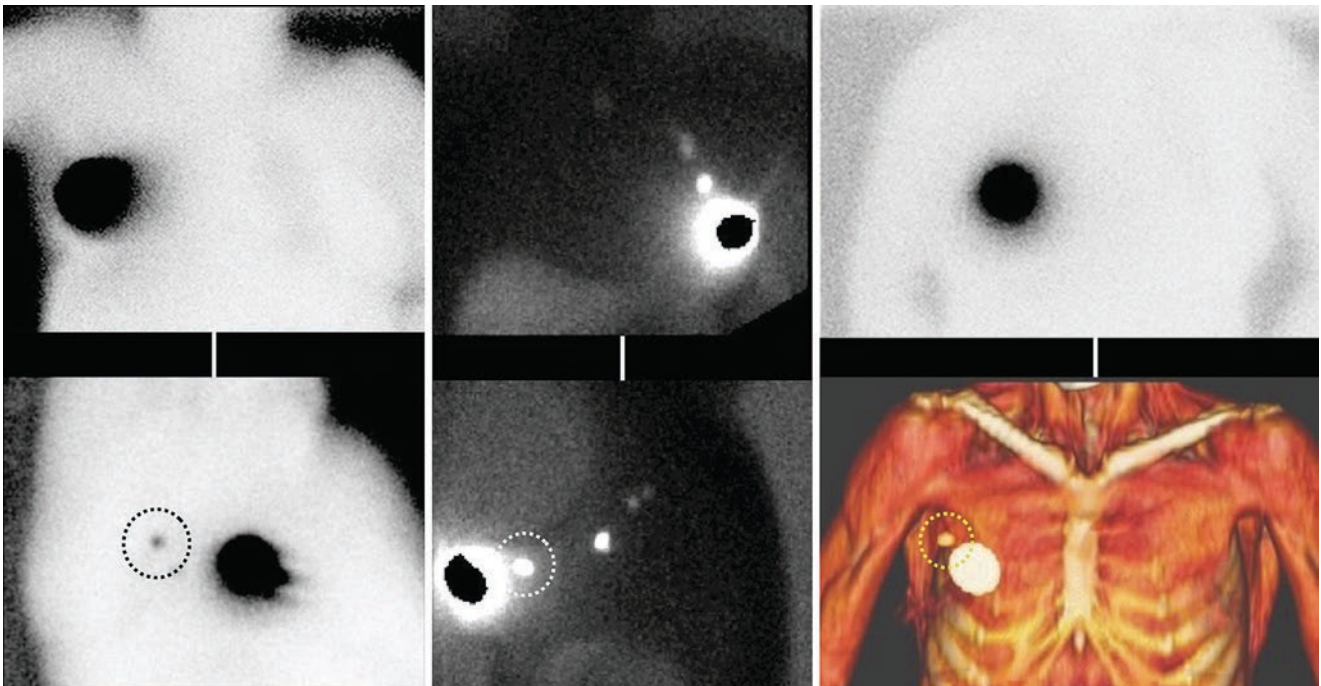


Fig. 9.7 Intervention possibilities (lower row) to depict no visualized SLNs (circles) during standard lymphoscintigraphy (upper row): in the right axilla by means of displacement of the breast with the opposite hand of the patient (left column), left intramammary by means of additional hanging breast patient position (middle column) and right axillary by means of SPECT/CT (right column)

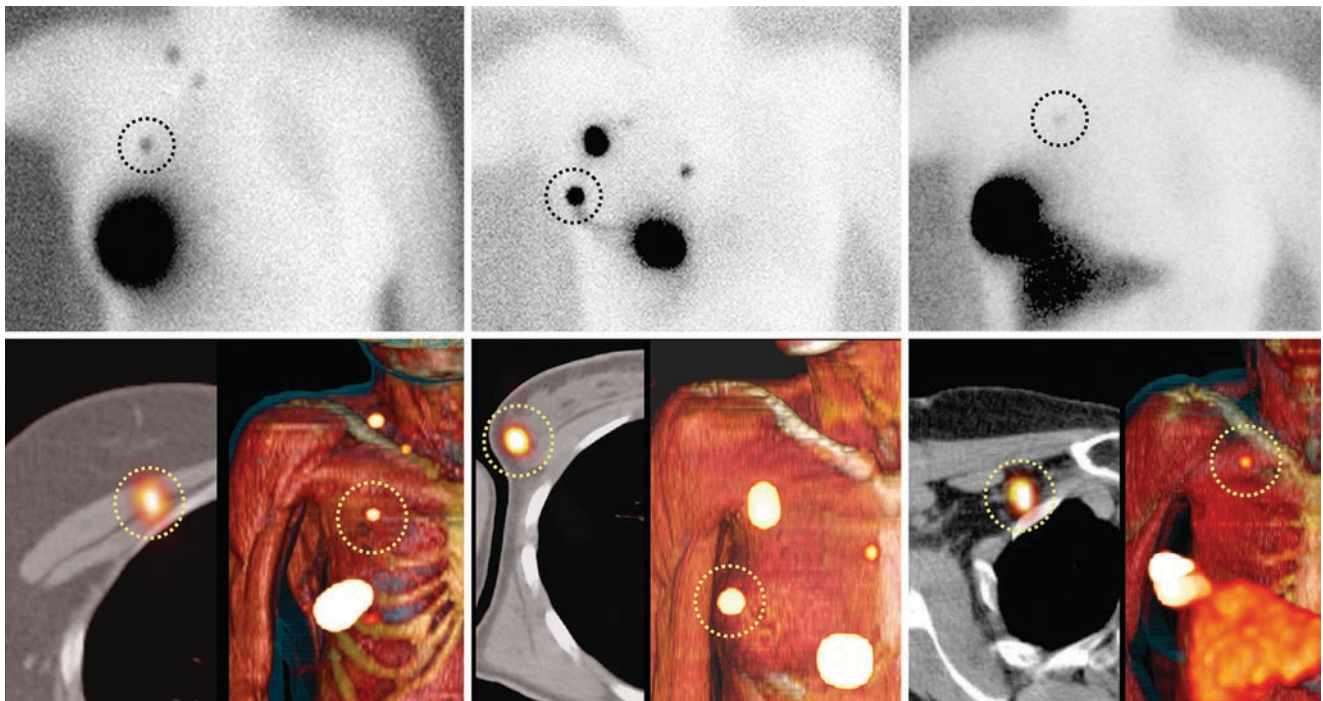


Fig. 9.8 Contribution of SPECT/CT to anatomically localize SLNs (circles) in cases with interpectoral (left column), intramammary (middle column), and axillary level III (right column) lymphatic drainage

Table 9.1 Advantages of SPECT/CT imaging versus planar imaging in breast cancer

1. Improved anatomical localization of SLNs, especially outside the axilla
2. Improved recognition of non-lymph node radiocolloid accumulation
3. Improved characterization of equivocal findings
4. Greater sensitivity, resulting in detection of additional SLNs
5. Greater specificity, resulting in fewer false-positive findings

Adapted from Ref [42]

probes. The use of 3D volume rendering enables identification of better anatomical reference points and incorporates an additional dimension in the recognition of SLNs (Fig. 9.8).

Key Learning Points

- A radiocolloid with particles ranging in size between 100 and 200 nm represents a practical compromise between fast and efficient lymphatic drainage and satisfactory retention in the SLN.
- ^{99m}Tc -tilmanocept (Lymphoseek[®]) is a new radio-tracer for lymphatic mapping with faster clearance

from the injection site and prolonged retention in SLNs compared to conventional radiocolloid tracers.

- Variations in lymphatic drainage of the breast have important implications for the performance of lymphoscintigraphy: a subareolar plexus-related injection rarely identifies SLNs outside the axilla.
- In patients at low risk for lymph node metastases a superficial injection technique may be adequate, while in high-risk patients in whom the purpose of lymphatic mapping is to determine the stage as accurately as possible, a tumor-related injection technique may be more appropriate.
- Preoperative imaging is essential to determine which lymph nodes should be considered as a SLN and to identify unpredictable lymph drainage patterns.
- The addition of SPECT/CT to standard lymphoscintigraphy is indicated in specific situations, such as in cases of unusual or complex drainage or non-visualization of SLNs at planar imaging or when the injection site masks adjacent lymph nodes.

9.5 Intraoperative SLN Detection in Patients with Breast Cancer

After positioning the patient on the operating table before starting the surgical procedure, location of the SLNs should be confirmed further by external counting with the γ -probe. Minor variations in the sequence of operating procedures exist: some surgeons remove the primary tumor first and then proceed to perform SLNB, whereas other surgeons perform SLNB first and then proceed to remove the tumor while waiting for the results of intraoperative frozen section histopathology, although routine intraoperative pathologic assessment has become unnecessary and less indicated after the appearance of large trial results showing that ALND is not indicated in all patients with positive SLNs (see below).

In most recent reports, the overall success rate of lymphoscintigraphy for SLN identification is very high, around 95%. Usually the radioguided procedure is combined with blue dye, using the blue dye in the lymphatics as a roadmap helping to find the radioactive SLN, especially when a non-involved lymph node is only few millimeters in diameter and very soft to palpation. A γ -probe-guided search of the SLN is based on detecting a focal spot of radioactivity accumulation in the area of interest (open surgical field). The probe is now in direct contact with the hot spot and is adequately shielded from radiation scattered from the injection site.

Thus, counting rates change almost instantly from tens or hundreds of counts per second to nearly zero (as the patient's background virtually corresponds to room background) when moving the detector—for instance, simply changing the angle—from the hot spot (lymph node) to nearby tissues. Therefore, the concept of target-to-background ratio as commonly used for in vivo nuclear medicine procedures takes on a new meaning; typically, the ratio of counts in the hot spot relative to background is in the 10–100 range, though with wide variations depending on the activity injected, type of radiocolloid injected, time elapsed between radiocolloid injection and surgery, and type of γ -probe used.

