Radioguided Surgery for Breast Cancer

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Abstract

Sentinel lymph node biopsy is the standard surgical procedure for staging clinically tumor-free regional nodes in patients with early-stage breast cancer. This technique has spared the additional morbidity of axillary lymph node dissection without compromising diagnostic accuracy and prognostic information. However, it is still important to discuss current techniques and some controversies. Current data indicate that the combined radiocolloid injection approach (both superficial and deep injections) results in a higher identification rate of sentinel lymph nodes. Routine preoperative scintigraphic imaging helps the intraoperative search for sentinel lymph nodes and is vital for detecting extra-axillary or aberrant nodes, as well as for patients who have had prior core breast biopsy or surgery. SPECT/CT imaging, in addition to conventional lymphoscintigraphy, leads to improved preoperative visualization and localization of sentinel lymph nodes, especially if performed for specific indications. The combined use of radioactive tracers and blue dyes is more effective in detecting sentinel lymph nodes than either modality used alone and is therefore recommended for routine use.

Intraoperative imaging with portable gamma cameras is being increasingly employed, enhancing the reliability of the gamma probe by adding clear imaging of the surgical fields, especially when the injection site is close to the lymphatic basin. Portable gamma cameras can also be useful during radioguided occult lesion localization procedures in patients with non-palpable breast lesions.

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Advances in radiopharmaceuticals and computer technology make it possible to integrate optical, hybrid tracers and 3D rendering systems that facilitate intraoperative sentinel lymph node identification.

Keywords

Breast cancer • Sentinel lymph node biopsy • Nuclear medicine • Axillary lymph node dissection • Radiocolloid injection • Radioguided occult lesion localization

Glossary

[^{18}F]FDG	2-Deoxy-2-[^{18}F]fluoro-D-glucose
^{99m}Tc-MAA	^{99m}Tc-macroaggregated albumin
ALND	Axillary lymph node dissection
ART	Axillary radiotherapy
ASCO	Americal Society of Clinical Oncology
CT	X-ray computed tomography
DCIS	Ductal carcinoma in situ
FOV	Field of view
GOSTT	Guided intraoperative scintigraphic tumor targeting
H&E	Hematoxylin and eosin staining
ICG	Indocyanine green
IHC	Immunohistochemistry staining
IMC	Lymph nodes of the internal mammary chain
IMN	Internal mammary lymph nodes
LEHR	Low-energy high-resolution
LEUHR	Low-energy ultra-high resolution
LN	Lymph node
MRI	Magnetic resonance imaging
NACT	Neoadjuvant systemic chemotherapy
PET	Positron emission tomography
PET/CT	Positron emission tomography/computed tomography
ROLL	Radioguided occul lesion localization
SLN	Sentinel lymph node
SLNB	Sentinel lymph node biopsy
SNOLL	Sentinel node occult lesion localization (a combined procedure of simultaneous SLNB and ROLL in the same surgical session)
SPECT	Single photon emission computed tomography
SPECT/CT	Single photon emission computed tomography/computed tomography
SPIO	Superparamagnetic iron oxide
US	Ultrasonography

Contents

Introduction

General Background

Radioguided surgery constitutes a wide range of procedures which involve close collaboration between different specialties (nuclear medicine and surgery, often pathology) [1].

"Radioguided surgery" includes a set of pre-, intra-, and postoperative techniques and procedures that are designed to optimize oncologic surgery. All these technologies and applications can be encompassed in the recently coined concept of guided intraoperative scintigraphic tumor targeting (GOSTT) [2]. The basic feature that most obviously characterizes GOSTT is the preoperative administration of a radiopharmaceutical (either interstitially or systemically), associated with the intraoperative use of a handheld radioactivity counting probe (most often the so-called gamma probe) that facilitates the task of the

surgeon – that is, the identification and removal of the target tissue, either a lymph node or the tumor itself – by virtue of preferential radioactivity accumulation in the target tissue. Intraoperative exploration of the surgical field with the gamma probe (which has recently evolved to allow intraoperative imaging as well) is made possible by a set of preoperative techniques employed by the nuclear medicine physician to achieve accumulation of the radiopharmaceutical in the specific target lesion. In this scenario, the most recent advances are based on growing interaction among different components of the complex armamentarium now available to the imaging community (including hybrid imaging, hybrid imaging agents, and/or virtual navigation systems) and to the surgical community (including robot-assisted surgery) [2–6].

The concentration of a radiopharmaceutical in a target lesion can be achieved by three main mechanisms: (1) interstitial administration of an adequate radiopharmaceutical, typically a radiocolloid, that scintigraphically depicts the pattern of lymphatic drainage from the site of a solid epithelial tumor, i.e., performing lymphoscintigraphy to identify the sentinel lymph node (s) (SLN) of the tumor; (2) systemic administration of a radiopharmaceutical that preferentially accumulates in the target lesion, e.g., ^{99m}T-sestamibi for localization of parathyroid adenomas or [^{18}F]FDG for [^{18}F]FDG-avid tumor lesions; and (3) direct intralesional administration of a radiopharmaceutical such as ^{99m}Tc-macroaggregated human albumin (^{99m}Tc-MAA, comprised of particles that, by virtue of their relatively large size, are virtually indefinitely retained at the injection site) for the so-called radioguided occult lesion localization (ROLL) for non-palpable breast tumors.

In the last few years, GOSTT applications have rapidly expanded especially to perform sentinel lymph node biopsy (SLNB). The sentinel lymph node (SLN) procedure is a diagnostic staging procedure that is applied in a variety of tumor types. The procedure aims to determine the tumor status of the SLN(s). Although historically the term "sentinel lymph node" was used to describe a group of nodes seen in patients with penile carcinoma [7], an SLN is currently defined as the first lymph node on a direct drainage pathway from the primary tumor [8, 9]. The concept is based on the premise that lymph flow from the primary tumor travels sequentially to the SLN and then onto the other regional lymph nodes (Fig. 1). The SLN is the node most likely to harbor metastases.

The histopathologic status of this node should reflect the histopathologic status of the entire nodal basin, and additional treatment of the nodal basin (e.g., surgery) is routinely performed in case of metastatic involvement of the SLN – although the presence per se of metastatic tumor cells in the SLN is not the only factor determining lymph node dissection of the basin of interest (see further below in this chapter). A negative SLN, however, would justify a wait-and-see policy avoiding unnecessary elective lymph node dissections and the associated morbidity, hospital stay, and costs.

In addition to being continually applied in patients with breast cancer and cutaneous melanoma, radioguided SLNB is being explored in patients with a wide variety of other solid epithelial cancers. In particular, malignancies where the feasibility and/or clinical impact of radioguided SLNB is increasingly being investigated include head and neck cancers, gynecological cancers (vulvar, cervical, and endometrial), gastrointestinal cancers (esophagus, stomach, colorectal, anus), prostate cancer, non-small cell lung cancer, differentiated thyroid carcinoma, and others [10–15].

Breast Cancer

Breast cancer is the most frequent cancer diagnosed in women worldwide [16]. In patients with breast cancer, accurate lymph node (LN) staging is essential for both prognosis (of early-stage disease) and treatment both for regional control of disease and for adjuvant therapies [17].

Clinical examination (i.e., palpation) is not accurate enough for assessing the axillary status, and preoperative imaging modalities including PET/CT with [^{18}F]FDG and ultrasound have low sensitivity, especially in case of micrometastatic disease [18–24]. Thus, in breast cancer, the traditional staging approach has been axillary LN dissection (ALND). However, ALND results in a

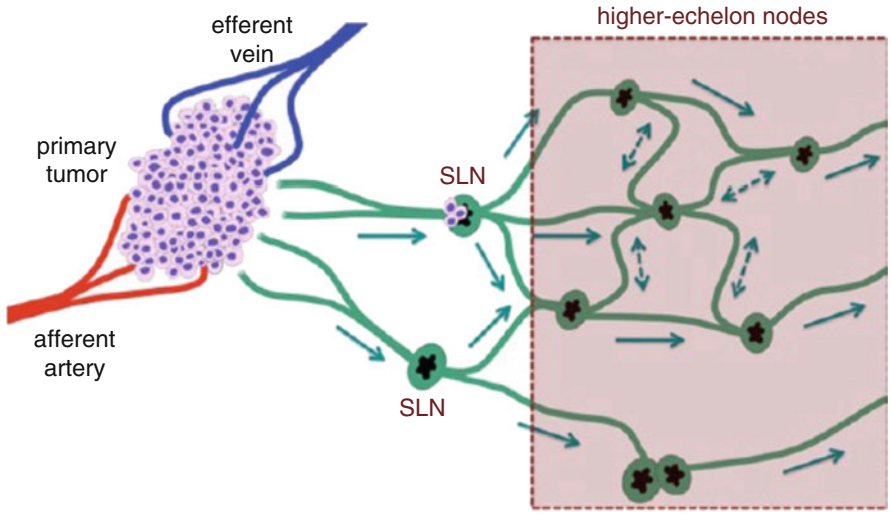

Fig. 1 Schematic representation of the sentinel lymph node concept. Assuming that lymph drainage from a solid tumor proceeds in an orderly way from lower-echelon to higher-echelon lymph nodes, the first node (s) encountered in such pathway, that is, the sentinel node (s), should be the site where tumor cells migrating through lymphatic channels are most likely to be entrapped and possibly originate metastasis before spreading to higher-echelon lymph nodes. As illustrated in the figure, even in any given lymphatic basin, there can be more than one sentinel lymph node, as lymph can drain from the site of the primary tumor via different lymphatic channels toward the same basin. The diagram also illustrates the complex interconnections that can exist at higher levels, with variable directions of lymph flow at intermediate levels within the general pattern of overall centripetal flow. The pattern of lymph flow is even more complex when considering that lymph from the tumor site can drain to more than one lymphatic basin, each one repeating the basic pattern represented here for a single basin

high incidence (about 25–30%) of postoperative complications that can reduce quality of life, such as delayed wound healing; lymphedema; peripheral nerve injury or even brachial plexus injury, with sensory/motor impairment; and pain. Furthermore, in early breast cancer, nearly 80% of axillary dissections reveal no metastasis and, therefore, could have been avoided [25].

Based on the definition of SLNs as those regional nodes that directly drain lymph from the primary tumor, SLNs are the first nodes to potentially receive the seeding of lymph-borne metastatic cells [26, 27]. After the initial description by Morton et al. of a method of SLNB in the management of melanoma patients, more than two decades ago [28, 29], SLN mapping and biopsy were applied in breast cancer [30, 31]. Since then, SLN mapping and biopsy have become routine techniques in breast cancer management, contributing to the development of less invasive surgical procedures [32–44]. Sentinel node biopsy is extremely accurate and effective. A systematic review showed an axillary 0.6% relapse rate in negative SLN patients and no benefits to completion ALND in terms of survival after negative SLNB [42, 45]. Thus, when the SLN is free of metastasis, the patient can be spared an ALND that until a few years ago was considered the standard staging procedure for breast cancer [31, 46, 47].

Despite the widespread application of SLNB for early-stage breast cancer, there is significant variation in performance characteristics reported for such procedures. Differences in institutional experience and in lymphatic mapping techniques are two of the main contributing factors to variations in the proportions of successful mappings [48–50]. The ranges of rates for false-negative findings and for SLN identifications emphasize the variability of this procedure. Learning curves for this technical procedure also vary [48]. Nevertheless, once a multidisciplinary team is experienced with the procedure, reasonable levels of accuracy are achieved, with identification rates of more than 95% reported routinely [25, 47, 51–54].

