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GUIDELINES

The EANM and SNMMI practice guideline for lymphoscintigraphy and sentinel node localization in breast cancer

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Abstract
Purpose The accurate harvesting of a sentinel node in breast cancer includes a sequence of procedures with components from different medical specialities, including nuclear medicine, radiology, surgical oncology and pathology. The aim of this document is to provide general information about sentinel lymph node detection in breast cancer patients.
Methods The Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the European Association of Nuclear Medicine (EANM) have written and approved these guidelines to promote the use of nuclear medicine procedures with high quality. The final result has been discussed by distinguished experts from the EANM Oncology Committee, the SNMMI and the European Society of Surgical Oncology (ESSO).
Conclusion The present guidelines for nuclear medicine practitioners offer assistance in optimizing the diagnostic information from the SLN procedure. These guidelines describe protocols currently used routinely, but do not include all existing procedures. They should therefore not be taken as exclusive of other nuclear medicine modalities that can be used to obtain comparable results. It is important to remember that the resources and facilities available for patient care may vary.

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Preamble

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the European Association of Nuclear Medicine (EANM) have written and approved guidelines to promote the use of nuclear medicine procedures with high quality. These guidelines are intended to assist practitioners in providing appropriate nuclear medicine care for patients. They are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care. For these reasons and those set forth below, the SNMMI and EANM caution against the use of these guidelines in litigation in which the clinical decisions of a practitioner are called into question.

The ultimate judgment regarding the propriety of any specific procedure or course of action must be made by medical professionals taking into account the unique circumstances of each case. Thus, an approach that differs from the guidelines does not necessarily imply that the approach was below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in the guidelines when, in the reasonable judgment of the practitioner, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology subsequent to publication of the guidelines.

The practice of medicine involves not only the science, but also the art of dealing with the prevention, diagnosis, alleviation, and treatment of disease. The variety and complexity of human conditions make it impossible at times to identify the most appropriate diagnosis or to predict with certainty a particular response to treatment. Therefore, it should be recognized that adherence to these guidelines will not assure an accurate diagnosis or a successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The sole purpose of these guidelines is to assist practitioners in achieving this objective.

Introduction

The accurate harvesting of a sentinel node in breast cancer includes a sequence of procedures with components from different medical specialities, including nuclear medicine, radiology, surgical oncology, and pathology. The topics covered are presented under the headings: Goals; Background and Definitions; Common Clinical Indications and Precautions; Qualifications and Responsibilities of Personnel; Procedures in Nuclear Medicine; Procedures in the Surgical Suite; Radiation Dosimetry; and Issues Requiring Further Clarification.

The present guideline has been prepared for nuclear medicine practitioners. The intent is to offer assistance in optimizing the diagnostic information that can be obtained from sentinel lymph node (SLN) procedures. If specific recommendations given cannot be based on evidence from original scientific studies, referral is made to "general consensus" and similar expressions. The recommendations are designed to assist in the referral, performance, interpretation, and reporting of the SLN procedure.

Goals

The aim of this document is to provide general information about SLN detection in breast cancer patients. This guideline describes protocols currently used routinely, but does not include all existing procedures. It should therefore not be taken as exclusive of other nuclear medicine modalities that can be used to obtain comparable results. It is important to remember that the resources and facilities available for patient care may vary. The present guideline for nuclear medicine practitioners offers assistance in optimizing the diagnostic information from the SLN procedure. The final result has been discussed by distinguished experts from the EANM Oncology Committee, the SNMMI, and the European Society of Surgical Oncology (ESSO).

Background and definitions

Breast cancer is the most frequent cancer diagnosed in women worldwide [1]. SLNs are the regional nodes that directly drain lymph from the primary tumour. Thus, SLNs are the first nodes to receive lymph-borne metastatic cells [2]. After the description by Morton et al. of a method for SLN biopsy in the management of melanoma patients [3] two decades ago, SLN mapping and biopsy have been used in breast cancer [4]. Since then, SLN mapping and biopsy have become routine techniques in breast cancer management, contributing to the development of less-invasive surgical procedures [4–12].