Reexamination of the operative site should then be performed to ensure that the area of focal radioactivity accumulation has been removed and that a second lymph node is not also active; if this is the case, such lymph node should also be removed and the axilla reexamined. Complete removal of the SLNs is confirmed by reduction of the counting rate in the axilla to background levels. Reduction of the activity to 10–20% of the counting rate in the most active SLN is commonly accepted as background level [44, 45].

9.5.1 Combining Existent Technologies with New Modalities for SLN Mapping in Patients with Breast Cancer

Although high identification rates are achieved using the combination of dye and γ -probe, together with optimal preoperative imaging including SPECT/CT when indicated, intraoperative detection can be further improved using portable imaging devices, such as portable gamma cameras, freehand SPECT, and hybrid approaches (Fig. 9.9). This is especially helpful in case of complex drainage, deep-seated lymph nodes or when lymph nodes are located close to the injection site [46, 47].

Appropriate perioperative use of a portable gamma camera enhances the reliability of the SLNB, by providing high-resolution imaging of the surgical field. The use of these techniques implies the possibility to better plan the surgical approach, to localize surgical targets just before making the surgical incision, to monitor the lymphatic basin before and after removal of the SLNs, and, above all, to verify completeness of SLNB.

The freehand SPECT-based device integrates a positioning system attached to the conventional gamma probe and permits a virtual reconstruction in a 3D environment [47]. This 3D information may be further used for precise localization and targeting of radioactive SLNs. The device can ensure permanent assistance and transparent documentation of soft-tissue removal during surgery. Although the contribution of these new portable devices in breast cancer surgery is still unclear, they definitely will play an increasing role in the future within the evolving GOSTT (guided intraoperative scintigraphic tumor targeting) concept.

The use of hybrid tracers has been shown to improve further the accuracy of lymphatic mapping and SLN localization. A hybrid compound has been developed combining ^{99m}Tc -albumin nanocolloid with indocyanine green (ICG) [48]. In contrast to single-fluorescent agents [49], this bimodal tracer procedure may allow the surgeons to integrate the standard approach based on radioguided detection with a portable gamma camera with a new optical modality based on fluorescent signal detection. This approach is being successfully applied in various malignancies with promising results; it makes the SLNB procedure more accurate and independent of the use of blue dye [50], although its role in breast cancer still needs to be elucidated.

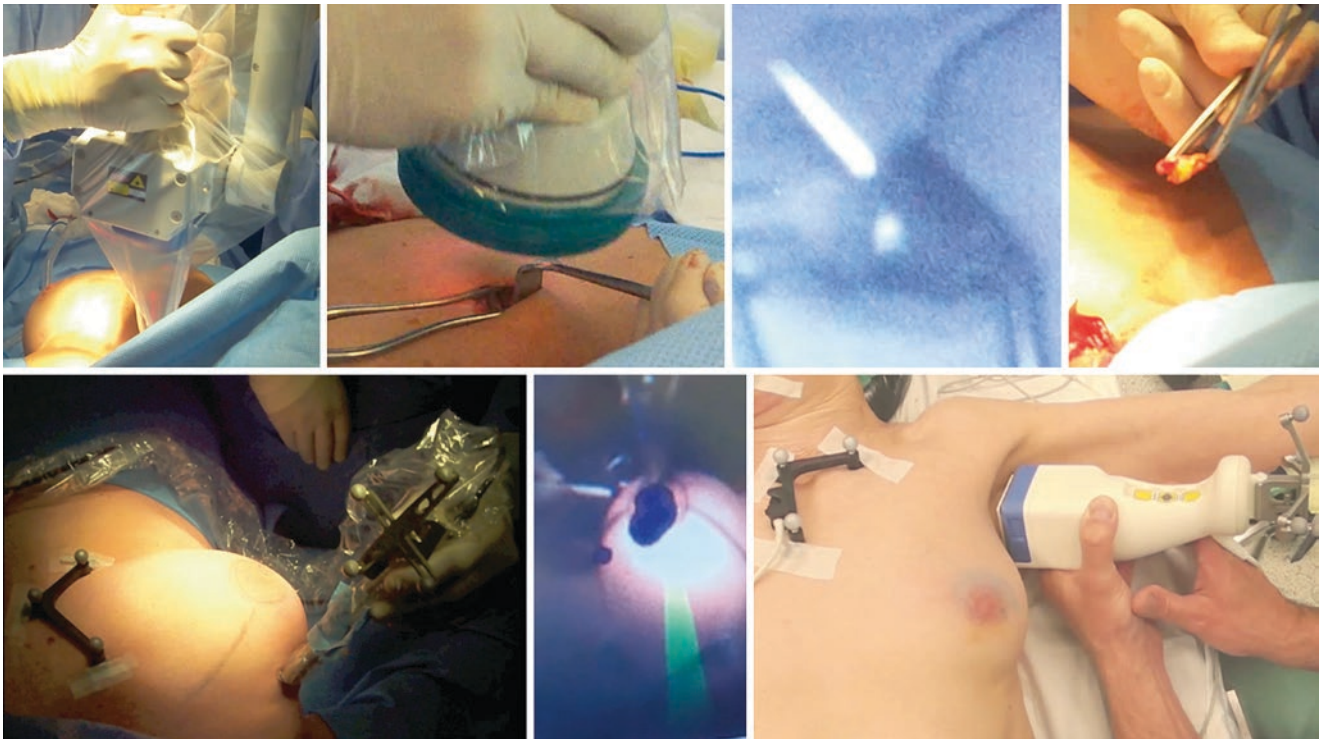


Fig. 9.9 Intraoperative SLN procedure using new modalities. The images of the *upper row* illustrate the hybrid approach following administration of ICG-^{99m}Tc-nanocolloid, which enables the combination of a portable gamma camera with a fluorescence camera to localize

and remove an internal mammary SLN. In *lower row*, the freehand SPECT technology using a tracked gamma probe (left image) or hand-held gamma camera (right image) to generate an augmented reality navigation protocol for breast radioguided surgery

Key Learning Points

- The overall success rate of lymphoscintigraphy in SLN identification is very high, around 95%.
- The radioguided procedure is frequently combined with blue dye, using the blue dye in the lymphatics as a roadmap helping to find the radioactive SLN.
- Complete removal of the SLNs is confirmed by reduction of the counting rate in the axilla to background levels.
- Reduction of the activity to 10–20% of the counting rate in the most active SLN is commonly accepted as background level.
- Intraoperative detection of SLNs may be further improved using portable gamma cameras and freehand SPECT cameras and/or hybrid radiofluorescent tracers, although their role in breast cancer patients needs to be elucidated.

9.6 Indications and Controversies for SLN Mapping in Patients with Breast Cancer

There is general consensus that the SLNB procedure is indicated in patients with early-stage breast cancer (cT1-2 tumors) without cytological or histological evidence of axillary lymph node metastases; SLNB is contraindicated in patients with inflammatory breast cancer.

9.6.1 Pregnancy

The international guidelines concerning the use of lymphatic mapping in pregnant and/or lactating women are inconsistent; while the ASCO guidelines do not recommend SLNB in pregnant women, the EANM and SNMMI guidelines state that SLNB is justified in these women by the low risks of the procedure relative to the risks of axillary dissection. However, vital blue dye should only be included if there is a clear medical need to do so.

9.6.2 Internal Mammary Chain

Although, like the axilla, the IMN are a first-echelon nodal drainage site, the importance of its treatment has long been debated in breast cancer. Parasternal recurrences are uncommon and studies in the past have failed to demonstrate a survival benefit from IMN treatment. However, more recent studies provided evidence that lymphatic drainage toward the internal mammary chain is associated with a worse disease-free survival (DFS) [51]. The results of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) established the importance of locoregional control (including the internal mammary chain) on long-term survival even when systemic therapy is given [52]. Large randomized trials have demonstrated a limited but significant improvement in DFS, metastatic-free survival (MFS), and to a smaller extent overall survival (OS), when additional regional radiotherapy was applied on the IMNs and medial supraclavicular nodes in patients with increased risk for IMN metastases [53].

Hence, this suggests that besides patients with macroscopic disease in these lymph nodes, a selective group of breast cancer patients at high risk for subclinical involvement of the internal mammary chain might also benefit from parasternal irradiation, for example in patients with proven metastatic axillary SLNs in combination with parasternal lymphatic drainage identified on lymphoscintigraphy. Other recent studies have also led to renewed interest in IMN staging, regarding particularly its implications for systemic therapy. Madsen and coworkers found that patients with metastatic IMNs without axillary involvement tended to have a significantly worse outcome than patients with no regional lymph node metastases at all [54]. Therefore, the development of the SLNB aided by lymphoscintigraphy, providing a less invasive method of assessing the IMNs than surgical dissection, may affect decisions regarding not only locoregional treatment, but also systemic therapy. In this regard, one could plead for performing lymphoscintigraphy with tumor-related injections only, since the rate of parasternal drainage reflects the method of tracer injection used.