Sentinel Lymph Node in Breast Cancer

Pathophysiological Aspects

The breast embryologically originates from ectodermal tissue, as a skin appendage, and therefore shares a pattern of lymphatic drainage with the overlying skin. The mammary gland is interposed between the superficial (subdermal) and the deep (subcutaneous) lymphatic plexuses, the two systems being interconnected by a dense network of lymphatic vessels (Fig. 2a). Lymphatic vessels surrounding the mammary lobules predominantly drain to the subareolar Sappey's plexus, which is part of the superficial plexus of the skin. Most of the lymph produced in the breast is therefore drained to the subareolar region, progressing then toward the ipsilateral axillary nodes (Fig. 2b). A small fraction of the lymph produced in the breast (about 3%) is instead drained to lymph nodes of internal mammary chain, while an even smaller amount drains to other lymph nodes such as the intercostal, pectoral muscles, contralateral breast, or even abdominal nodes [55].

By following these routes of drainage, lymph and cancer cells entering the lymph space spread initially to the first node, which is the SLN. If the SLN is free of metastasis, the probability of tumor cells skipping that lymph node and metastasizing to second- or third-echelon nodes is an exceptionally rare event [39, 46, 56–64].

Indications

The main objective of SLN mapping and SLNB in breast cancer patients is axillary staging. These procedures are an appropriate alternative to routine staging axillary LN dissection for patients with early-stage biopsy-proven breast carcinoma without cytologically or histologically proven axillary lymph node metastases [65]. Appropriately identified patients with negative SLN biopsy do not need to undergo axillary LN dissection.

Currently, the SLNB procedure is recognized as the standard treatment for stage I and stage II breast cancer patients [40, 66, 67]. In these stages, the results showed that SLNB has a positive LN rate similar to that observed after ALND [40, 68, 69], yet with a significant reduction in morbidity [68] and similar gold standard (i.e., axillary LN recurrence rates at 5 years) [40]. The technique is validated if SLNs are found in more than 95% of the cases (i.e., the probability of detecting tumor cells in non-sentinel nodes is less than 5%). False-negative rates are higher in grade 3 lesions and when a single SLN is harvested, compared to cases where multiple SLNs are harvested [70].

The recognized indications for SLNB, together with recommendations as to whether an SLN procedure is the established standard of care, are listed in Table 1 [71].

Procedures

Generally, the procedure for SLN mapping and SLNB involves interstitial tracer injection, preoperative scintigraphic imaging, and intraoperative gamma probe localization for surgical removal of the detected LNs. Although there is consensus on some broad aspects of SLN protocols for breast cancer, consensus does not exist on all details. Controversies exist with regard to the particle size of the radiotracer, the optimal route for injection, timing and type of scintigraphy and intraoperative detection, and whether or not extra-axillary LNs should be considered for harvesting and analysis. The specific radiotracer and technique used are additionally guided by local availabilities, regulations, and practices [71].

Procedures in Nuclear Medicine

Three main parameters define an optimal tracer administration technique for radioguided SLNB: injection site, injected volume, and injected activity. A fourth parameter to be taken into account is the time elapsed between injection and surgery, as it specifically influences the amount of radioactivity to be injected [72, 73].

Radiopharmaceuticals

Several ^{99m}Tc-based agents have been used for radioguided SLNB for breast cancer (see Table 2) [74]. The radiopharmaceuticals most widely used

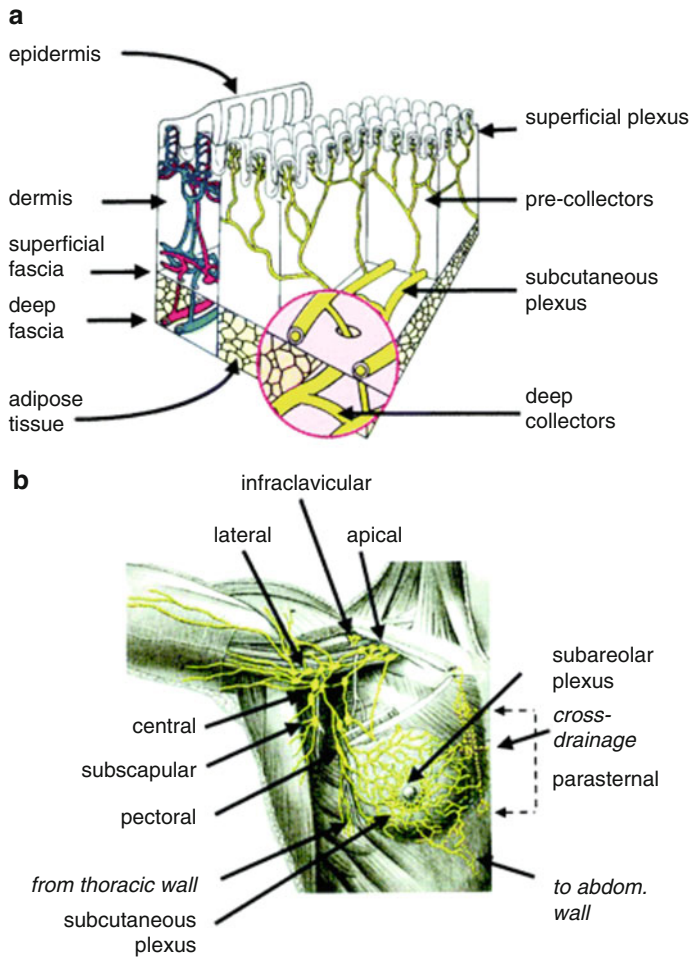

Fig. 2 (**a**) Schematic structure of cutaneous blood and lymph vessels. For easier comprehension, the lymph and blood vessel networks (which are actually embedded in each other) are represented separately, respectively, on the *right* (*yellow*) and on the *left* (*red* and *blue*). Due to its embryologic origin in the ectoderm, the mammary gland can be placed in an ideal space between the subcutaneous plexus and the deep lymphatic collectors (magnified insert in the figure). Branches of the periductal plexus drain lymph mostly toward the skin surface (via the subareolar plexus), while a minor component drains toward the deep collectors (which in turn drain toward the internal mammary chain). Radiocolloids injected intradermally over the mammary gland drain to the subcutaneous plexus that also receives most of the lymph draining from the mammary gland. (**b**) Pathways of the lymphatic vessels and lymph node stations draining the mammary gland. Most of the lymph produced in the breast drains to the subareolar plexus, then merges with the subcutaneous plexus of overlying skin, and flows mostly toward the axilla. Lymph from deeper portion of mammary gland drains either through the same pathway or through deep lymphatics that reach the parasternal, internal mammary chain (and even the contralateral side). *abdom* abdominal (From [38] with permission)

are ^{99m}Tc-sulfur colloid (particle size: 15–5,000 nm, but usually filtered to select a more restricted range of particles' size), ^{99m}Tc-nanocolloid (5–100 nm), and ^{99m}Tc-antimony trisulfide (3–30 nm).

The ideal radiotracer should show rapid transit to SLNs with prolonged retention in the nodes. In general, the drainage, distribution, and clearance of radioactive colloids by the lymphatic system may vary and are dependent on the size of the particles. Small particles are drained and cleared first; large particles are drained and cleared last and may be retained longer at the injection site.

Table 1 Recommendations on the use of SLN biopsy (Modified from [71])

Clinical circumstance	Use of SLN biopsy
T1 or T2 tumor	Established
T3 or T4 tumor	Controversial
Multicentric or multifocal tumor	Controversial
Inflammatory breast cancer	Not recommended
DCIS with mastectomy	Established
DCIS without mastectomy, but with suspected or proven microinvasion	Established
DCIS without mastectomy	Controversial
Suspicious, palpable axillary nodes	Controversial
Older age	Established
Obesity	Established
Male breast cancer	Established
Pregnancy	Controversial
Evaluation of internal mammary lymph nodes	Controversial
Prior diagnostic or excisional breast biopsy	Controversial
Prior axillary surgery	Controversial
Prior non-oncologic breast surgery	Controversial
After preoperative systemic therapy	Controversial
Before preoperative systemic therapy	Established

Controversial indications are those for which SLN biopsy is not universally accepted or for which the evidence behind the practice is limited or entirely missing. *DCIS* ductal carcinoma in situ

Table 2 Radiopharmaceutical characteristics (Modified from [74])

^{99m}Tc-based agents	Particle size max (nm)	Particle size mean (nm)
Sulfur colloid	350–5,000	100–220 (filtered)
Antimony trisulfide	80	3–30
Sulfide nanocolloid (Lymphoscint®)	80	10–50
Nanocolloidal albumin (Nanocoll®)	100	5–80
Rhenium sulfide nanocolloid (Nanocis®)	500	50–200
Tin colloid	800	30–250
Labeled dextran	800	10–400
Hydroxyethyl starch	1,000	100–1,000
Stannous phytate	1,200	200–400
Tilmanocept (Lymphoseek®)	~7 (equivalence)	~7 (equivalence)

Studies have shown that the success rate of identification of axillary SLNs is not significantly affected by the particle size of the radiotracer [38, 75–77]. Thus, the selection of radiotracer is based more on local availability than on differences in SLN detection. However, there is general agreement that a 100–200nm sized radiocolloid should be considered the best compromise between fast lymphatic drainage and optimal retention in SLNs [78].

New tracers have been developed in recent years. The tracer most recently made commercially available is Lymphoseek®, which is composed of a dextran backbone with multiple glucose and mannose residues attached to DTPA for ^{99m}Tc-labeling. The potential advantages of its small molecular size (7.1 nm) and the receptor-targeted nature of the mannose moieties in ^{99m}Tc-Tilmanocept include rapid transit from the primary site to the SLN as well as selective accumulation in that node, with limited pass-through to second-echelon nodes [79–82].

Activities and Volumes

Literature supports the use of small volumes with high specific activity to improve SLN detection. Nevertheless, consensus on the activity to be administered in an SLN procedure has not been reached. Activities as low as 3.7 MBq (0.1 mCi) [83] and as high as 370 MBq (10 mCi) [84] have been used. In current practice, a total injected activity of 5–30 MBq (depending on the elapsed time between scintigraphy and surgery) is generally considered sufficient for surgery planned for the same day. Prior day injection has been shown to be technically feasible by adequately increasing the amount of radioactivity injected (up to 150 MBq) [85].

Injection of large volumes may disrupt local lymphatics; therefore, a quantity of 0.2–0.5 mL should be injected. Moreover, the syringe should also contain a sufficient amount of air to clear any dead space within the syringe and the needle.