Accurate lymph node staging is essential for both prognosis (of early-stage disease) and treatment (for regional control of disease) in patients with breast cancer. Lymphoscintigraphy (LS) allows the surgeon to easily identify and biopsy a SLN. No imaging modality is accurate enough to detect lymph node metastases when a primary breast cancer is at an early stage (I or II), but SLN biopsy is a highly reliable method for screening axillary nodes and for identifying metastatic and micrometastatic disease in regional lymphatic nodes [12–14].

Despite the widespread use of SLN biopsy for early-stage breast cancer, there is significant variation in performance characteristics reported for the procedure. Differences in study volumes and in lymphatic mapping techniques are two of the factors contributing to variations in the proportions of successful mappings [15]. 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 [15]. 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 [16].

Common clinical indications and precautions

Indications for a SLN procedure include, but are not limited to, those in the following discussion. Table 1 is a list of several indications, together with recommendations as to whether a SLN procedure is established standard care.

Table 1 Recommendations regarding use of SLN biopsy

Clinical circumstance	Use of SLN biopsy
T1 or T2 tumour	Established
T3 or T4 tumour	Controversial (see "T3 and T4 tumours")
Multicentric or multifocal tumour	Controversial (see "Multifocal and multicentric tumours")
Inflammatory breast cancer	Not recommended
DCIS with mastectomy	Established (see "Ductal carcinoma in situ")
DCIS without mastectomy	Controversial, except for DCIS with suspected or proven microinvasion (see "Ductal carcinoma in situ")
Suspicious, palpable axillary nodes	Controversial (see "Suspicious palpable nodes")
Older age	Established
Obesity	Established
Male breast cancer	Established
Pregnancy	Controversial (see "Precautions")
Evaluation of internal mammary lymph nodes	Controversial (see "Evaluation of internal mammary and other extra-axillary nodes")
Prior diagnostic or excisional breast biopsy	Controversial (see "Prior breast surgery other than excisional biopsy")
Prior axillary surgery	Controversial (see "Prior axillary surgery")
Prior nononcological breast surgery	Controversial (see "Prior breast surgery other than excisional biopsy")
After preoperative systemic therapy	Controversial (see "Neoadjuvant chemotherapy")
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 (see "Issues requiring further clarification")

DCIS ductal carcinoma in situ

Common indications

SLN localization and biopsy are now the "standard of care" for staging the axillary lymph nodes in breast cancer patients. These procedures have replaced routine staging axillary lymph node dissection (ALND) in patients with early-stage biopsy-proven breast carcinoma without cytologically or histologically proven axillary lymph node metastases [17, 18].

ALND is a standard treatment for patients with axillary metastases identified on SLN procedures. ALND is also an often-used option in the management of patients in whom a SLN is not identified intraoperatively, but what should be the standard care in such patients is unresolved. A treatment alternative in patients with metastatic axillary SLNs is axillary radiotherapy. These two treatment options (ALND and radiotherapy) are being compared in the EORTC AMAROS trial (ongoing) [19]. A concern regarding these patients arises from data suggesting fewer than 40 % of those with positive axillary SLNs have non-sentinel nodes with metastases [20]. Investigations to identify risk factors for non-sentinel node metastases have been conducted with the goal of identifying a subgroup in whom ALND could be omitted despite metastatic findings in axillary SLNs. The identified risk factors can be combined and normograms created to evaluate the risk of residual disease in the axilla [21–23]. Another concern regarding these patients arises from data obtained in a recent randomized study in which it was concluded ALND provides no advantage in SLN-positive patients with breast-conserving surgery and whole-breast radiotherapy [24, 25]. However, patients with micrometastases were overrepresented in this study, especially in the arm without ALND [25]. Also, the follow-up was too short to draw definitive conclusions regarding survival. Nevertheless, results suggest the majority of SLN-positive patients may not benefit from ALND [26–28].

Patients with negative axillary SLN biopsy by routine histopathological evaluation do not require ALND. The clinical significance of isolated tumour cells detected by immunohistochemistry is currently controversial [29]. Neither the St Gallen nor the American Society of Clinical Oncology (ASCO) guidelines recommend ALND in patients with isolated tumour cells in their SLNs [30–32].