9.6.3 Large and Multifocal/Multicentric Breast Cancers

The application of SLNB in T3–T4 tumors and multifocal disease is controversial. The debate is related to the

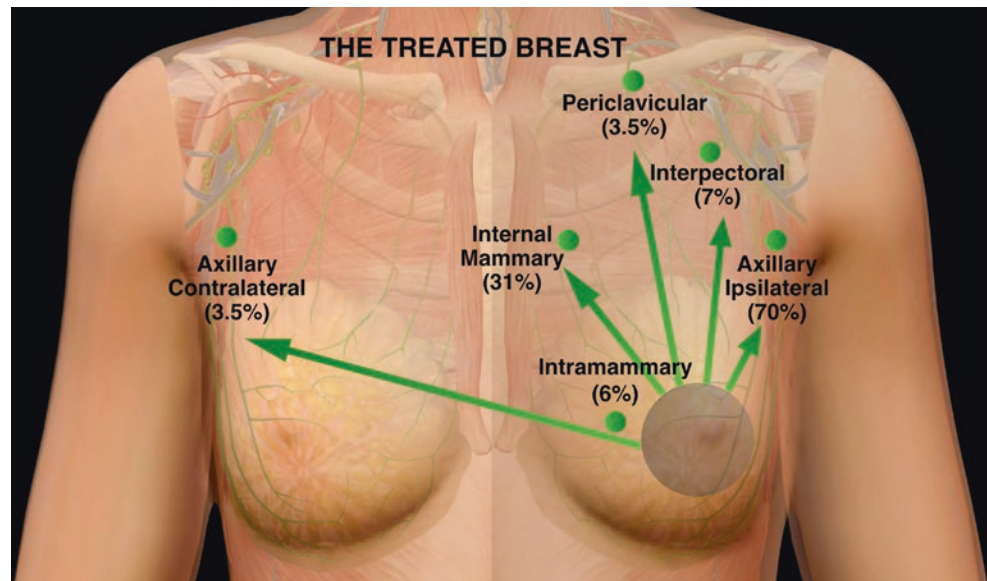
lack of consensus on the drainage routes in the breast. If drainage from any site of the breast would pass the subareolar plexus, the presence of more than one tumor or a large tumor would not affect the accuracy of the SLN procedure when a single (superficial) injection is performed. However, if multiple drainage routes exist, this actually would theoretically affect the accuracy and could lead to a higher false-negative rate, which is undesirable considering that multifocality and multicentricity are associated with a higher rate of lymph node metastases, as is the case in large tumors. Studies addressing this issue show heterogenic results, with false-negative rates ranging from 4 to 14% [55–57]. Moreover, application of multiple tumor-related injections in patients with multiple tumors in the breast leads to a significant amount of additional SLNs after the second injection: 64% in the study of Brouwer and coworkers [25]. However, in only 4% of these patients, metastatic disease was found in the additional SLNs only, so the clinical implication of these discrepancies is not yet clear. In summary, one should be aware of the fact that the accuracy of the SLN procedure in multifocal disease is probably lower, while these patients have a higher risk of lymph node metastases, which has to be weighed up against the benefits of SLNB in the individual patient.

9.6.4 Ductal Carcinoma In Situ

Ductal carcinoma in situ (DCIS) is an intraductal proliferation of malignant cells, without invasion of the stroma, and is considered as a precursor of invasive ductal carcinoma. Still, in one out of four patients upstaging to microinvasion or invasion cancer occurs after surgery [58], leading to unexpected lymph node metastases in 10% of patients with pure DCIS in the biopsy specimen (macro-metastases in 2.4%). The strongest predictor for lymph node metastases is occult invasion; other risk factors include a lesion >2–2.5 cm, palpable DCIS lesion, high-grade DCIS, contrast enhancement on MRI, and age >55 years [58, 59].

Although SLNB should not be considered a standard procedure in the treatment of all patients with DCIS, it should be considered if risk factors for lymph node metastases are present, independent of the type of surgery (breast conserving or mastectomy).

Fig. 9.10 Lymphatic drainage from the treated breast according to data from van der Ploeg et al. [62] showing increased SLN visualization outside the ipsilateral axilla



9.6.5 Recurrent Disease and SLN Mapping in Patients with Breast Cancer

Use of SLNB in patients with recurrent disease has been a debated issue, related to the consideration that the lymph drainage pathways may be disrupted by previous SLNB and therapy, presumably leading to a less reliable SLN procedure. However, based on the data of a recent meta-analysis in 1053 patients, it may be concluded that SLNB in these patients, on the contrary, is feasible. The investigators reported a SLN identification rate of 63% on lymphoscintigraphy and 60% at surgery; since metastatic disease in SLNs was found in 10% of patients, ALND could be avoided in approximately 500 of the patients studied (50%) [60]. The SLN identification rate was significantly higher in patients who underwent SLNB at primary surgery compared to ALND.

Perhaps even more important than the impact on the axilla is the identification of aberrant lymphatic drainage, providing options for targeted surgical excision of SLNs outside the ipsilateral axilla, using lymphoscintigraphy and SPECT/CT as a surgical roadmap [61]. This is relevant in light of the changes in lymphatic drainage due to previous surgery and radiotherapy with significant increase of SLN visualization outside the ipsilateral axilla [62] (Fig. 9.10). Ahmed and coworkers reported an aberrant lymphatic drainage identification rate of 26% of patients on lymphoscintigraphy, being highest in patients who had undergone ALND at primary surgery. It allows alteration of the treatment plan in patients with metastatic disease in lymph nodes outside the ipsilateral axilla, either by targeted surgery, adjuvant systemic treat-

ment, or radiotherapy. Examples of modified radiocolloid migration on lymphoscintigraphy and SPECT/CT are shown in Fig. 9.11.

9.6.6 SLNB in the Neoadjuvant Setting

Neoadjuvant chemotherapy (NAC) is being increasingly used not only in patients with locally advanced breast cancer, but also in patients with early-stage breast cancer, raising a new dilemma: when to perform SLNB. The timing of SLNB in patients receiving NAC is under debate. SLNB before NAC is most accurate, but leads to overtreatment of the axilla, since 20–50% of patients with metastatic disease in the axilla achieve complete pathological response after NAC, with a remission rate being highest in patients with triple-negative tumors and tumors with HER2 overexpression.

Recent studies have shown that in patients without clinical evidence of axillary lymph node involvement at diagnosis (cN0), SLNB after NAC is approaching the globally accepted false-negative rate threshold of 5% without a decrease in efficacy [63]; this is generally considered as acceptable, conferring the benefit of sparing these patients from an extra surgical intervention and more important unnecessary treatment of the axilla and associated morbidity. To achieve a high accuracy, thorough examination of the axilla at diagnosis is necessary, using physical examination and ultrasound. One should take into account the fact that in cN0 patients, persistence of tumor in the breast and the luminal subtype are factors that determine lymph node involvement after NAC.

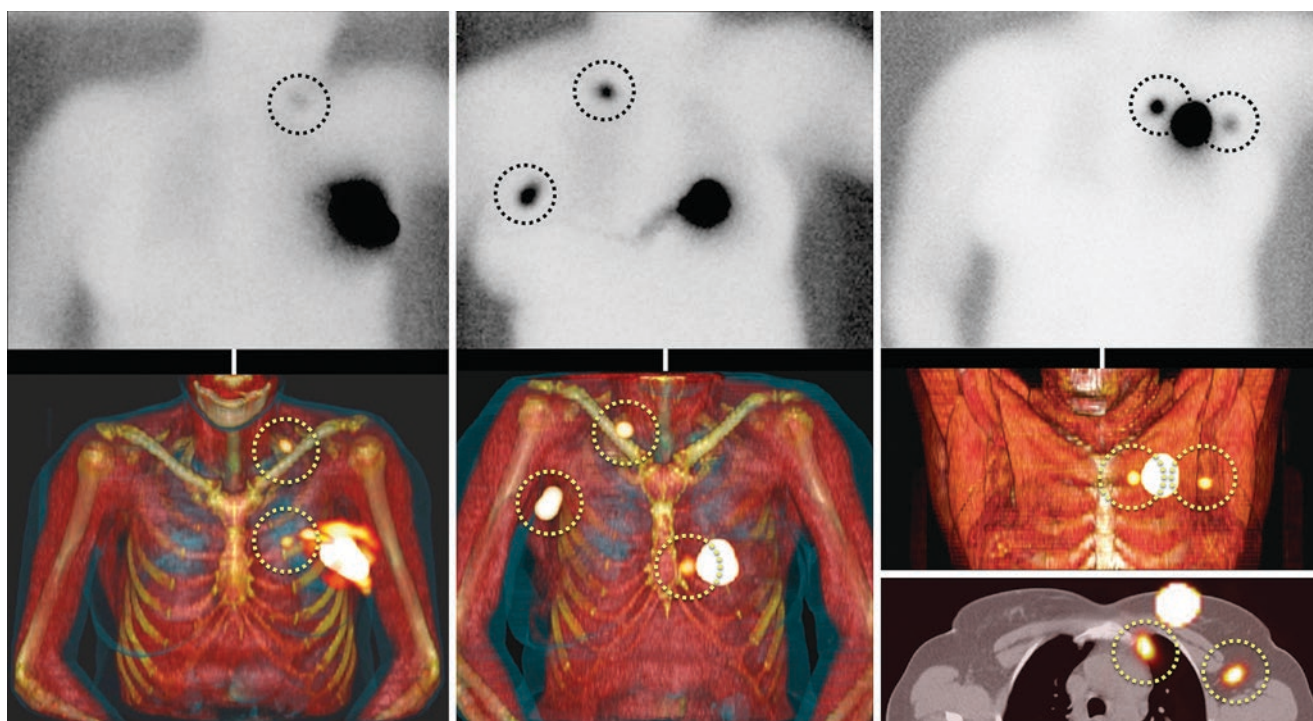


Fig. 9.11 Patterns of radiocolloid migration from the treated breast. Visualized drainage on lymphoscintigraphy (upper row) is anatomically localized using SPECT/CT (lower row) with SLNs (circles) in the ipsilateral internal mammary and supraclavicular regions (left column),

ipsilateral mammary chain as well as contralateral axilla and supraclavicular (middle row), and ipsilateral in axilla as well as retrosternal (right column)

More complex is the situation in patients with lymph node involvement at diagnosis (cN+). Noninvasive staging, in the form of physical examination, ultrasound, MRI, or PET-CT, is not reliable for detection of complete pathological nodal response after NAC. In addition, the reliability of SLNB after NAC is questionable; with increasing tumor load in the first-echelon nodes, the risk of aberrant drainage increases, leading to a lower efficacy and higher FNR. This negative effect is enlarged by the chemotherapeutic treatment related to disruption of the lymph drainage. In recent years, many studies addressing this issue have been published. Two large prospective cohort studies, the SENTINA trial and ACOSOG 71071 trial, investigated the accuracy of the SLNB procedure after NAC in patients with cT0-4N1-2 breast cancer. They reported false-negative rates of 14% and 13%, respectively, with SLN detection rates of 80% and 93%. Subgroup analyses in both trials showed that the false-negative rate could be significantly limited to <10% if (a) the radiocolloid is combined with blue dye, (b) more than two SLNs are removed, and (c) accurate clinical axillary lymph node evaluation is performed before and after chemotherapy [64, 65]. Thus, accurate evaluation of the axilla is essential after NAC and should consist of at least a thorough physical

examination and ultrasound examination. With magnetic resonance imaging (MRI) and [^{18}F]FDG PET/CT the accuracy may be increased.