Injection Procedure

The injection site of the mapping agent is another controversial issue, mainly because lymphatic

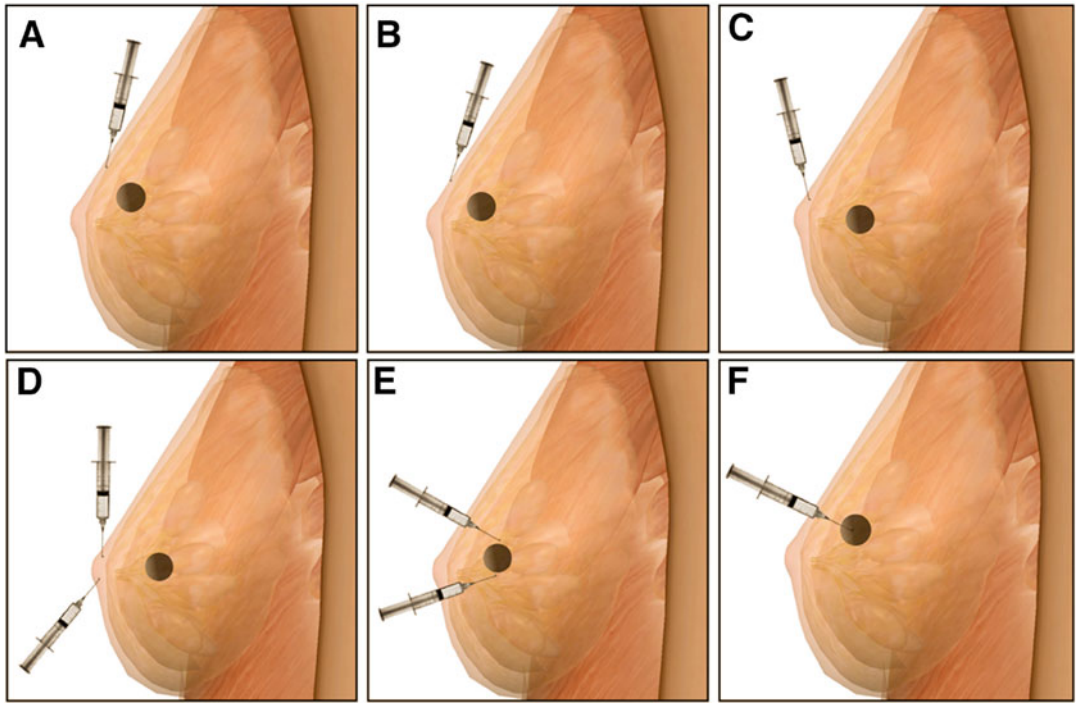

Fig. 3 Modalities of interstitial radiocolloid injection for SLNM in breast cancer. Superficial injections (**a**–**d**) and deep injections (**e**, **f**): intradermal (**a**), subcutaneous (**b**), subareolar (**c**), periareolar (**d**), peritumoral (**e**), and intratumoral (**f**)

drainage of the breast is not completely understood [86]. The most commonly used injection sites can be classified into two categories: deep (intratumoral and peritumoral) and superficial (intradermal, subdermal, subareolar, and periareolar) injection (see Fig. 3).

All injection modalities enable axillary sentinel nodes to be identified accurately, and satisfactory SLN detection rates have been reported for all injection approaches [87]. Lymphatic circulation within solid tumors (including breast cancer) is generally grossly abnormal, disrupted, and inefficient. Thus, intratumoral administration requires the injection of high activities (up to 370 MBq or 10 mCi) and large volumes (even up to over 1 mL). Injection of such large volumes can substantially increase interstitial pressure at the injection site, thus possibly altering the pattern of lymphatic drainage and forcing drainage routes different from those prevailing in baseline conditions. Furthermore, most of the injected radioactivity is retained at the injection site, often causing interference – the so-called "shine-through" effect – in scintigraphic and intraoperative sentinel lymph node detection. Finally, the slow drainage from the tumor can cause poor scintigraphic visualization of the lymphatic channels and possibly lead to failure of lymphoscintigraphic imaging and of intraoperative identification of the sentinel lymph node.

All the above considerations explain why, at present, most nuclear medicine centers prefer peritumoral or superficial injections versus the originally proposed intratumoral route of administration, although the high reproducibility of intratumoral injection has been well demonstrated [88].

Lymphatic circulation in the peritumoral area is normal and actually represents the entrance site to lymph vessels of cancer cells detached from the growing edge of the tumor, which eventually gives rise to lymph nodal metastasis. Indeed, 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 [87, 89]. Peritumoral injection is considered the gold standard for accurate SLN detection, because the tracer is injected near the same lymph vessels draining the tumor and is able to reveal extra-axillary drainage [90]. However, the validity of this approach has been questioned especially in non-palpable and multicentric tumors. Peritumoral administration is usually performed by depositing two aliquots on each side of the tumor, while intra-/subdermal administration is performed in or just under the skin overlying the tumor. Intradermal injection should produce a small wheal. More than one injection could be performed in adjacent sites. Periareolar administration is generally performed with two to four aliquots, each one at the edge of the areola at Sappey's plexus.

The rationale of intra-/subdermal administration stems from the fact that lymph is drained from the intra-/subdermal space to the subcutaneous plexus, which is the merging point for lymph originating from the underlying breast parenchyma (see Fig. 2a). Thus, a tracer injected intra-/subdermally displays the same pathways of lymphatic drainage as the underlying breast gland and of cancer cells entering the lymphatic space. Similar considerations apply to the periareolar route of administration: the lymph produced in the breast flows to the periareolar Sappey's plexus, before draining to axillary LNs (see Fig. 2b).

Superficial injection sites have numerous advantages, including simplicity, shorter time between injection and SLN identification, and increased radiotracer nodal uptake which may result in improved nodal identification rates. Nevertheless, superficial injection allows almost exclusive identification of axillary nodes. The use of peritumoral injections requires careful investigation of a patient's prior imaging and medical records, particularly if the tumor is non-palpable. Tumor location and injection sites may be identified by ultrasound and/or x-ray stereotactic guidance. If a tumor is in the upper outer quadrant, the relatively intense activity at the injection site may make it difficult to localize of a nearby SLN with less intense uptake [91, 92].

Regardless of the injection site, after injection, the patient is asked to gently massage the breast to facilitate lymphatic drainage of the tracer. Massage can also be employed if the passage of activity from the injection site is delayed at any time during the study [93, 94].

Results of multiple studies support the validity of both the deep and the superficial injection approaches; in particular, all injection modalities enable axillary SLN to be identified accurately, and satisfactory SLN detection rates have been reported for all injection approaches [87]. A clinical trial comparing the injection routes demonstrated, in 400 breast cancer patients, the superior intraoperative gamma probe localization of the axillary SLNs for the intradermal route (100%) compared to the subareolar route (95%) and the intraparenchymal route (90%) [95]. A preferential drainage to the same few axillary SLNs has been postulated for most of the breast tissue and its overlying skin, after merging initially to the retroareolar Sappey plexus; therefore, accurate identification of *axillary* SLNs is supposed not to be affected by the injection route [93, 94, 96, 97]. Thus, if the goal is axillary staging only, a superficial tracer injection (periareolar, subareolar, subdermal, intradermal) may be preferable to a deep injection (peritumoral, intratumoral) due to better and quicker visualization of axillary SLNs [98]. On the other hand, an important advantage of deep injection is the improved detection of extra-axillary SLNs: after peritumoral administration, lymphoscintigraphy shows drainage to the internal mammary chain in 20–30% of the cases, while this fraction is much lower (<3%) after intra-/subdermal or periareolar administration [66, 99, 100]. Thus, if one's aim is to stage extra-axillary nodal basins as well as the axilla, deep injection is recommended.

The superficial routes of administration are generally preferred in the case of superficial, easily palpable tumors and the peritumoral route for deeply seated tumors. The periareolar route can be used mainly in upper quadrant tumors to avoid possible cross talk owing to the short distance between the peritumoral depot and the axillary SLNs and is particularly recommended in cases of non-palpable or multifocal tumors [101, 102].

The combination of both injection techniques (deep and superficial) in the same patient may improve SLN detection [90].

Imaging Procedures

Lymphatic mapping allows determination of the number of LNs that are on a direct drainage pathway and to locate the SLNs [71] [103]. Preoperative imaging is strongly recommended due to variability in breast lymphatic drainage into the axilla and extra-axillary nodes [104]. Thus, preoperative lymphatic mapping has the potential to both improve accuracy (especially in extra-axillary LN) and reduce morbidity relative to the use of handheld gamma probes alone [34, 71]. Preoperative imaging also serves as quality control on the use of the appropriate tracer, failure of the injection, failure of the radiopharmaceutical, and management of the appropriate breast and axilla – injection of the proper side (L/R). Reasons not to use preoperative lymphoscintigraphy are logistical or because there is no definite evidence of a higher intraoperative success rate in the harvesting of axillary SLNs [105, 106].

Timing: In order to identify all SLNs and to avoid confusion with radiocolloid stasis in a lymphatic vessel, images are acquired with an adequate delay after injection. This delay may vary according to the radiopharmaceutical used, the injection site, and the patient's characteristics (lymphatic drainage can be slower in elderly or overweight patients). While smaller particles allow quick visualization of SLNs, larger particles have slow transit in the lymphatic system that tends to minimize visualization of non-sentinel second-tier nodes (lymph nodes downstream of SLNs) [107]. After superficial tracer administration, lymphatic drainage and subsequent lymph node visualization is usually quicker than after peritumoral injection (20–30 min compared to 2–3 h on average). After 15–18 h, during surgery, the amount of radiocolloid migrated to LNs represents about 1% of the injected activity after superficial administration, while it is about 0.1% after peritumoral administration.

SLNs are generally visualized within 1–2 h, and the patient should be in the operating theater within 2–30 h of radiocolloid injection, depending on the facility's schedule [71, 107]. In the event a surgery is scheduled for early morning, injection and imaging may be safely performed the afternoon prior to the surgery [108].

Gamma camera parameters: A single- or dual-head gamma camera system with large field-of-view (FOV) detectors is generally used to acquire planar emission and, if desired, single-photon computed tomographic (SPECT) or SPECT/computed tomographic (SPECT/CT) images. Low-energy, high-resolution, or low-energy high-resolution collimators should be used. The energy window should be 15% (±5%) centered on the 140 keV photopeak of ^{99m}Tc.

Image acquisition: Dynamic (flow) imaging is not often used in SLN procedures for breast cancer, but can provide information useful for SLN localization.

Planar (static) imaging should be performed 15–30 min, and 2–4 h post injection, and as needed thereafter up to 18–30 h. At least two, preferably all three, of the following images should be acquired: anterior, 45° anterior oblique, and lateral. Each image is typically 3–5 min in duration. For a system with large FOV detectors, the pixel size is recommended to be approximately 2 mm and the matrix size 256 × 256 with zoom 1 or, rarely, 128 × 128 with zoom 2. If 2 mm pixel size is not feasible on the system, the smallest pixel size available should be used.

Figure 4 shows different patterns of lymphatic drainage and SLN distribution as obtained by planar scintigraphic imaging in preparation for radioguided SLNB. Although conventional planar imaging certainly enables to identify the draining pattern to SLNs, it does not provide the exact anatomic location of the detected LNs, an information that is instead very useful intraoperatively [109]. By combining tomographic functional lymphoscintigrams registered with anatomic data from CT, SPECT/CT imaging provides better contrast and resolution than planar imaging and has the possibility to correct for attenuation and scatter. Fused SPECT/CT imaging considerably improves the topographic localization of the SLN within an anatomical landscape, thus providing a valuable surgical road map [110].