Axillary SLN biopsy procedures are now preferred to ALND for routine axillary staging in early breast cancer [14, 30–34] in many if not most clinical scenarios, as detailed in Table 1 and in guidelines of the ASCO [32]. In these patients, SLN biopsy has a positive node rate similar to that observed in patients who have axillary lymphadenectomy [14, 35]. SLN biopsy has significantly lower morbidity than axillary lymphadenectomy [36], and it has nodal relapse rates at 5 years similar to those of axillary lymphadenectomy [37]. No significant differences in disease-free survival, overall survival, or local control of disease have been seen with a negative SLN [35].

Precautions

Pregnant patients

Pregnancy is not a contraindication for radiotracer-based SLN biopsy [18, 38, 39]. Blue dye should only be included in SLN biopsy in a pregnant woman if there is clear medical need. The use of SLN mapping involving the limited doses of radiotracers outlined in this guideline has been demonstrated to expose a fetus to a negligible dose, particularly when activities below 10 MBq are used [40]. In the case of pregnancy or lactation, LS and SLN biopsy are justified by the low risks of the procedure relative to the risks of axillary dissection [41]. Nonetheless, admission of a pregnant woman to a nuclear medicine department and potential psychological concerns must be considered before allowing the procedure.

Nursing mothers

Nursing mothers should suspend breast feeding for 24 h after radiopharmaceutical administration.

Qualifications and responsibilities of personnel

SLN studies should only be performed by surgeons and nuclear medicine specialists who have undergone specific training in such procedures [41]. At this time, no definition of required training has been validated for either surgeons or nuclear medicine specialists, although a requirement of at least 30 procedures under guidance has been proposed for each surgeon intending to perform SLN biopsies [42–44].

Procedures in nuclear medicine

The procedure for SLN detection and localization may include a combination of radiopharmaceutical, coloured or fluorescent dye, preoperative scintigraphic imaging, and intraoperative gamma probe localization followed by surgical removal of detected SLNs.

Although there is consensus on some broad aspects of SLN protocols in 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 of scintigraphy and intraoperative detection, and whether or not extra-axillary lymph nodes should be considered. The specific radiotracer and technique used are additionally guided by local availabilities, regulations, and practices.

False-negative rates and axillary recurrence rates have proved to be similar regardless of the site of injection [45]. 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 visualization of axillary SLNs [44]. Some centres prefer dual injections, superficial and deep. The use of dual injections captures the advantages of both techniques and is associated with lower false-negative results [46]. If one's aim is to stage extra-axillary nodal basins as well as the axilla, tumour-related deep injection is recommended [37].

Preoperative radiotracer lymphoscintigraphic mapping is highly recommended because of the potential added benefits in both improving accuracy and reducing morbidity relative to the use of the hand-held gamma probe alone [8]. 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). Some surgeons do not use preoperative LS because in their environments doing so results in scheduling delays; others do not do so because there is no evidence that LS is associated with a higher intraoperative success rate in the harvesting of axillary SLNs [47, 48].

Patient preparation

No special preparation is required of a patient prior to her or his arrival in the nuclear medicine department. In all patients, recent (not older than 1 month) mammograms should be available, as should all recent breast ultrasound images and magnetic resonance images. All available images should be reviewed by the nuclear medicine physician. In female patients, pregnancy status and lactating status should be determined so that appropriate steps are taken to keep the exposure to radiation of patients, fetuses, and infants (through milk) as low as reasonably possible.

In the nuclear medicine department, in preparation for imaging, the patient should remove all clothing and jewellery above the waist.

In all patients, a physical examination of the breast should be performed by the nuclear medicine physician before injection of the radiopharmaceutical. If localization wires are in place or if a patient has recently undergone an excisional biopsy, such should be known by the nuclear medicine practitioners.

It is strongly recommended that the nuclear medicine physician communicate with the surgeon prior to and after the imaging procedures and that such communications be documented. The communication should take place particularly if the final report is not available prior to surgery. The surgeon should, at the time of surgery, have access to all images.

Radiopharmaceuticals

Several ^{99m}Tc-based agents have been used for radioguided SLN biopsy in breast cancer. Table 2 provides a summary of those most widely investigated, including colloid particles (antimony trisulphide—Australia and Canada; nanocolloid albumin—Europe; sulphur colloid—USA) [49] and a novel receptor-targeting small molecule.