A different approach is to evaluate the response to NAC by marking the involved lymph node prior to treatment. Marking methods include tattooing the node with a carbon particle suspension or placing a metallic clip or a magnetic or radioactive iodine-125 (^{125}I) seed in the involved lymph node. Marking the node with a ^{125}I seed was first described in 2010, better known as the MARI procedure [66]. Initial evaluation of this method reported a detection rate of 97% and false-negative rate of 7%, including lymph nodes with isolated tumor cells [67]. To improve the accuracy of post-NAC axillary staging, nodal clipping may be combined with the post-NAC SLNB procedure, further decreasing the false-negative rate (only 2% in the study of Caudle and coworkers) [68].

Thus, combining the MARI procedure (or other lymph node marking method) with SLNB post-NAC in patients with cN+ breast cancer at diagnosis is feasible and seems to be the most effective way to restage the axilla post-NAC, providing an approach to preserve the axilla. Other proposed axillary treatment algorithms include information regarding

the nodal tumor load at diagnosis (using [¹⁸F]FDG PET/CT) and result of the MARI procedure post-NAC, without including SLNB (see below) [69].

Key Learning Points

- The SLNB procedure is indicated in patients with early-stage breast cancer (cT1-2 tumors) without cytological or histological evidence of axillary lymph node metastases.
- SLNB is justified in pregnant women due to the low risks of the procedure relative to the risks of axillary dissection.
- Lymphatic drainage toward the internal mammary chain is associated with a worse disease-free survival and a selective group of breast cancer patients at high risk for subclinical involvement of the internal mammary chain might benefit from parasternal irradiation.
- The accuracy of SLNB in large and multifocal/multicentric tumors is decreased, which has to be weighed up against the benefits of SLNB in the individual patient.
- In DCIS, SLNB should be considered if risk factors for lymph node metastases are present.
- SLNB in patients with recurrent disease is feasible and may avoid ALND in a significant proportion of patients and identify aberrant lymphatic drainage in these patients, providing options for targeted therapy.
- SLNB before NAC is most accurate, but leads to overtreatment of the axilla, since 20–50% of patients with metastatic disease in the axilla achieve complete pathological response.
- In clinically negative axillary disease at diagnosis, SLNB after NAC is accurate, approaching the globally accepted false-negative threshold of 5%.
- In clinically positive axillary disease at diagnosis SLN post-NAC is less accurate, although false-negative rate may be limited to <10% when dual mapping is applied, more than two SNs are removed, and accurate clinical axillary lymph node evaluation is performed before and after chemotherapy.
- Combining the SLNB procedure post-NAC with a lymph node marking method such as the MARI procedure seems to be the most accurate way to restage the axilla post-NAC.

9.7 Clinical Impact of SLNB in Breast Cancer

9.7.1 The Paradigm Shift in Axillary Management

SLNB has become the “standard of care” for staging patients with early-stage breast cancer with clinically negative nodes. As mentioned earlier, SLNB is associated with reduced arm morbidity and better quality of life and has replaced the ALND for staging the axilla. Extensive evaluations have proven the safety of this technique showing high detection rate and acceptable false-negative rate, especially when preoperative lymphoscintigraphy and dual mapping are applied [70–72].

In the latest years an increasing tendency has emerged to preserve the axilla, based on the ALND-related arm morbidity and reduced quality of life, together with the fact that clinical presentation of the disease and (systemic) treatment have changed over time. Furthermore, there are reasons to believe that axillary metastases do not always become clinically relevant, as may be concluded from earlier studies in the 1970–1980s. For example, in the NSABP B-04 trial, a trial that did not include systemic therapy, the axillary recurrence rate in patients with no axillary treatment was approximately half of the expected rate from the prevalence of metastases found in patients in whom axillary contents were removed and examined [73]. These results are supported by more recent studies such as the ACOSOG Z0011 trial (see below), showing a non-inferior outcome in a group of patients in whom 27% had lymph node metastatic disease left in place. Besides the fact that these metastases were probably treated either by the adjuvant systemic treatment or by the whole-breast irradiation, this may also (at least partly) be related to the existence of biologic factors that determine the clinical growth of axillary metastases.

This gain in knowledge over time has resulted in the emergence of a treatment paradigm shift: not all SLN-positive patients need to receive local axillary treatment in terms of ALND or axillary radiotherapy. In addition, in the near future, SLNB will probably increasingly be omitted in specific low-risk or comorbidity situations (such as T1 luminal A, age >70 years). However, whether and how this will happen depend on the results of current ongoing studies.

9.7.2 SLN-Negative Breast Cancer

There is general consensus that patients with negative axillary SLNB by routine histopathological evaluation do not require ALND. A randomized controlled study in 516 histopathologically node-negative patients treated with either SLNB alone or SLNB plus ALND reported overt axillary metastases in only two cases in the SLNB-alone arm during 8-year follow-up and a slightly greater overall survival in the SLNB-alone arm [74]. Another large study in patients with hematoxylin-eosin (H&E)-negative, tumor-free SLNs, who did not undergo completion ALND, revealed a remarkably low axillary recurrence of 0.2% and high disease-free survival [75]. Similar long-term results were reported by the American College of Surgeons Oncology Group. This ACOSOG Z0010 trial included 3904 patients with H&E-negative SLNs and reported only 0.5% regional recurrences, 3.3% local recurrences, and 3.4% distant recurrences at a median follow-up of 8.4 years [76]. The NSABP B-32 trial showed similar results [18].

Factors associated with local-regional recurrence were younger age and hormone receptor-negative disease. Locoregional recurrence is less often seen in patients with hormone receptor-positive tumors and those who receive chemotherapy.

9.7.3 SLN-Positive Breast Cancer

The addition of immunohistochemistry (IHC) analysis to the standard H&E examination has led to increased detection of metastases (isolated tumor cells or micrometastases) in SLNs. Isolated tumor cells are defined as “small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section” and micrometastases as “tumor deposits greater than 0.2 mm but not greater than 2.0 mm in largest dimension” [30]. These occult metastases may be found in up to 16% of H&E-negative SLNs [77]. However, large trials as the ACOSOG Z0010 and NSABP B-32 revealed that IHC detection of these H&E-occult SLN metastases does not contribute to survival [7, 77]. Ram and coworkers performed a meta-analysis pooling results of three randomized trials. They concluded that for patients with a clinically negative axilla and micrometastases in the SLN, SLNB alone was non-inferior to completion ALND [19].

While safety and efficacy of SLNB alone, with no reduction in survival, have been proven for patients with tumor-free or SLN micrometastatic disease, no consensus exists on the management of patients with “limited

SLN macrometastatic” disease (“limited” commonly defined as one or two positive SLNs). As mentioned earlier, the tendency to preserve the axilla, together with the fact that clinical presentation and management of breast cancer have changed over time, has raised questions concerning the necessity of ALND in these patients. In the AMAROS trial, 1425 patients with T1 or T2 invasive primary breast cancer and positive SLNs were randomized between completion ALND and locoregional (axillar and periclavicular) radiotherapy only; they concluded that excellent and comparable axillary control was achieved with locoregional radiotherapy in this patient population [78]. The ACOSOG Z0011 trial randomized 891 patients with T1 or T2 invasive breast cancer, clinically negative axillary disease, and one or two H&E-positive SLNs between completion ALND and SLNB alone; this trial revealed that 10-year overall survival for patients treated with SLNB alone was non-inferior to overall survival for those treated with completion ALND [79]. It is important to note that most of the patients in both treatment arms received adjuvant systemic therapy. The results of both trials have changed the management of breast cancer at major centers throughout the United States and Europe. Early metastatic breast cancer patients with SLN metastases who have limited axillary disease found at operation may be spared the morbidity of ALND, further increasing the role of SLNB in the management of early breast cancer.

Based on these recent reports, neither the St. Gallen nor the American Society of Clinical Oncology (ASCO) guidelines recommend ALND in patients with isolated tumor cells in their SLNs. In addition, ASCO also recommends to omit ALND in most patients with 1–2 metastatic SLNs who are planning to undergo breast-conserving surgery with whole-breast radiotherapy, albeit controversy persists around the question whether axillary radiotherapy should be added in these cases, as appeared from a recent St. Gallen Consensus Conference in 2019 [80].

9.7.4 SLN-Positive Breast Cancer, Downstaged After Neoadjuvant Therapy

As mentioned earlier, axillary staging after NAC in patients with cN+ breast cancer at diagnosis may prevent overtreatment of the axilla in a significant number of patients. Because of the reduced accuracy of SLNB when performed after NAC, combination of SLNB with a lymph node marking method such as the MARI procedure should be considered to restage the axilla.