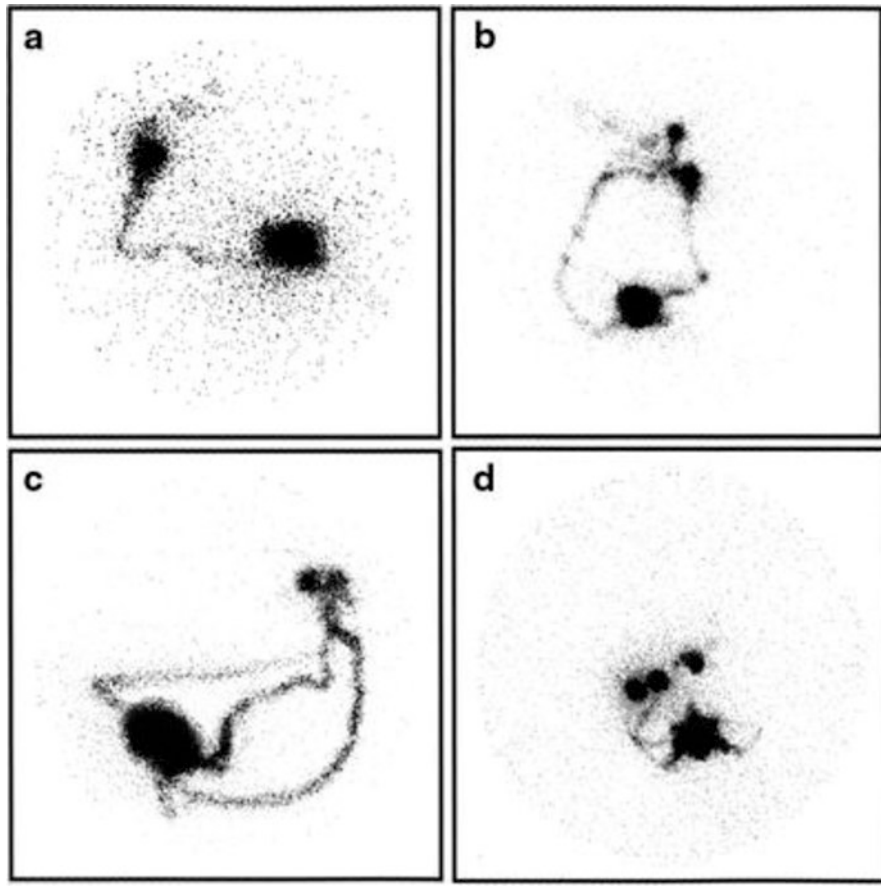

Fig. 4 Variable lymphoscintigraphic patterns visualized between 30 and 60 min after intradermal injection of ^{99m}Tc-nanocolloidal albumin in patients with breast cancer. (**a**) Single lymphatic vessel leading to a single sentinel lymph node, with faint visualization of subsequent-tier lymph nodes (right anterior oblique view). (**b**) Two separate lymphatic vessels widely diverging in their initial pathway, eventually leading to two separate but adjacent sentinel lymph nodes, with faint visualization of subsequent-tier nodes (left anterior oblique view). (**c**) Three separate lymphatic vessels widely diverging in their initial pathway, eventually leading to two separate but very close sentinel nodes (left anterior oblique view). (**d**) Multiple lymphatic vessels leading to at least three separate sentinel lymph nodes (right anterior oblique view) (From [38] with permission)

SPECT acquisition for SLN detection should be performed with a dual-detector SPECT system equipped with LEHR or LEUHR collimators. Acquisition parameters should include matrix size of 128 × 128 (4–5 mm pixels) and 120 or 128 projections over 360° with 20−25 s/projection.

Both low-dose CT (140 kVp, 2.5 mA) and conventional CT (140 kVp, 30–150 mA) can provide useful anatomical detail that can be used for anatomical localization and, if desired, attenuation correction.

Mapping of all direct tumor-draining LNs requires knowledge of the number and location of these SLNs, which will be provided by SPECT/CT in addition to planar images. SPECT/CT imaging provides significant information in the large majority of patients, with useful preoperative complimentary information to the surgeons: better location, reduced surgical time, and greater confidence of the surgeons with the technique [111].

It has been shown that SPECT/CT images can detect additional SLNs not visualized on planar images in a substantial number of patients in whom the conventional images are difficult to interpret [110–112]. In the majority of cases, the surgical team appreciates the anatomic

information provided by the fused SPECT/CT images and the surgical time is reduced [113]. However, because the current conventional approach based on combined radiocolloid and blue dye injection, preoperative planar scintigraphic imaging, and intraoperative gamma probe counting has proven very successful (with SLN detection rates over 95%), the added value of SPECT/CT imaging seems to be limited to a small fraction of breast cancer patients undergoing SLNB. Current recognized indications for SPECT/CT imaging in breast cancer patients are non-visualization of SLNs at conventional imaging, obesity, and presence of extra-axillary SLNs or otherwise unusual drainage (e.g., in cases of previous breast surgery) [71]. SPECT/CT imaging might also be performed if the conventional images are difficult to interpret (e.g., if contamination is suspected or an SLN is located near to the injection area) [112, 113].

When acquiring planar imaging, a ^{57}Co flood source can be positioned between the patient's body and the collimator in order to obtain some reference anatomic landmarks in the scintigraphic image (see Fig. 5). Alternatively, the body contour can be delineated by moving a ^{57}Co point source during scintigraphic acquisition (see Fig. 6). SPECT/CT acquisitions obviate the problem of identifying anatomic landmarks as a reference for topographic location of the SLN(s) (see Figs. 7 and 8) [109, 114–118].

Surface marks that provide a method to triangulate SLNs and to estimate their depths are desired by some surgeons. Surface locations should be marked on the skin with a small spot of indelible ink, and the depth of the node should

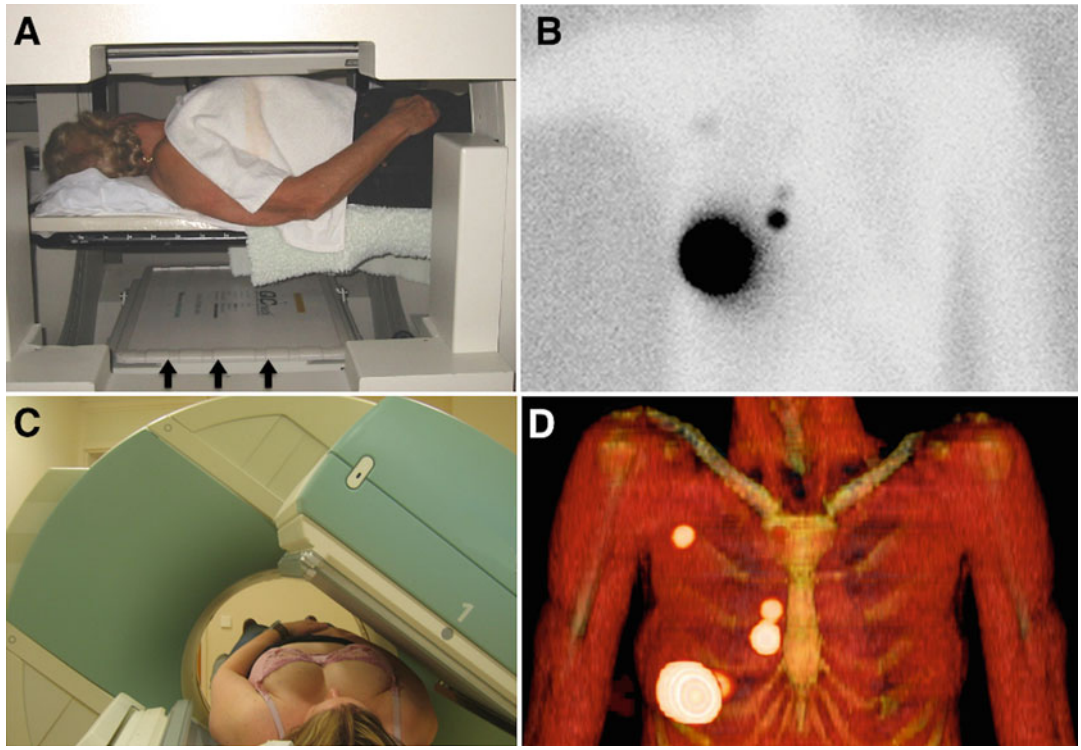

Fig. 5 Anatomical information in lymphatic mapping. (**a**) The use of a ^{57}Co flood phantom placed opposite to the gamma camera head (*black arrows*) provides body contour delineation in the anterior planar image (**b**) in a patient with cancer of the right breast and drainage to the right axilla and right internal mammary chain. In the same patient, subsequent SPECT/CT acquisition (**c**) leads to anatomically identify the axillary and parasternal sentinel lymph nodes after reconstruction of the fused SPECT/CT using volume rendering (**d**)

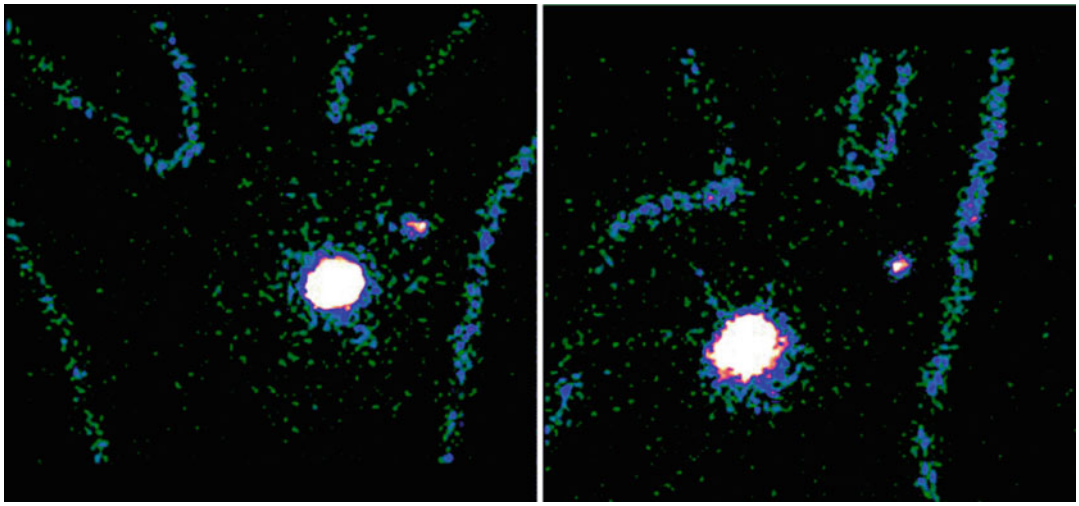

Fig. 6 Body contour delineation obtained by moving a ^{57}Co point source along the body of the patient during acquisition of the planar scintigraphic images. In this patient with cancer of the left breast, ^{99m}Tc-nanocolloidal albumin was injected at four spots periareorally. Images acquired both in the anterior projection (*left panel*) and in the left anterior oblique projection (*right panel*) visualize migration of the radiocolloid to a single sentinel lymph node in the axilla

be described. When marking the skin in the imaging process, an attempt should be made to position the patient's arm in the same position as it will be placed during surgery.

Image Interpretation

Early and delayed lymphoscintigraphic planar images identify SLNs in a majority of cases [71]. Major criteria to identify LNs as SLNs are the time of appearance and, occasionally, visualization of lymphatic channels (if dynamic imaging was performed). Usually, SLNs cannot be readily distinguished from second-tier LNs. The SLN is not necessarily the hottest node, although that is often the case. Separate lymphatic channels that drain to different LNs identify each of those as distinct SLNs, even though they may be located in the same anatomic region. When drainage to more than one anatomic region is seen, each of those regions has at least one SLN.

In current protocols SPECT/CT is performed following delayed planar images. This sequential acquisition is helpful to clarify the role of both modalities. For imaging interpretation the major criteria to identify LNs visualized on lymphoscintigraphy as SLNs are the visualization of lymphatic ducts, the time of appearance, the lymph node basin, and the intensity of lymph node uptake [105, 119]. Following these criteria visualized radioactive lymph nodes may be classified as:

(A) Definitively SLNs: this category concerns all LNs draining from the site of the primary tumor through their own lymphatic vessel or a single radioactive LN in a certain lymphatic basin.
(B) Highly probable SLNs: this category includes LNs appearing between the injection site and a first draining node or LNs with increasing uptake appearing in other lymph node stations.
(C) Less probable SLNs: all higher-echelon LNs may be included in this category.

Axillary LNs represent the main basin for breast lymphatic drainage, but different patterns can also occur in some cases. Drainage to the internal mammary basin is present in up to 35–40% of patients after intratumoral/peritumoral radiocolloid injection. Other unusually located SLNs are also observed in a non-negligible fraction of patients:

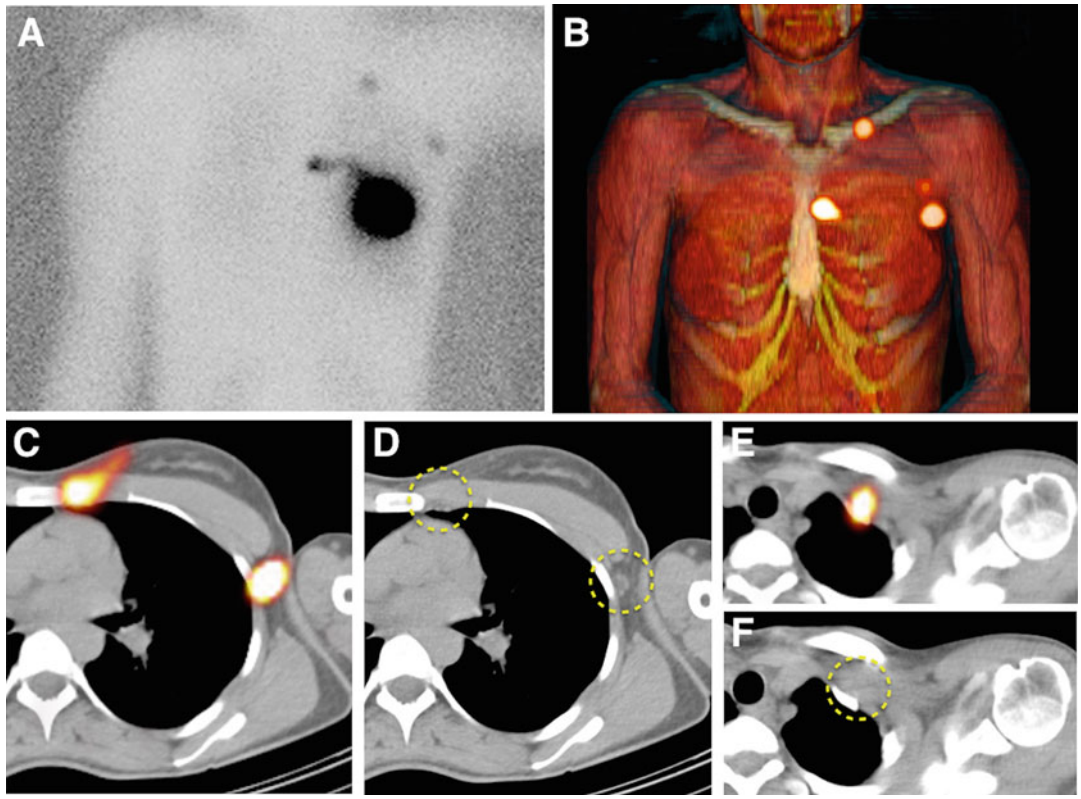

Fig. 7 Anatomical sentinel lymph node localization in breast cancer. Following deep injection of ^{99m}Tc-nanocolloidal albumin in the left breast, lymphatic drainage to the axilla, periclavicular area, and internal mammary chain is observed on anterior planar image (**a**) and on SPECT/CT fused imaging displayed with volume rendering (**b**). Lymph nodes are subsequently localized in the second intercostal space, level I of the left axilla, and behind the left clavicle (**c**–**f**)

intramammary (prepectoral) in 6%, interpectoral in 2%, and infraclavicular in 3% [120, 121].

The report to the referring physician should describe the orientations of the images acquired, the radiopharmaceutical, the method of administration, the amount and volume of activity injected, the location of the SLNs on each image, and any source of error or inaccuracy of the procedure.

The images and report should be available by the time the patient arrives in the surgical suite – in electronic form or as hard copy. If this is not possible, the critical information should be relayed directly to the surgeon. A close working relationship between the imaging department and the surgeon is critical for accurate dissemination of information regarding numbers and locations of sentinel lymph nodes.

Procedures in the Surgical Suite

Blue Dye Lymph Node Localization

Regarding the use of blue dye for optical guidance during surgery, there is general agreement that combined administration of radiocolloid and blue dye using both superficial injection and deep injection enhances SLN detection [38, 94, 97]. A possible advantage of the combined technique is where macrometastasis in the SLN may inhibit tracer accumulation [122, 123].

Blue dye can be injected around the primary tumor 10–20 min prior to surgery in a volume of 2–5 mL. The site of injection can be gently massaged after the administration or if the drainage of activity from the injection site is delayed at any time during the study [94]. Within 5–15 min, the

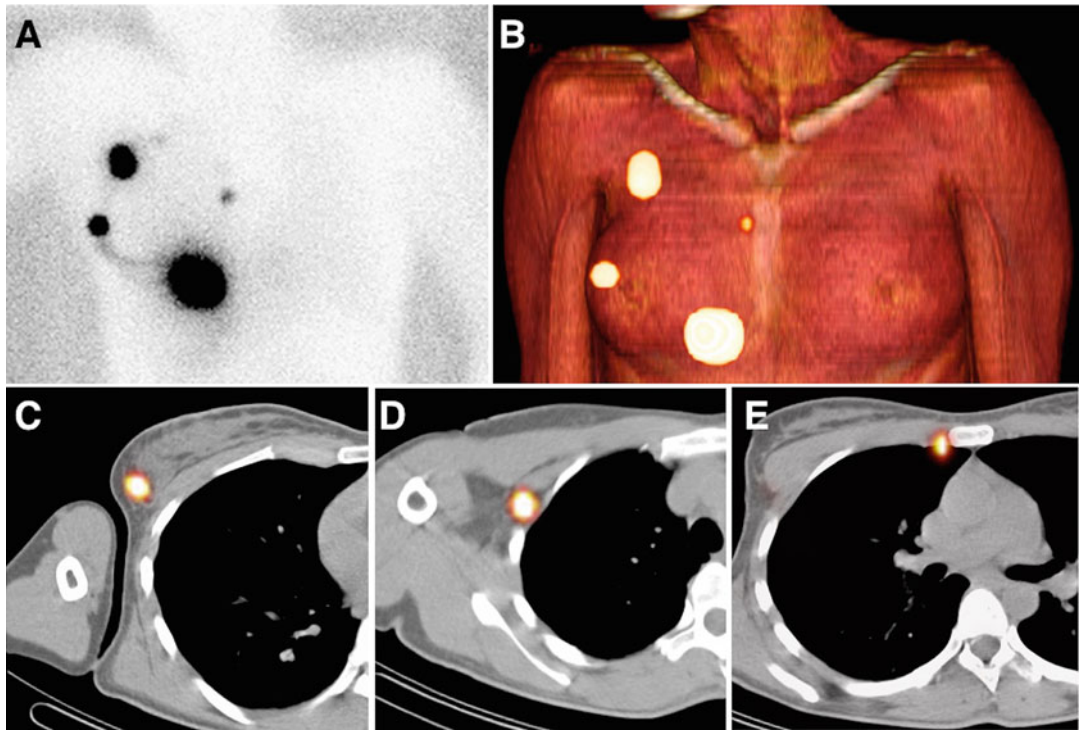

Fig. 8 Multidirectional lymphatic drainage after deep injection of ^{99m}Tc-nanocolloidal albumin on anterior planar image (**a**) in a patient with breast cancer in the medial inferior quadrant of the right breast. SPECT/CT with volume rendering (**b**) and axial fused SPECT/CT sections (**c**–**e**) depict ipsilateral sentinel lymph nodes in the breast, in the axilla, and in the internal mammary chain

SLNs are colored. Washout is evident after approximately 45 min.

Multiple studies have established the validity of blue dyes as markers for SLNs with reasonably high detection rates (ranging from 75% to 80%) [124]; nevertheless such rates are slightly lower than those achieved with radiocolloids. In most cases, the same SLNs are detected by the two methods. Disadvantages of using blue dyes are as follows: (i) impossibility to evaluate extra-axillary nodes, (ii) temporary blue tattooing of the skin or areola (for patients with breast conservation surgery), and (iii) induction of anaphylactic reactions (which require resuscitation in 0.5–1.0% of patients and that contraindicate its use in pregnant women) [124–131].

Radioguided Surgery

Intraoperative detection of SLNs is usually radioguided by a gamma-detection probe. Such probes should be designed and constructed to be suitable for intraoperative use, in order to be able to detect the SLN from the skin surface as well as within the exposed surgical cavity [26]. The probe is placed in a sterile bag to be used in the sterile surgical field. A display capable of providing clear instantaneous and cumulative counts is a major requirement. It is helpful if the instantaneous count rate is fed to an audio signal that conveys count rate information.

The count rates obtained with the gamma probe during surgery are recorded per unit time with the probe in the surgical field, over the node before excision (in vivo) and after excision (ex vivo). A background tissue count is also recorded with the probe pointing away from the injection site, nodal activity, or other physiological accumulation sites (i.e., liver) [71].

Just before starting surgery and with the patient positioned on the operating table, using the

images and skin markings as guides, the gamma probe scans the axilla or any other region where tracer accumulation has been visualized in order to confirm correct identification and localization of the SLN(s) and to select the optimum location for incision. This task requires the sensitivity of the detector to be sufficient to identify a weakly active SLN when attenuated by, typically, up to 5 cm of soft tissue. The surgeon then introduces the probe through the skin incision to guide dissection to the hot node(s). Discriminating activity counts within the SLN from those originating from nearby sites requires the probe to be well collimated with a small angle of view. The detector should offer a high level of shielding against radiation hitting the side of the probe assembly. However, when working with the probe, it is important to direct the probe away from activity at the injection sites.

When a hot SLN has been removed, the surgical bed should be checked to confirm removal of the hot node(s) and to evaluate remaining activity. Owing to the limited spatial resolution of the gamma camera, LNs closer than approximately 15–20 mm may appear on lymphoscintigraphy as one single hot spot; so, in some cases another hot node may still be present at a close location after removal of the hottest SLN. In this regard, the use of SPECT/CT imaging is very helpful because it may provide information about the actual presence of a cluster of LNs rather than a single SLN. When other sources of activity are found in the lymphatic basin, the decision of whether to remove them will depend upon the report from lymphoscintigraphy and the working definition of "nodes to remove" [132, 133]. In principle, SLNB requires the removal of all SLNs receiving direct lymphatic drainage from the site of the primary tumor. In practice, this is not always achieved. In cases with multiple radiolabeled LNs, it is often difficult to distinguish between SLNs and second-tier LNs. The issue of how many SLNs should be biopsied when multiple radioactive LNs are found is still debated. In this regard, while removing too few nodes may miss potential metastases in regional LNs, indiscriminate removal of all radioactive axillary nodes may cause morbidity similar to that experienced after conventional ALND (in addition to the unnecessarily increased burden for histopathological analysis).