A different approach to spare the axilla in these patients is to implement a tailored axillary treatment algorithm based on the lymph node marking procedure together with the known axillary tumor load at diagnosis, omitting the (less accurate) SLNB in these patients. Koolen and coworkers constructed and tested a treatment algorithm for tailored axillary treatment after NAC in a cohort of axillary node-positive patients, based on the results of [¹⁸F]FDG PET/CT pre-NAC and the MARI procedure in 93 patients [69]. Based on this algorithm, axillary treatment would be omitted in patients with 1–3 [¹⁸F]FDG-avid axillary lymph nodes on PET/CT and a tumor-negative MARI node; those with a positive MARI node would receive axillary radiotherapy, as would patients with four or more [¹⁸F]FDG-avid axillary lymph nodes and a negative MARI node. An ALND would be performed only in patients with four or more [¹⁸F]FDG-avid axillary lymph nodes and a positive MARI node after NAC. In their hands, treatment according to this algorithm would have resulted in 74% of patients avoiding an ALND, with potential undertreatment in 3% and overtreatment in 17% of patients. Although promising, long-term results are lacking at the moment for both mentioned strategies.

Key Learning Points

- Occult metastases may be found in up to 16% of H&E-negative SLNs after immunohistochemistry analysis; however detection of ITCs and micrometastases in SLNs does not contribute to survival.

- An increasing tendency has emerged to preserve the axilla, based on the ALND-related morbidity on one side and the changed clinical presentation of the disease and improved (systemic) treatment on the other side.
- Treatment of the axilla has changed from a dichotomized treatment plan based on negative or positive SLNs toward a more tailored axillary treatment based on the axillary tumor load.
- Comparable axillary control seems to be achieved with locoregional radiotherapy compared to ALND in patients with SLN-positive disease.
- In patients with cT1 or T2 disease and 1–2 positive SLNs who are planned to undergo breast-conserving surgery with whole-breast radiotherapy, ALND may be omitted since ALND in these patients does not lead to improved survival.
- In patients with clinically positive axillary disease at diagnosis receiving NAC, a tailored axillary treatment algorithm based on a lymph node marking procedure pre-NAC and axillary tumor load at diagnosis ([¹⁸F]FDG PET/CT) may lead to a significant reduction of ALND procedures while omitting the SLNB in these patients.

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Clinical Cases

Case 9.1: SLN Mapping in Breast Cancer with Ipsilateral Drainage to the Axilla

Daphne D. D. Rietbergen, Lenka M. Pereira Arias-Bouda, and Renato A. Valdés Olmos

Background Clinical Case

A 75-year-old woman with invasive ductal breast carcinoma was referred for SLNB. During staging of the left axilla no lymph node abnormalities had been detected on

physical examination and ultrasonography (clinical stage T1N0).

Planar Lymphoscintigraphy and SPECT/CT Imaging

In the afternoon before surgery a subareolar injection with 78 MBq ^{99m}Tc -tilmanocept was administered in the left breast. After tracer administration, 5-min planar anterior and lateral static images were acquired at 15 min and 3 h using a dual-head gamma camera (Symbia T6, Siemens, Erlangen, Germany) equipped with low-energy high-resolution collimators. In addition, SPECT/CT imaging was acquired after acquiring the delayed planar images using the same gamma camera.



Fig. 9.12 Anterior early (on the left) and delayed (on the right) planar images, displayed in superposition to anatomical models, showing unilateral drainage to the left axilla with visualization of a single lymphatic duct and increasing uptake in a lymph node

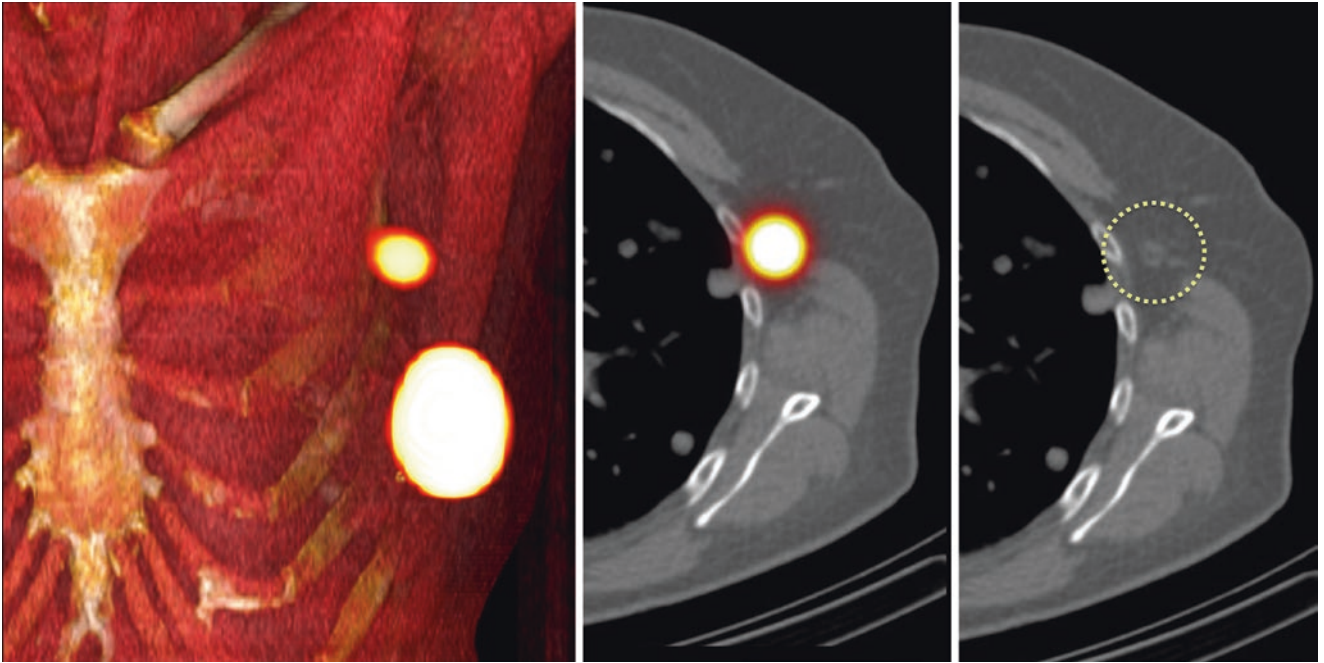


Fig. 9.13 SPECT/CT images displayed with volume rendering (first image) and transaxial (second image) show the SLN in level 1 of the left axilla and corresponding on low-dose CT (third image) to a round lymph node (circle)

Case 9.2: SLN Mapping in Breast Cancer with Ipsilateral Drainage to the Axilla

Daphne D. D. Rietbergen, Lenka M. Pereira Arias-Bouda, and Renato A. Valdés Olmos

Background Clinical Case

A 74-year-old woman with invasive ductal carcinoma of the left breast was referred for the SLN procedure. During staging no lymph node abnormalities had been detected on physical examination and ultrasonography of the ipsilateral axilla (clinical stage T2N0).

Planar Lymphoscintigraphy and SPECT/CT Imaging

In the afternoon before surgery 75 MBq ^{99m}Tc -tilmanocept was administered by means of a single subareolar injection in the left breast. After tracer administration, 5-min planar anterior and lateral static images were acquired at 15 min and 3 h using a dual-head gamma camera (Symbia T6, Siemens, Erlangen, Germany) equipped with low-energy high-resolution collimators. In addition, SPECT/CT imaging was acquired after acquiring the delayed planar images using the same gamma camera.

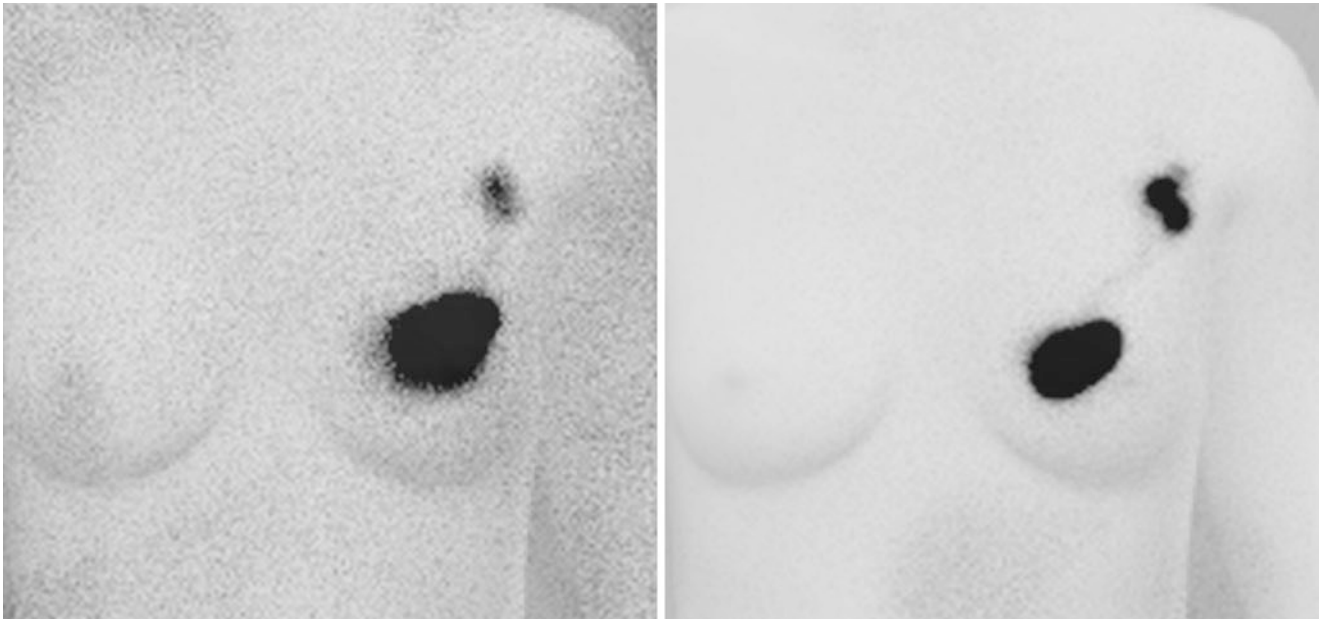


Fig. 9.14 Anterior early (on the left) and delayed (on the right) planar images, displayed in superposition to anatomical models, showing unilateral drainage to the left axilla with visualization of a single lymphatic duct and increasing uptake in two lymph nodes