Several operational definitions of the SLN have evolved over time in order to decide exactly which nodes should be removed to maximize the likelihood of locating the "true" biologic SLN and to minimize the superfluous removal of non-SLNs. Some authors base SLN identification on the absolute number of counts per second recorded for the presumed nodes, while others consider the ratio of the "in vivo" or "ex vivo" radioactive counts in the SLNs relative to background or to neighboring non-SLNs. Empiric thresholds corresponding to (i) 10% or 20% of the counting rate in the first LN removed (which is usually the most radioactive) or (ii) at least ten times the background count, taken at a location remote from the injection site, are widely reported in the literature [98, 134–137]. It is generally accepted that removing more than five LNs from the axilla does not result in marked improvement in the sensitivity of axillary SLNB [138–143]. If blue dye is used, it can be a useful adjunct for aiding SLN localization and harvesting. Blue dye generally results in a lower SLN detection rate than radiotracers, but it can be used in addition to radiocolloids. Following injection, the blue dye drains to the SLNs, staining the channels, which can be followed to the first-echelon nodes. Direct visualization and dissection of these channels facilitate SLN localization.

Deeply located SLNs are difficult to detect intraoperatively because of tissue attenuation; furthermore, the large amount of radioactivity retained at the injection site may cause nearby located SLNs to be hidden because of the shine-through effect. Patients who have undergone previous breast surgery or radiation may demonstrate nodes in locations not typically seen in patients without a history of prior surgery. The lymphatic duct to the original SLN may be obstructed by tumor growth or the original SLN may be entirely replaced by disease. Consequently, lymphatic drainage may be either diverted to a non-sentinel node or no lymph

nodes may be visualized, increasing false-negative results.

The use of SPECT/CT images can help localization of focal activity [144] as can the use of intraoperative imaging with portable gamma cameras; the latter imaging equipment is generally used simply to verify that all radioactive lymph nodes of interest are removed [4]. Finally, to minimize false-negative results, the open axilla should be palpated and suspicious lymph nodes harvested, even if these are neither hot nor blue.

SLN Non-visualization or Failed Intraoperative Detection

It is important to consider that when an SLN is not detected intraoperatively, this corresponds to a failure of the method and not to a false-negative case (better defined as when an axillary relapse is observed despite a prior negative SLNB). The majority of patients with preoperative lymphoscintigraphic SLN non-visualization will have at least one SLN detected intraoperatively, either by a gamma probe alone or by a gamma probe combined with blue dye. While logistically difficult in most centers, a second radiocolloid injection, following perhaps a different injection route, may be useful to visualize previously non-visualized SLNs.

In approximately 1–2% of the patients, SLNs will not be detected preoperatively or intraoperatively, and the status of axillary LNs cannot be determined. Old age, obesity, tumor location other than in the upper outer quadrant and non-visualization of SLNs on preoperative lymphoscintigraphy may be associated with failed SLN localization [142]. The significance of preoperative scintigraphic SLN non-visualization is not yet known. Some studies have suggested that patients with unsuccessful axillary mapping may have an increased risk of metastatic axillary involvement [145]. There is no definitive consensus on what to do if an SLN cannot be visualized. However, current standards of care recommend axillary LN dissection when intraoperative SLN identification is not achieved [146].

New approaches and strategies have been proposed in case of failure to visualize SLN(s) with conventional lymphoscintigraphy. Recently, Pouw et al. demonstrated in a large cohort of patients that SPECT/CT provided SLN visualization in 23.2% of cases with non-visualization of the SLN on planar imaging (66/284). In those patients receiving reinjection after persistent SPECT/CT non-visualization, the SLN visualization rate reached 62.1% (36/58). Thus, an adjustment of the clinical protocols (logistically not easy) may be proposed when no SLN is visualized during planar imaging [147].

Histopathology of SLNs

Detailed histopathological analysis of the SLN is the standard procedure on which to base selection of the postoperative management strategy of breast cancer patients. By focusing on only a few lymph nodes rather than on 15–20 nodes as generally harvested during an axillary dissection, the pathologist can completely dissect and examine at 50–100 μm intervals each SLN. However, protocols for SLN analysis have not yet been standardized; therefore, high variability in procedures still exists among different centers.

Immunohistochemistry (IHC) considerably improves sensitivity by identifying micrometastases and even isolated tumor cells, which are generally missed with conventional hematoxylin and eosin (H&E) staining alone [148, 149]. Methods for molecular biology analysis, such as those based on the reverse transcription polymerase chain reaction, are also being used for SLN analysis, although they are generally characterized by relatively poor reproducibility and longer time for analysis. Nevertheless, equipment for fast, even intraoperative, analysis has recently been made commercially available; a potential disadvantage of such new techniques is that the whole SLN is usually homogenized and processed for molecular analysis, without parallel conventional histopathologic analysis being conducted [150, 151].

Different procedures for intraoperative SLN analysis have been developed, including the touch imprint of one or more slices (relatively low sensitivity, but very high specificity), staining of one or several intraoperative frozen sections, and even IHC for cytokeratins as the most exhaustive method. In this case, if the SLN has

metastasis, it is possible to perform ALND immediately. On the other hand, if complete intraoperative histopathologic evaluation of the SLN is not performed, it is necessary to wait for definitive histology usually obtained within a week. If metastases are detected, ALND may be performed with a second procedure.

No significant difference exists in terms of 5-year survival rate between patients with SLN-positive and those with SLN-negative metastases by IHC. Consequently, it would seem that SLN micrometastases identified only by IHC are clinically insignificant and that IHC staining of SLNs appears to be unnecessary. IHC should be limited to particular cases, such as infiltrating lobular carcinoma, for which it is difficult to detect SLN metastases with H&E staining alone [78, 152, 153].

Qualifications and Responsibilities of Personnel

SLN studies should only be performed by surgeons and nuclear medicine specialists who have received specific training in such procedures [154].

An initial supervised learning phase is recommended to harmonize and optimize interaction between these specialists. The most important parameters to test such a multidisciplinary team are (a) percentage of SLNBs successfully identified and (b) percentage of false negatives.

It is often considered that 20–40 procedures under guidance are sufficient in order to implement radioguided SLNB into the routine clinical practice of a given hospital. These numbers, however, are highly variable, and SLNB should only be introduced to clinical practice where the team demonstrates high identification rate and accuracy [40, 71, 78, 98, 155, 156].

Clinical Controversial Aspects

T3–T4 Tumors

The evidence regarding the safety of sentinel node biopsy is mainly based on studies including T1 and small T2 tumors only [71, 78, 157–160]. However, a few reports suggest that false-negative rate and axillary recurrence reported in larger tumors are similar [63, 161].

Multiple (Multifocal/Multicentric) Tumors

Multifocal breast cancer is defined as separate foci of ductal carcinoma more than 2 cm apart within the same quadrant, while multicentric breast cancer indicates the presence of separate independent foci of carcinoma in different quadrants [101]. Until recently, SLNB was contraindicated in patients with multicentric and multifocal breast cancer because it was believed that it was difficult to localize the true SLN, and a negative SLNB would not exclude the possibility of positive LN metastasis in basins draining from other regions of the breast. However, most of the mammary gland can actually be considered as a single unit with lymph drainage to only a few designated lymph nodes in the axilla [93, 162]. In this regard, the efficacy of SLNB in patients with multifocal/multicentric cancer has been shown to be equal to that in patients with unicentric breast cancer. This means that the presence of multiple tumors should not affect lymphatic drainage and the possibility to perform SLNB with superficial injection [163, 164]. Nevertheless, it should be noted that the prevalence of axillary metastases seems higher in multifocal or multicentric tumors. Furthermore, high false-negative rates have been reported [165]. However, even if there are limited and heterogenic data on the efficacy and safety of SLNB in multiple breast cancer [102, 166], the reported axillary recurrence rates are acceptable, and the SLNb may be performed in patients with multifocal or multicentric tumors [63, 101, 163].

Ductal Carcinoma In Situ (DCIS) and Breast-Conserving Surgery

By definition, DCIS does not metastasize to regional lymph nodes. However, controversy exists over the use of SLNB in patients with preoperative diagnosis of DCIS [167]. In fact, core needle/vacuum-assisted minimally invasive biopsy may be affected by sampling error; invasive disease is found at surgery in about 15–30% of patients with DCIS [168, 169]. Because of the low prevalence of metastatic involvement and the feasibility of SLNB after breast-conserving surgery, SLNB should not be considered a standard procedure in the treatment of all patients with

DCIS, but only recommended in those patients undergoing mastectomy [170–172]. However, wide local excision before SLNB can alter lymphatic drainage, especially to the internal mammary nodes (IMNs) [173, 174]. Thus, SLNB could also be an option in women treated with breast-conserving surgery when there is a high risk of invasive cancer at final diagnosis (i.e., palpability of the lesion or presence of a mammographic mass) [175].

Suspicious Palpable Axillary Nodes

Palpable axillary LN may be tumor negative in up to 40% of the patients [176, 177]. The proportion is lower when considering suspected LN identified by noninvasive techniques during preoperative staging (US, CT, MRI, or [^{18}F]FDG-PET). In any case, axillary ultrasound with fine needle aspiration cytology or core needle biopsy from the suspicious nodes is a widely accepted policy. In that case, SLNB can be performed in patients with palpable LNs, if negative in the preoperative diagnosis. However, the suspicious, palpable LNs should be harvested for histopathological evaluation, even when neither hot nor blue.

Evaluation of Internal Mammary and Other Extra-Axillary Nodes

Although the IMNs, in the same way as the axilla, are a first-echelon nodal drainage site in breast cancer, the importance of their treatment has long been debated [71, 178]. Randomized trials have failed to demonstrate a survival benefit from surgical internal mammary chain (IMC) dissection, and several retrospective studies have shown that IMNs are rarely the first site of recurrence [179–184]. However, the recent widespread adoption of SLNB has stimulated a critical reappraisal of such early results. Furthermore, the virtually systematic application of adjuvant systemic and/or locoregional radiotherapy encourages reexamination of the significance of IMN metastases [185]. There is strong evidence that postmastectomy radiotherapy to chest wall and nodal basins (including IMC) reduces both recurrence and breast cancer mortality in axilla-positive patients, even when systemic therapy is given [186]. However, internal mammary radiation remains controversial, mainly because of the difficulties in selecting patients at risk of occult internal mammary involvement [187, 188].

It is generally recognized that mapping of IMNs requires deep injection of the lymphatic mapping agent, either peritumorally or intratumorally [99, 100, 189]. Moreover, the fused SPECT/CT images represent a further technical solution to increase the identification rate of IMNs. Nevertheless, the rates of detection and intraoperative harvesting of IMNs are much lower than those for axillary LNs. Visualization of the IMNs has been detected in approximately one third of patients with breast cancer receiving deep radiocolloid injection, of which about 63–92% could be harvested during surgery, and 11–27% of them had metastases [178, 190–192].

In conclusion, there is no doubt that IMN metastasis has prognostic significance similar to prognostic importance to axillary nodal involvement [193–195]. However, the significance of IMN biopsy is not clear. There is evidence that IMN mapping leads to upstage migration and to modifications of treatment planning with respect to radiotherapy and systemic therapy, but more evidence is necessary to support the idea that IMN mapping will improve the outcome of treatment and survival, perhaps because IMN drainage at lymphoscintigraphy is more difficult to demonstrate than axillary drainage [178, 196]. Thus, an "integrated and multidisciplinary technique" is required to evaluate IMN drainage [192, 197].

Previous Surgery

Although the lymph drainage is probably changed in patients who have undergone previous breast surgery, current data indicate that lymphatic mapping is feasible with accuracies comparable to the results obtained in the general population [198–200].

Prior excisional biopsy: The lymph drainage pattern may be altered in patients who have undergone prior procedures, as non-axillary drainage has been identified more often in reoperative SLNB than in primary SLNB. In 73% of such patients, migration to the regional nodal drainage basins has been noted in ipsilateral axillary, supraclavicular, internal mammary, interpectoral, and

contralateral axillary nodes [173, 201–203]. However, there is evidence that sentinel node biopsy performed in the area of previous breast biopsy is not affected significantly by the prior procedure as regards success of the second procedure [204, 205].

Prior other breast surgeries: SLNB can be performed in patients undergoing breast surgery due to a local recurrence after breast conservation surgery in patients with DCIS. Although plastic surgery for breast augmentation or reduction requires major tissue movements, it does not contraindicate the SLN procedure [206, 207].

Prior axillary surgery: A second SLNB can be performed in patients with a local recurrence after breast conservation surgery and negative axillary SLN biopsy, although the success rate may be lower when compared with a primary SLN biopsy. Furthermore, extra-axillary SLNs are visualized more frequently in this group of patients. Encouraging results have been reported regarding axillary recurrences but, due to the rarity of the cases, the evidence is not solid. On the other hand, there is no evidence that these patients benefit from diagnostic axillary lymph node dissection [208].

Axillary Lymph Node Dissection

Review of surveillance, epidemiology, and end-result data has shown that the use of ALND for SLN metastasis has decreased in recent years [53, 209]. Actually, the management of breast cancer continues to advance toward more minimally invasive approaches, and the role of ALND for patients whose SLNs contain metastases is likely to become less important in the future. Cancer biology is much better understood now than it was when ALND was introduced. Consequently, the decision to administer systemic therapy is influenced by a variety of patient- and tumor-related factors, with lymph node tumor status influencing [210–212], but not necessarily dictating the use of chemotherapy [213–215].

Indeed, a high rate of locoregional control is achieved with modern multimodality therapy, including axillary radiotherapy (ART), even without ALND. Likewise, no significant difference is observed in disease-free survival or in overall survival between SLN plus ALND and SLN-only groups for selected patients with early nodal metastases, suggesting that ALND might not be required for all SLN-positive breast cancer women [216–219].

Thus, the ASCO Update Committee recommended that clinicians should avoid ALND in cases of women affected by early-stage breast cancer with one or two SLN metastases, who will receive breast-conserving surgery with conventionally fractionated whole-breast radiotherapy. Instead, clinicians might offer ALND to women suffering from early-stage breast cancer with nodal metastases found on SLNB who will receive mastectomy [43, 44, 50, 220–222].

Neoadjuvant Chemotherapy

Neoadjuvant systemic chemotherapy (NACT) is established for locally advanced breast cancer and is increasingly used for early-stage disease as well [223, 224]. Debate is ongoing on whether SLNB is accurate enough after NACT or whether it should be performed before starting NACT. Performing SLNB before or after primary systemic treatment has advantages and disadvantages in both cases. Before NACT, SLNB yields a more precise axillary staging, with useful information about possible nodal spread. Nevertheless, the procedure can postpone the beginning of treatment, and two surgeries may be necessary. After NACT, SLNB may lead to an underestimation of the initial stage of the disease because the tumor regression pattern in the axilla is unknown [225–227]. On the other hand, axillary nodal status after NACT is a highly significant prognostic factor. Pathologic complete response in the axilla can be achieved in up to 40% of patients. These patients can be spared ALND and the associated morbidity. Available data show that SLNB following NACT in cN0 patients is acceptable [226, 228–238].

A second issue concerns the possibility to perform SLNB in patients with initial node-positive disease who are downstaged by NACT to cN0. At present, SLNB may not be routinely recommended after NACT in patients with prior metastatic nodes. Changes in approach and patient selection would be necessary to support

the use of SLN surgery as an alternative to ALND in this patient population [160, 239–243].

Pregnancy

Many studies have demonstrated that prenatal doses from sentinel node imaging, when properly performed, are low enough that they do not significantly increase the risk of prenatal death, malformation, or mental impairment (see further below in the "Radioprotection" section) [244–247]. Thus, pregnancy is not an absolute contraindication for SLNB, in patients with early lesions and clinically/US negative axilla, but it is recommended to reduce the time interval between lymphoscintigraphy and surgery in order to reduce the injected activity (i.e., using a single day protocol). Furthermore, since small quantities of the radioactive colloid may be excreted with breast milk, lactation should be suspended for 24 h after radiopharmaceutical administration. It is also important to consider that vital dyes may have some contraindications in pregnancy [248–250]. Pregnant women with breast cancer should be followed by a multidisciplinary team and be clearly informed about the potential risks of radioactive tracers balanced against the risk of delaying therapy or omitting nodal staging [248, 251].

Primary Localizing Techniques

ROLL

Screening programs for breast cancer have led to an increase in detection of non-palpable breast tumors. Current approaches to breast cancer surgery aim at removing the lesion with an adequate clearance margin while, at the same time, accurately assessing the risk of distant metastases. Effective localization procedures are required to ensure complete excision of small non-palpable lesions detected on either symptomatic mammography or screening mammography. Several localization techniques have been developed for this purpose.

Hook-wire localization of non-palpable lesions has been the most widely used preoperative technique for many years. Although this is a reasonably effective technique, it involves a number of disadvantages. First, the entry site of the wire is often not at the ideal location for surgical incision at the time of operation. This may lead to additional unnecessary dissection and suboptimal cosmetic results. In addition, the wire must be placed on the day of operation, necessitating the coordination of radiology and operative schedules. The most important disadvantage, however, is the inaccuracy of localizing the target lesion percutaneously and during dissection. This results in high rates of reoperation for tissue margins involved in carcinoma [252, 253].

Intraoperative US imaging without preoperative wire localization has been used to map excision of non-palpable breast lesions; however, this technique has limitations, as it is feasible only in patients whose breast lesion is visible at US imaging [254–259].

The "radioguided occult lesion localization" (ROLL) approach [260–262] has gained popularity for non-palpable tumor lesions, including breast cancer. ROLL involves injection, into the center of the lesion, of a small amount of radioactive tracer that does not migrate from the site of interstitial injection, typically ^{99m}Tc-MAA. Injection is performed on the same day or on the day before surgery, under mammographic or US guidance (activity injected ranges from 2 to 150 MBq). Surgeons identify the lesion intraoperatively as a hot spot by using a handheld gamma probe, which allows accurate lesion localization and removal with minimal excision of healthy tissue (the skin incision is made at the site with highest counts or at a site suitable for oncoplastic breast surgery). After specimen resection, residual activity in the surgical field must be checked to avoid the possibility of missing some residual involved tissue [263]. This technique enables a good cosmetic outcome.

ROLL is a well-tolerated and feasible technique for localizing early-stage breast cancer in the course of breast-conserving surgery and is a suitable replacement for wire-guided localization [264–268]. Reported advantages of the ROLL technique include (i) easy and precise intraoperative localization of the breast lesion; (ii) complete lesion resection, with free margins and reduced needs for second operations; (iii) an

Table 3 Studies comparing ROLL and hook-wire techniques [266]

Authors	*n* (ROLL–hook wire)	Detection (%)	Free margins (ROLL versus hook wire) (%)	*p*
Gallegos, 2004	132 (65–67)	100	83 versus 64	0.014
Macmillan, 2004	95 (48–47)	100	61 versus 72	NS
Nadeem, 2004	130 (65–65)	100	83 versus 57	0.001
Thind, 2005	140 (70–70)	100	84 versus 60	0.002
Zgajnar, 2004	143 (51–92)	100	70 versus 44	
Rönkä, 2005	78 (64–14)	100	89 versus 79	0.05
Fraile, 2005	233 (65–168)	100	80 versus 70	NS
Strnad, 2006	33 (21–12)	100	Hook wire < ROLL	NS

increased capacity to center the lesion within the specimen; and (iv) a surgical approach (skin incision) that is independent from the intralesional radiotracer injection procedure [269–273]. Some potential pitfalls have been described; these are related to possible radiotracer spillage, contamination of the skin, or the injection path or ductal diffusion, as well as the presence of microcalcifications or DCIS [270, 271]. However, a systematic review of the ROLL technique concluded that this approach compares favorably to conventional wire localization for non-palpable breast lesions (Table 3) [267].

It is important to notice that radiation doses at the injection site and patient and staff absorbed doses are maintained well within the recommended limits established by the International Commission on Radiological Protection (ICRP) [274]. Finally, the possibility of performing ROLL after systemic intravenous administration of ^{99m}Tc-sestamibi (as a nonspecific, tumor-seeking agent) on the day of surgery has also been described [275].

SNOLL

As ROLL is an excellent technique enabling the removal of small breast cancers, the possibility to simultaneously perform SLNB without compromising oncological safety and the SLN detection rate is very important. Different techniques have been described to identify the SLNs in combination with ROLL, the so-called sentinel node occult lesion localization (SNOLL) [269, 276–284].

An intratumoral injection of ^{99m}Tc-MAA for ROLL of a tumor may be associated with a subdermal injection of ^{99m}Tc-nanocolloid for SLN mapping and SLNB. When the lesions are located near to the areola, intraoperative interference between the tracers could be avoided by elevation of the dermis and the subdermal area after skin incision [276]. Another possibility is to use a single intratumoral injection for both ROLL and SNOLL in the same session [280]. As a single procedure for localization of breast lesions and sentinel nodes, SNOLL may improve the entire surgical procedure. The majority of the studies published so far show a high percentage of successful tumor resection and intraoperative SLN localization with reduced failure [267, 269, 276, 279–284].

Radioactive Seeds

Alternatives to hook-wire localization of occult breast lesions include carbon trace as well as the use of sealed radioactive seeds. The seeds are essentially the same as the ones used in brachytherapy for cancer of the prostate, namely, a 4.5–0.8 mm titanium capsule containing a ceramic cylinder enriched with ^{125}I-iodine. Iodine-125 has a long decay time (half-life of 59.4 days) and emits low-energy photons (27 keV). The use of one or two seeds with this low photon energy has a negligible effect on the surrounding tissue. The radioactive seed is placed in the center of the breast lesion using an 18 G needle fixed in a needle holder under mammographic or ultrasonographic guidance; after successful positioning, the exact location is confirmed by mammography. During surgery, excision of the lesion is guided by using a handheld gamma probe [285].

If a SNOLL technique is scheduled, the ^{99m}Tc-colloid is subsequently injected, around the tumor or through a superficial route. Thus, the handheld gamma probe can be switched between the 27 keV energy window of the ^{125}I source and the 140 keV of ^{99m}Tc, allowing discrimination between the emissions of the two radioisotopes. Effective seed removal is verified by the absence of ^{125}I activity in the breast and its presence in the specimen. X-ray of the surgical specimen may confirm the presence of the seed and the relation of the lesion to the resection margins.

It has been shown that radioguided seed localization in non-palpable breast lesions is at least equivalent to the hook-wire technique in terms of ease of procedure, removing the target lesion, volume of breast tissue excised, obtaining negative margins, avoiding a second operative intervention, and allowing for simultaneous axillary staging [285–289].

Added Value of Intraoperative Portable Gamma Cameras

Recently, several types of portable or handheld mini gamma cameras have become available for clinical practice; while some of these portable gamma cameras are not specifically designed for radioguided surgery, other models are focused on different applications of SLNB [4, 5, 290, 291].

Appropriate use of a portable gamma camera enhances the reliability of the gamma probe by adding a clear image of the surgical field. The use of an intraoperative imaging device implies the possibility to better plan the surgical approach, to localize surgical targets in complex anatomical areas, to monitor the lymphatic basin before and after removal of the hot nodes, and, above all, to verify the correct SLN excision. Moreover, the use of point sources (e.g., ^{133}Ba or ^{125}I) facilitates SLN localization, as these sources can be depicted separately on the screen of the portable gamma camera, thus functioning as a pointer in the search for the SLNs. Nevertheless, their role in breast cancer surgery is still to be clarified. Intraoperative imaging using a portable gamma camera might be useful only when no conventional gamma camera is available for preoperative imaging, in particular in cases with extra-axillary drainage. Portable gamma cameras have also been used with promising results in other GOSTT environments regarding breast cancer, such as in ROLL or SNOLL procedures [290–296].