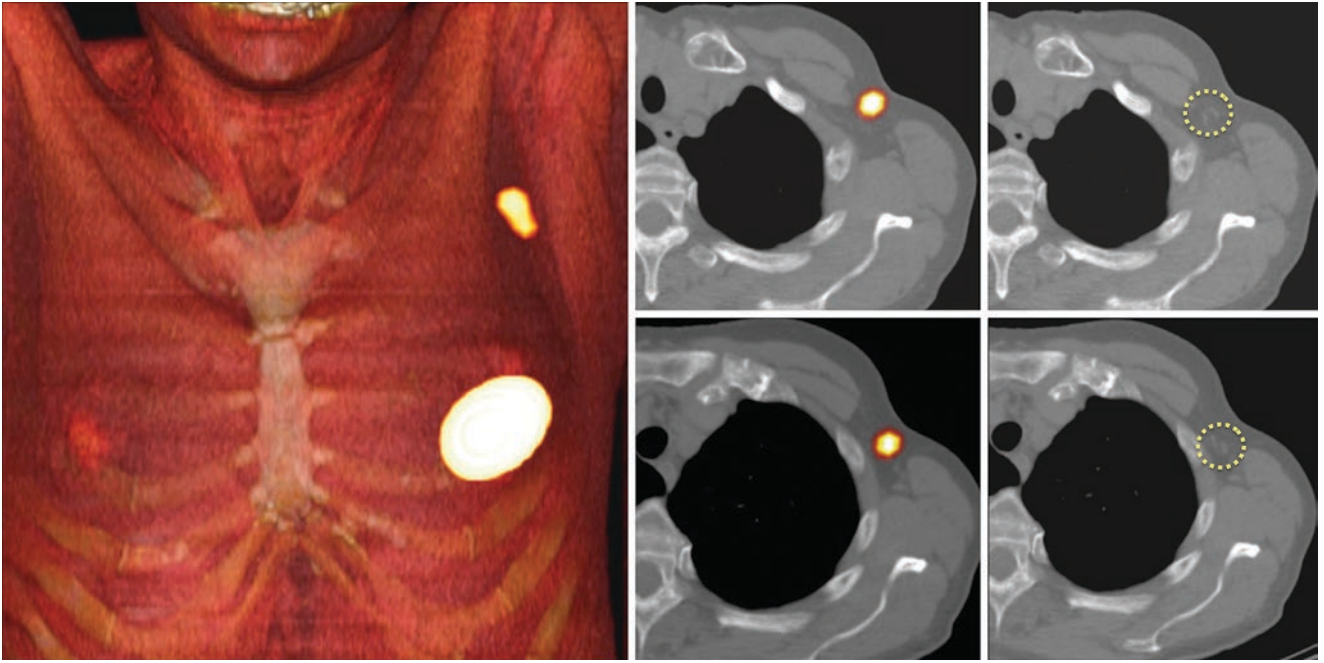


Fig. 9.15 SPECT/CT images displayed with volume rendering (first image) and transaxial (second image) show both SLNs in level 1 of the left axilla corresponding on low-dose CT (third image) to normal-size lymph nodes (circles)

Case 9.3: SLN Mapping in Breast Cancer with Ipsilateral Drainage to Interpectoral and Axillary Lymph Nodes

Lenka M. Pereira Arias-Bouda, Daphne D. D. Rietbergen, and Renato A. Valdés Olmos

Background Clinical Case

A 56-year-old woman with invasive ductal carcinoma of the right breast was referred for SLNB. During staging no lymph node abnormalities had been detected on physical examination and ultrasonography of the right axilla (clinical stage T1N0).

Planar Lymphoscintigraphy and SPECT/CT Imaging

In the afternoon of the day before surgery 112 MBq ^{99m}Tc -nanocolloid was administered by means of a single intratumoral injection in the right breast. After tracer administration, 5-min planar anterior and lateral static images were acquired at 15 min and 3 h using a dual-head gamma camera (Symbia T, Siemens, Erlangen, Germany) equipped with low-energy high-resolution collimators. In addition, SPECT/CT imaging was acquired after acquiring the delayed planar images using the same gamma camera.

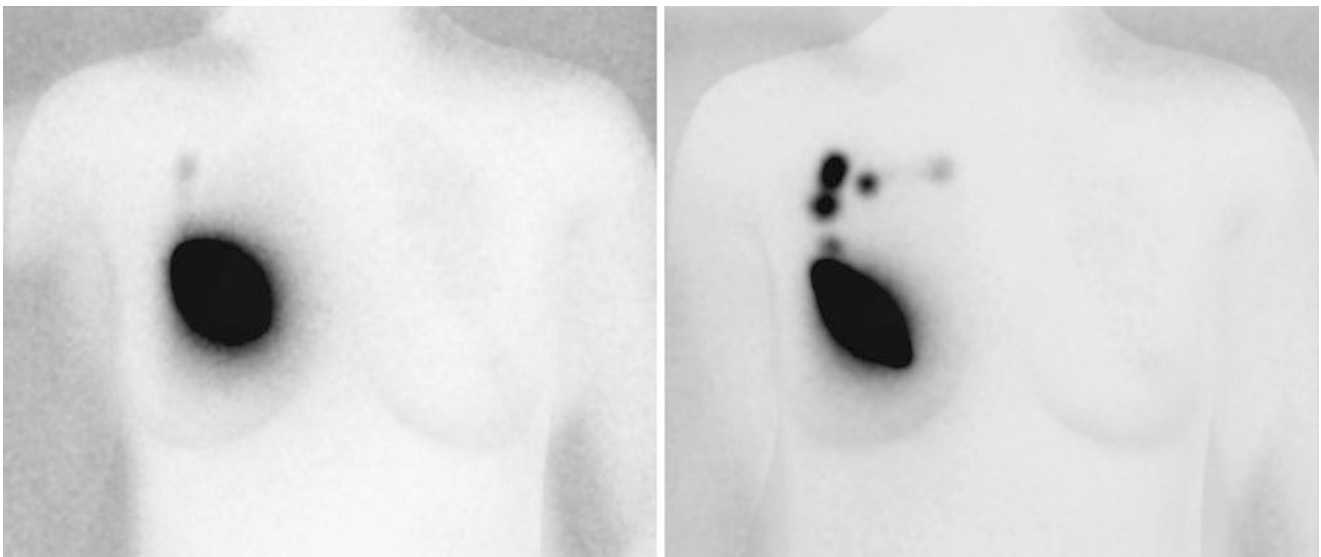


Fig. 9.16 Anterior early planar image (on the left) showing ipsilateral drainage to the right axilla with visualization of a single lymphatic duct and initial uptake in a lymph node. In the delayed planar image (on the right) multiple radioactive lymph nodes are visualized

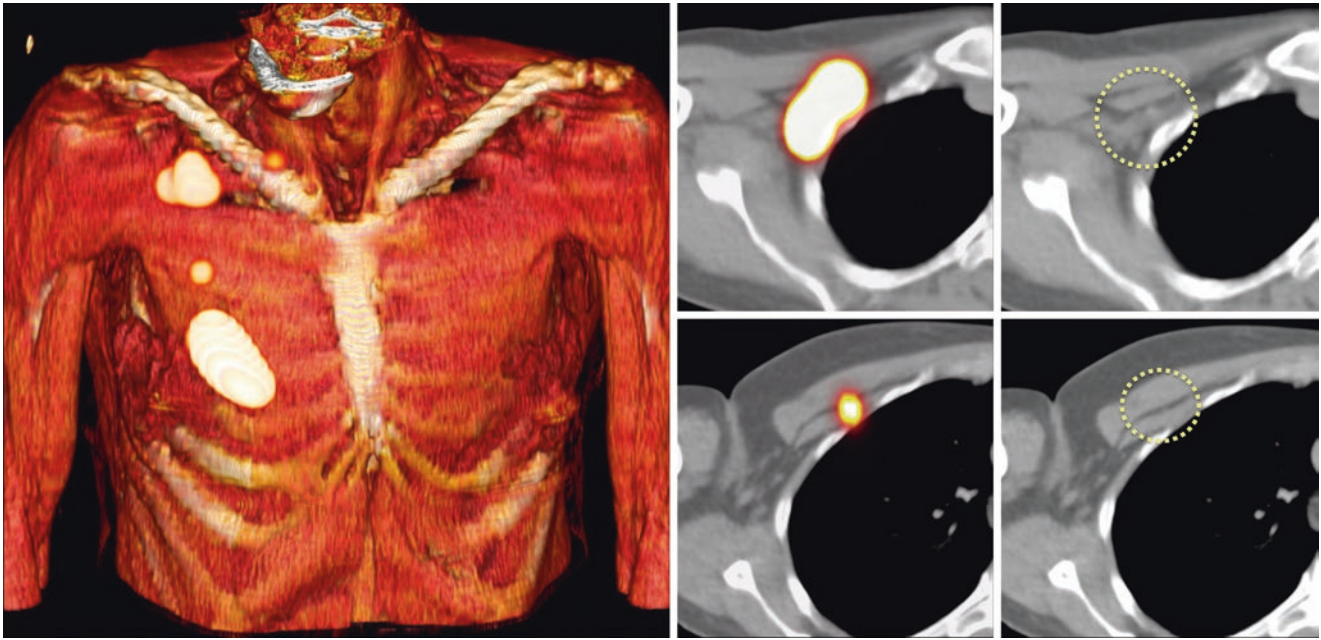


Fig. 9.17 SPECT/CT images displayed with volume rendering (first image) and transaxial (second column) show two SLNs in level 2 of the right axilla as well as an interpectoral SLN. These radioactive lymph

nodes correspond on low-dose CT (third column) to normal-size lymph node (circles)

Case 9.4: SLN Mapping in Breast Cancer with Drainage to the Ipsilateral Internal Mammary Chain and Axilla

Lenka M. Pereira Arias-Bouda, Daphne D. D. Rietbergen, and Renato A. Valdés Olmos

Background Clinical Case

A 55-year-old woman with invasive ductal carcinoma of the left breast was submitted for SLNB. During staging no lymph node abnormalities had been detected on physical examination and ultrasonography of the left axilla (clinical stage T2N0).

Planar Lymphoscintigraphy and SPECT/CT Imaging

In the afternoon of the day before surgery 108 MBq ^{99m}Tc -nanocolloid was administered by means of a single intratumoral injection in the left breast. After tracer administration, 5-min planar anterior and lateral static images were acquired at 15 min and 3 h using a dual-head gamma camera (Symbia T, Siemens, Erlangen, Germany) equipped with low-energy high-resolution collimators. In addition, SPECT/CT imaging was acquired after acquiring the delayed planar images using the same gamma camera.

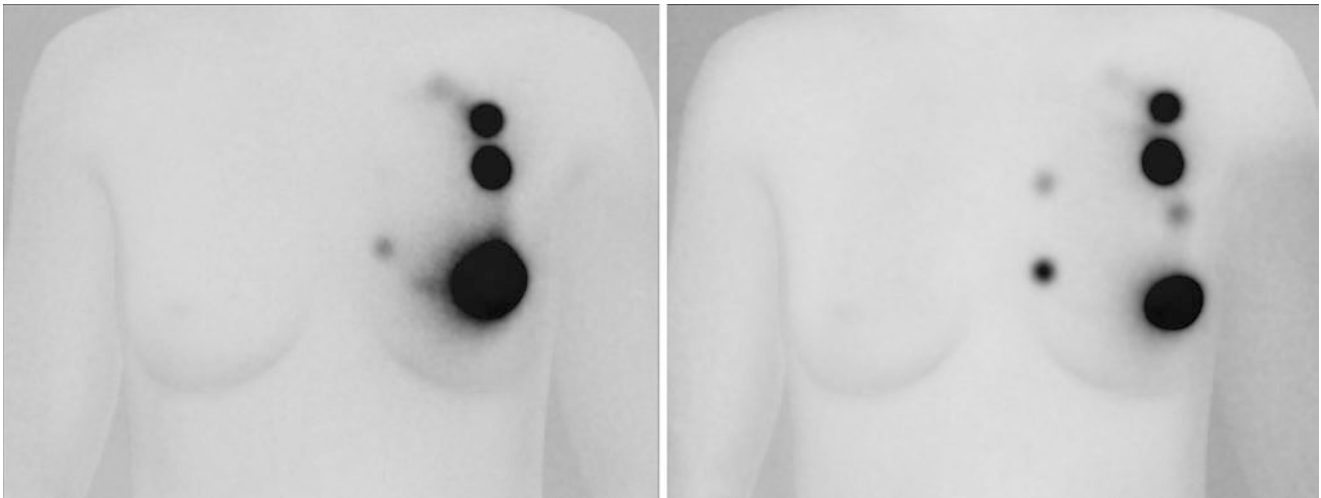


Fig. 9.18 Anterior early planar image (on the left) showing ipsilateral drainage to the left axilla and internal mammary chain with visualization of lymphatic ducts. On delayed planar imaging (on the right) mul-

tiple radioactive axillary lymph nodes are visualized as well as increasing uptake in the first draining internal mammary lymph node

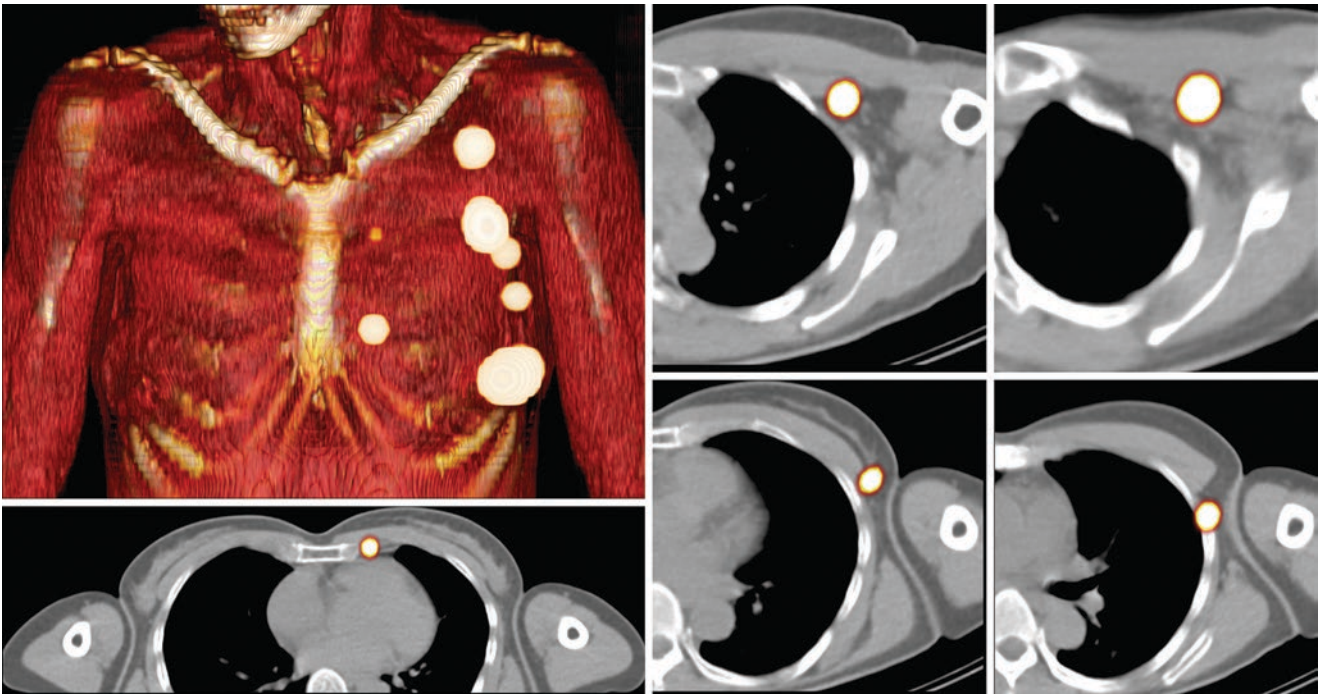


Fig. 9.19 In the SPECT/CT image displayed with volume rendering (first image left above) four radioactive lymph nodes are visualized in the area of the left axilla as well as an internal mammary lymph node

with intense uptake at the left third intercostal space. On cross-sectional SPECT/CT slices the intercostal SLN is depicted (bottom on the left) as well as SLNs behind the breast, lower part of the axilla, and in level 2

Case 9.5: SLN Mapping in Relapsed Breast Cancer with Tracer Migration to the Ipsilateral Internal Mammary Chain and No Axillary Drainage

Renato A. Valdés Olmos, Lenka M. Pereira Arias-Bouda, and Daphne D. D. Rietbergen

Background Clinical Case

A 51-year-old woman with relapsed invasive ductal carcinoma of the left breast was referred for SLNB. In the past the patient had been treated with lumpectomy and SLN surgery due to a T1N0 tumor in the same breast. During current staging no

lymph node abnormalities had been detected on physical examination and ultrasonography of the left axilla (clinical stage T2N0).

Planar Lymphoscintigraphy and SPECT/CT Imaging

In the afternoon of the day before surgery 110 MBq ^{99m}Tc -nanocolloid was administered by means of a single intratumoral injection in the left breast. After tracer administration, 5-min planar anterior and lateral static images were acquired at 15 min and 3 h using a dual-head gamma camera (Symbia T, Siemens, Erlangen, Germany) equipped with low-energy high-resolution collimators. In addition, SPECT/CT imaging was acquired after acquiring the delayed planar images using the same gamma camera.

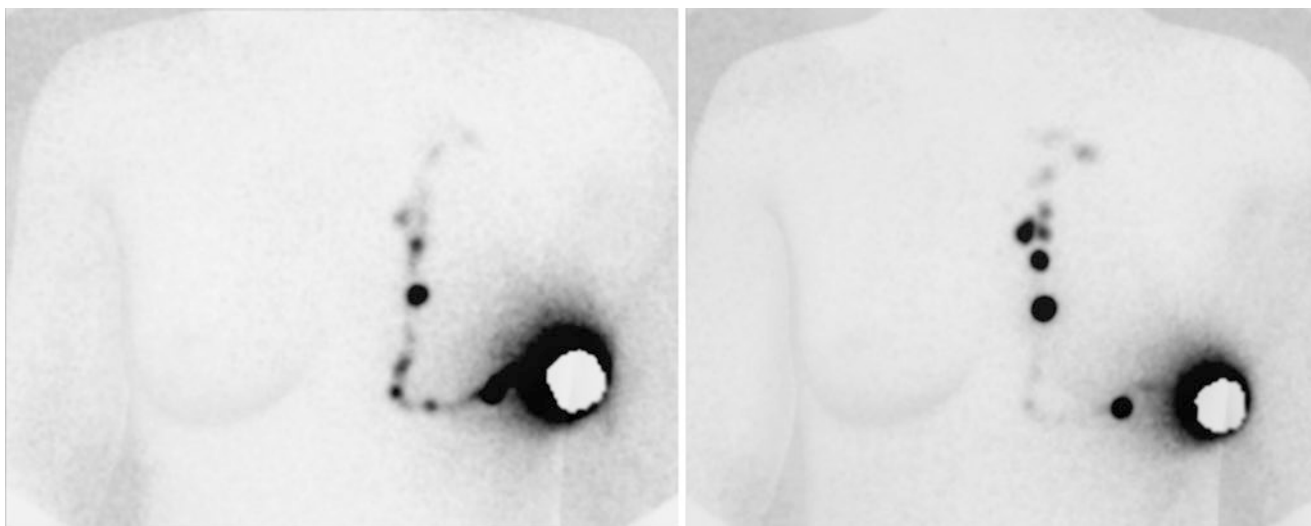


Fig. 9.20 Anterior early planar image (on the left) showing ipsilateral drainage to the internal mammary chain with visualization of a lymphatic duct. On delayed planar imaging (on the right) multiple radioac-

tive internal mammary lymph nodes are visualized. There is no drainage to the left axilla