An interesting recent development of intraoperative imaging consists in combining conventional gamma probes with position and orientation tracking systems such as the so-called freehand SPECT, which permits a virtual reconstruction in a 3D environment (see Fig. 9) [4, 5, 293]. All these technologies will play an increasing role in the future extension of the GOSTT concept, in order to provide a better roadmap for radioguided surgery [2, 5].

Radioprotection

Nuclear medicine, surgery, and pathology professionals are involved if a radiopharmaceutical is used in a sentinel node procedure. Each involved practitioner (nuclear physician, surgeon, personnel in the surgical suite, pathologist) and the patient undergoing SLN and/or ROLL procedures are exposed to radiation. The exposures received by each, when radioactive activities standard for SLN procedures are administered, are well below recommended limits for both public and occupational exposures.

Estimates of radiation exposures for patients [244, 297–302], surgeons [299–301, 303–309], and pathologists [299–311] have been reported by several investigators. Table 4 presents a summary and interpretation of most of the available data. The estimates in the second column were extracted or derived from information in the included references. The values in the third column assume that SLN procedures were conducted on 100 patients in a year and assume that each patient was injected with an activity of 18.5 MBq. Columns four and five are International Commission on Radiological Protection (ICRP) recommended public and occupational limits [310].

Repeated measurements have clearly demonstrated that exposures to patients and personnel involved in radioguided SLN procedures (surgeon, nurse, pathologist) are minimal. Since exposures in SLN procedures of all nonnuclear medicine personnel are sufficiently low, none

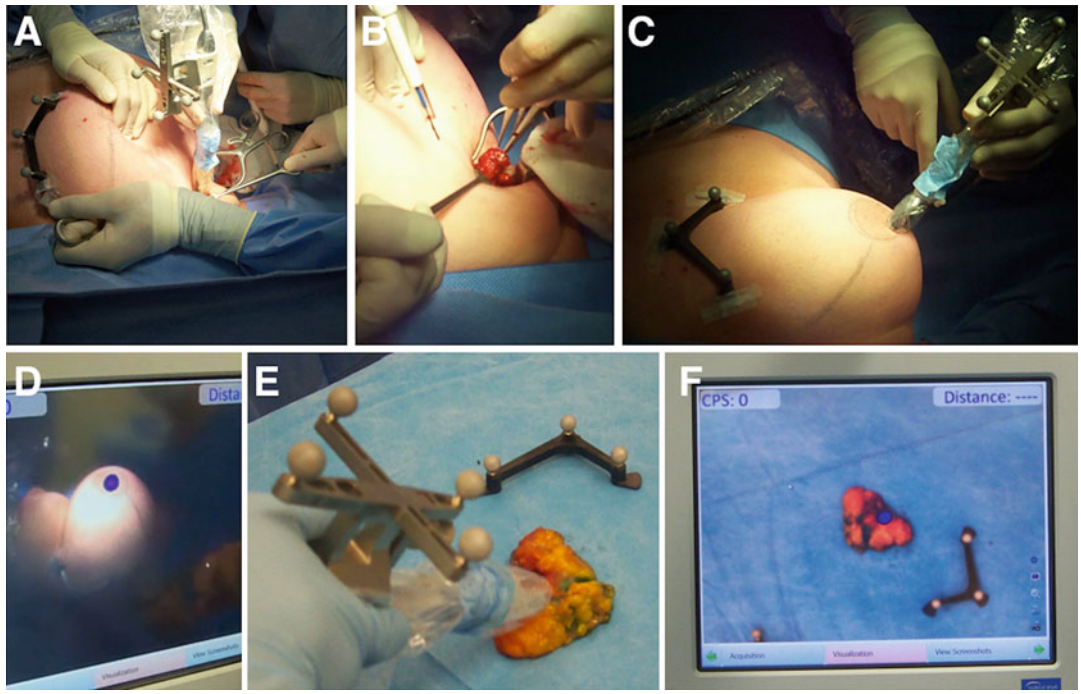

Fig. 9 Radioguided sentinel lymph node and occult lesion localization (SNOLL) in a patient with breast cancer using a single intratumoral injection of ^{99m}Tc-nanocolloidal albumin. Using a freehand SPECT probe (**a**), first the axillary sentinel lymph node is removed (**b**). Subsequently, the primary lesion is detected (**c**) following an image-guided procedure (**d**). Finally, the freehand SPECT probe (**e**) is used to visualize the primary tumor in relation to the margins of the specimen (**f**)

need be monitored routinely for occupational radiation exposure. Low patient effective doses and very low fetus/uterus equivalent doses [244, 299, 312–314] indicate that exposure to radiation is not a contraindication for an SLN procedure on any patient, including pregnant women. However, prudence dictates care should be exhibited when conducting an SLN procedure on any patient. For patients who are breastfeeding, nursing should be suspended for 24 h following radiopharmaceutical administration. Obviously, when using a ^{57}Co flood transmission source or SPECT/CT imaging, the total exposure is the emission-generated dose plus the transmission-generated dose [315].

Although the dose absorbed at the injection site can be relevant (see Table 4), there are no known negative consequences at the injection site. In fact, the site is often, though not always, excised. Furthermore, the radiation dose caused by the radionuclide-based procedure is very small relative to that received from postoperative radiation therapy.

Because exposures in SLN procedures of all nonnuclear medicine personnel are sufficiently low, none need be monitored routinely for radiation exposure. Finally, contamination with residual radioactivity of material from the operating room (surgical gauzes, liquids, and biological tissues of the patient) is minimal already at the time of surgery. Due to the fast physical decay of ^{99m}Tc, it is sufficient to wait only a few hours before disposal of operating room material to ensure an almost nonexistent radioactivity exposure to personnel [299].

Future Perspectives

The possibility of combining currently used radiotracers with other imaging agents opens new avenues for further developments. In this regard, hybrid tracers containing both a radioactive and a fluorescence label have recently been introduced (see Fig. 10), thus enabling the direct

Table 4 Ranges of estimates of radiation exposures (Modified from [71])

Radiation exposure	Range of estimates (mSv/MBq)	×18.5 MBq	×100 patients/ year (mSv/year)	Public limit (mSv/year)	Occupational limit (mSv/year)
Injection site absorbed dose	1–50	<925			
Injected breast equivalent dose	0.03–0.8	<15			
Patient effective dose	0.002–0.03	<0.56		<1	
Fetus/uterus equivalent dose	0.00003–0.0009	<0.017		<1	
Surgeon lens-of-eye equivalent dose	0.00009		<0.17	<15	<150
Surgeon hand equivalent dose	0.0004–0.01		<19	<50	<500
Surgeon effective dose	0.00004–0.0003		<0.56	<1	<20
Pathologist lens-of-eye equivalent dose	0.00001–0.00003		<0.056	<15	<150
Pathologist hand equivalent dose	0.00001–0.001		<1.9	<50	<500
Pathologist effective dose	0.000004–0.0002		<0.37	<1	<20

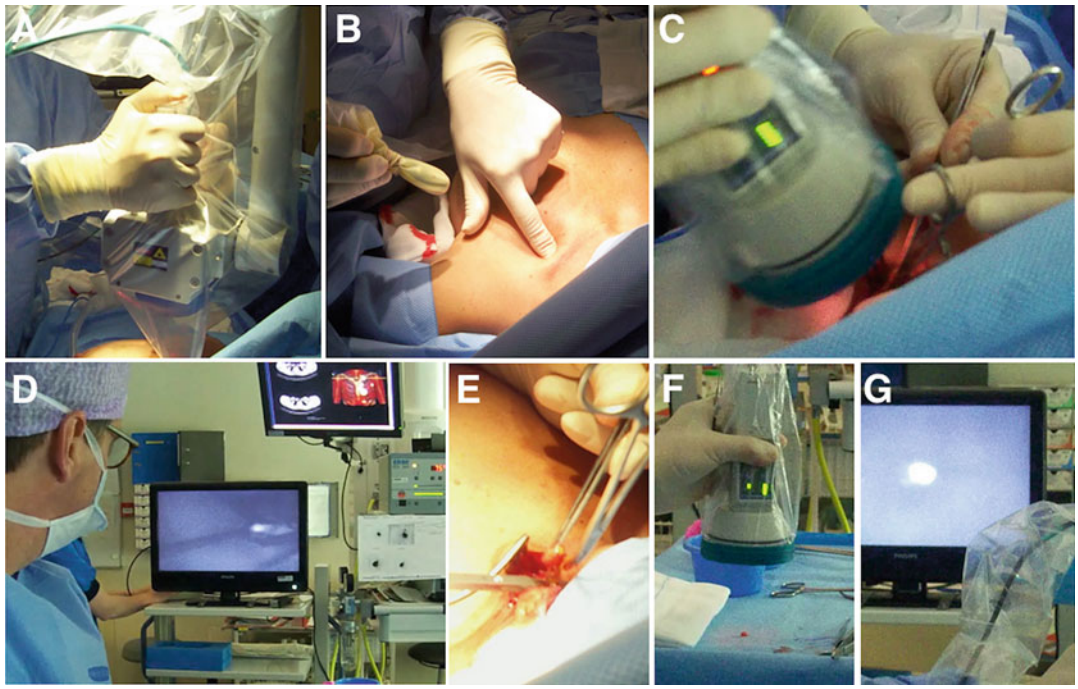

Fig. 10 Resection of an infraclavicular sentinel lymph node in a patient with high-risk breast cancer using the hybrid tracer ICG-^{99m}Tc-nanocolloid. The sentinel lymph node is first located on the skin projection using a portable gamma camera (**a**) and a handheld gamma probe (**b**). Subsequently, a portable near-infrared camera (**c**) is used to depict the fluorescence signal on the screen (**d**). This enables to remove the node (**e**) and to perform ex vivo control of the fluorescence signal (**f**, **g**)

integration of conventional preoperative imaging with intraoperative radio- and fluorescence guidance to the SLN via one single tracer injection [54].

Competitive methods are emerging: the techniques for SLNB that are not radioactivity-dependent or that refine the existing method (i.e., indocyanine green fluorescence, contrast-enhanced ultrasound using microbubbles, and superparamagnetic iron oxide nanoparticles) are particularly interesting [316–332]. In particular, the SentiMAG Multicentre Trial demonstrated that the magnetic technique with superparamagnetic iron oxide (SPIO) is feasible for SLNb, with an identification rate that is not inferior to the standard technique [333–337]. Recently, it has been shown that the SLN status can be evaluated with high accuracy preoperatively using contrast-enhanced color Doppler ultrasonography [338, 339].

However, a systematic review suggested that these new methods have clinical potential but yield high levels of false-negative results and presently cannot challenge the existing standard procedure. Further assessment of these techniques against the standard dual technique in randomized trials is thus needed [340].

Concluding Remarks

The development and wide acceptance of SLNB has deeply affected the management of breast cancer. Several technical and clinical controversies have been raised during the development of this technique. The resolution of these controversies should result in the standardization of the procedure and in the expansion of the number of patients evaluated with SLNB in the future. The modern approach in breast cancer care, which includes more detailed screening diagnostics, pathological evaluation, improved planning of surgical and radiation therapy, and more effective systemic treatment, emphasizes the need for ongoing re-evaluation of the "standard" locoregional therapy [341, 342].

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