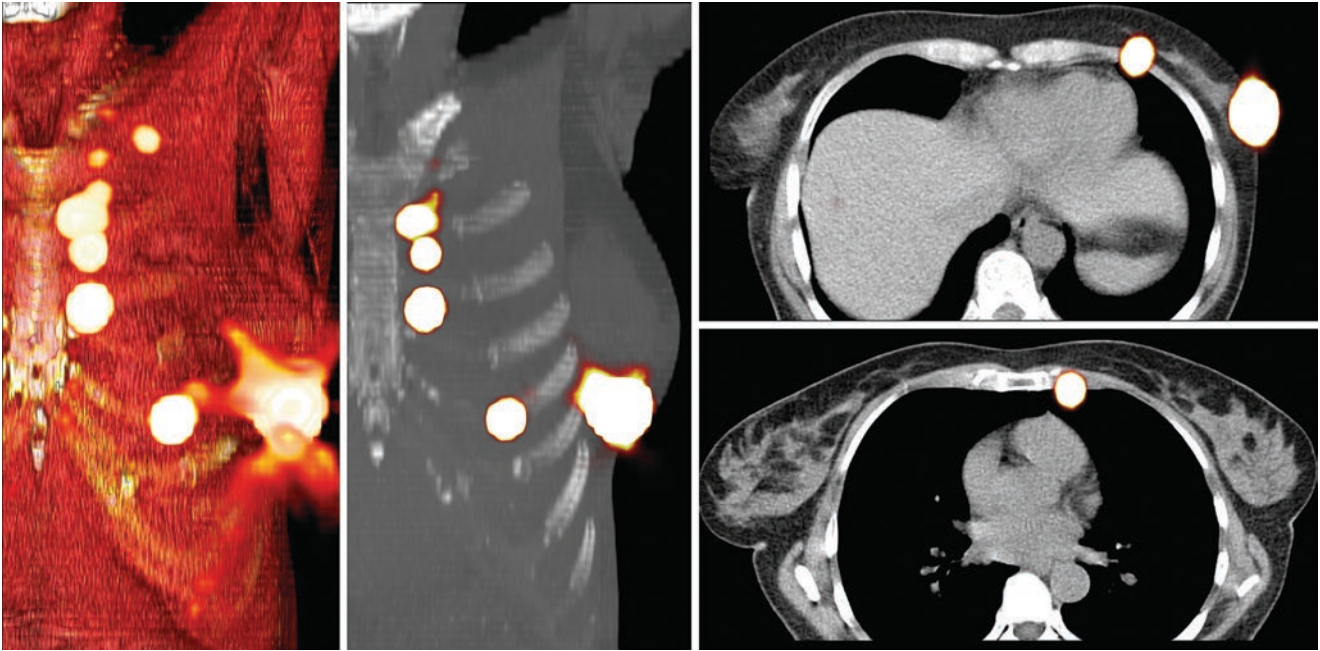


Fig. 9.21 SPECT/CT images displayed with volume rendering (first image) and coronal SPECT/CT with multiple intensity projection (second image) show drainage solely to the ipsilateral internal mammary

chain. The radioactive lymph nodes at the first rib and third intercostal space were identified as SLNs, as were further displayed on cross-sectional SPECT/CT slices (third image)

Case 9.6: SLN Mapping in Relapsed Breast Cancer with Drainage to the Contralateral Axilla

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Background Clinical Case

A 56-year-old woman with relapsed invasive ductal carcinoma of the left breast was referred for SLNB. In the past the patient had been treated with lumpectomy, axillary lymph node dissection, and radiotherapy due to a T2N1 tumor in the same breast. During current staging no lymph node abnormalities had been detected on physi-

cal examination and ultrasonography of the axilla (clinical stage T1N0).

Planar Lymphoscintigraphy and SPECT/CT Imaging

In the afternoon of the day before surgery 105 MBq ^{99m}Tc -nanocolloid was administered by means of a single ultrasound-guided intratumoral injection in the left breast. After tracer administration, 5-min planar anterior and lateral static images were acquired at 15 min and 3 h using a dual-head gamma camera (Symbia T, Siemens, Erlangen, Germany) equipped with low-energy high-resolution collimators. In addition, SPECT/CT imaging was acquired after acquiring the delayed planar images using the same gamma camera.

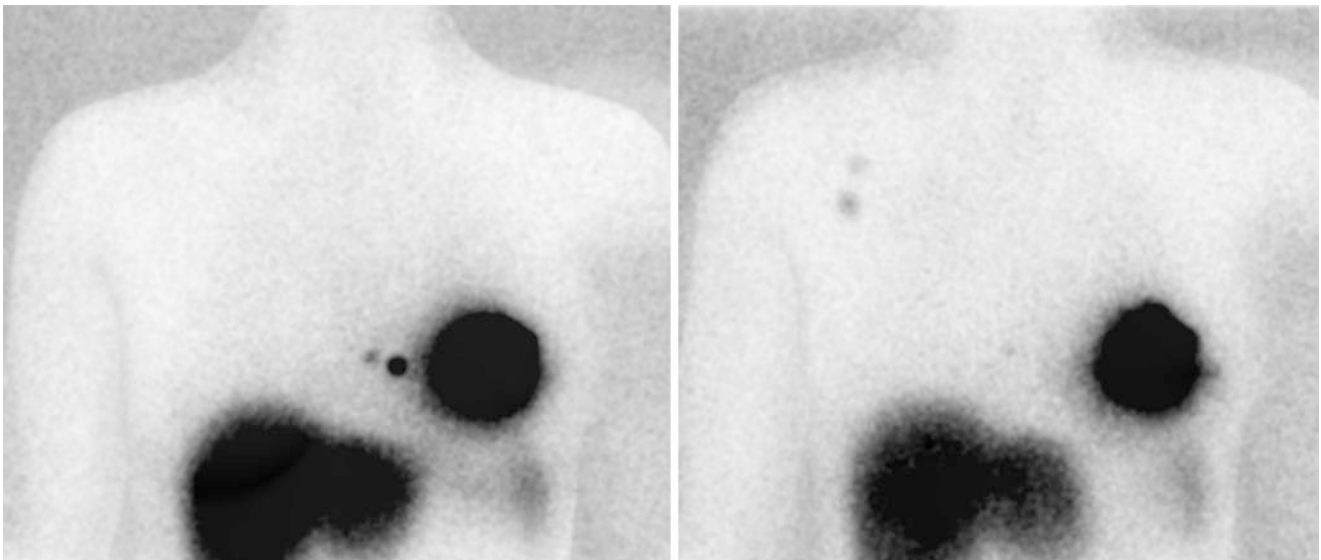


Fig. 9.22 Anterior early planar image (on the left) showing initial tracer migration close to the injection site. On delayed planar image (on the right) two radioactive lymph nodes are visualized in the contralat-

eral axilla. Note that the radioactivity in the vicinity of the injection site has disappeared

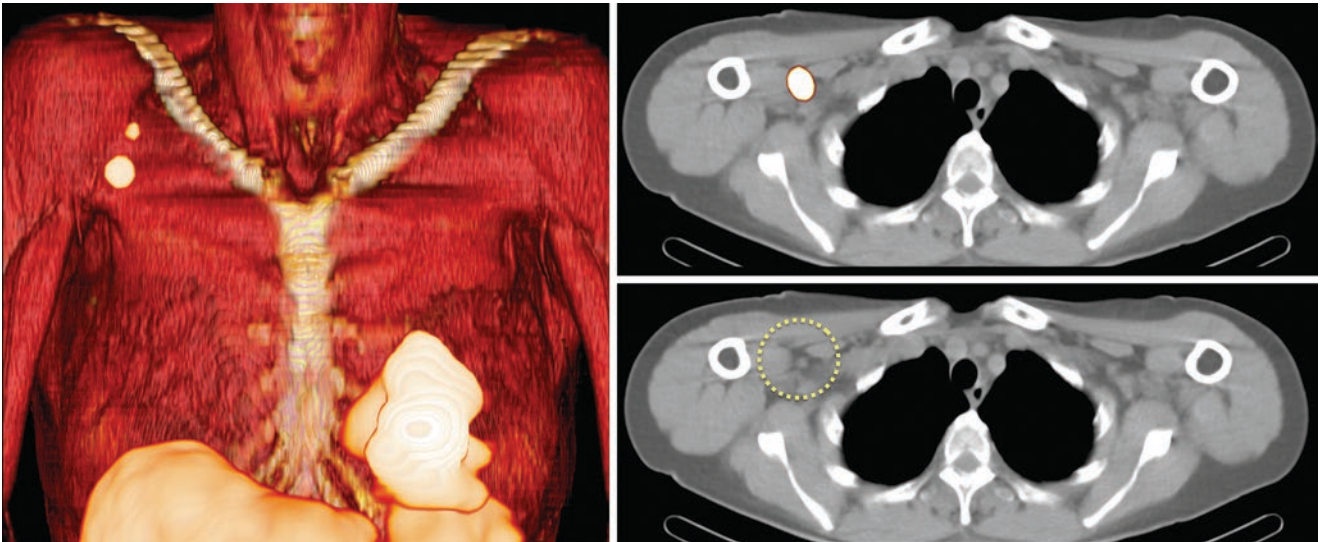


Fig. 9.23 SPECT/CT image displayed with volume rendering (first image) showing a SLN and a second-echelon lymph node in the right axilla. Cross-sectional SPECT/CT section (above on the right) shows

the SLN in level 1 of the axilla. This corresponds to a normal-size lymph node (circle) on low-dose CT (bottom on the right)

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