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. There is general agreement that a radiocolloid should be a good compromise between fast lymphatic drainage and optimal retention in SLNs [30, 50]. Ideally, the draining lymphatic collectors (channels) are visualized so that the SLN receiving tracer from a collector can be identified and distinguished from any second tier node that may appear later.

The particle size also determines the timing of preoperative scintigraphy and intraoperative detection of SLNs. 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) [17]. SLNs are generally visualized within 1–2 h, and the patient should be in the operating theatre within 2–30 h of the injection of the colloid, depending on the facility's schedule [2, 15, 17]. If surgery is scheduled for early morning, injection and imaging may be safely performed the afternoon prior to the surgery [51].

Table 2 Characteristics of ^{99m}Tc-based radiopharmaceuticals

Agent	Particle size (nm)	
	Maximum	Mean
Sulphur colloid	350–5,000 (see text)	100–220 (filtered)
Antimony trisulphide	80	3–30
Sulphide nanocolloid (Lymphoscint®)	80	10–50
Nanocolloidal albumin (Nanocoll®)	100	5–80
Rhenium sulphide nanocolloid (Nanocis®)	500	50–200
Tin colloid	800	30–250
Labelled dextran	800	10–400
Hydroxyethyl starch	1,000	100–1,000
Stannous phytate	1,200	200–400
Tilmanocept (Lymphoseek®)	About 7 (equivalence)	About 7 (equivalence)

Studies have shown the success rate of identification of axillary SLNs is not significantly affected by the particle size of the radiotracer [52–55]. Thus, the selection of radiotracer is based more on local availability than on differences in SLN detection. In the US, ^{99m}Tc-sulphur colloid is the radiocolloid commonly used for SLN biopsy. Unfiltered ^{99m}Tc-sulphur colloid comprises particles with a wide range of sizes (15–5,000 nm, depending on the preparation method), with an average size ranging from 305 to 340 nm. Filtered ^{99m}Tc-sulphur colloid is usually obtained using a 0.22-μm filter. The result is a suspension with colloid particles that are mostly between 100 nm and 220 nm. A small-particle colloid, ^{99m}Tc-nanocolloidal albumin (Nanocoll®), is the licensed and preferred agent in most of Europe; the size of its particles ranges from 5 to 100 nm. The colloid used most in Australia and Canada is ^{99m}Tc-antimony trisulphide; the size of the particles most commonly used ranges from 3 to 30 nm.

The tracer must be prepared and labelled with ^{99m}Tc-pertechnetate using the relevant manufacturer's instructions. A labelling yield greater than 90–95 % must be confirmed before the radiopharmaceutical is injected into a patient. Hypersensitivity reactions to radiopharmaceuticals are rare but have been reported. See the SNM Guideline on Radiopharmaceuticals for general requirements [56].

An alternative to radiocolloids is the radiopharmaceutical ^{99m}Tc-tilmanocept (Lymphoseek®), which was approved by the US Food and Drug Administration (FDA) in 2013. Tilmanocept is mannosyl diethylene-triamine-pentaacetate (DTPA) dextran. Its molecular size is approximately 7 nm. Its uptake mechanism in lymph nodes is not dependent on particle size as it is a macromolecule-targeting agent; it targets dextran-mannose receptors on the surface of macrophages, including dendritic cells in lymph nodes [50]. Dendritic cells efficiently present the mannose receptor-mediated uptake of Lymphoseek to T cell lymphocytes in lymph nodes [57].

Activities and volumes

Consensus on the activity to be administered in a SLN procedure has not been reached. The investigated and suggested activities vary considerably. Activities as low as 3.7 MBq (0.1 mCi) [58] and as high as 370 MBq (10 mCi) [59] have been used. A total injected dose of 5 to 30 MBq is generally considered sufficient for surgery planned for the same day. When injection is done the afternoon prior to surgery, up to 150 MBq is considered sufficient [60]. When using superficial (periareolar, subdermal, intradermal, or subareolar) injections, large volumes of injectate may interfere with normal lymphatic flow; therefore, volumes of 0.05–0.5 mL are preferred [17]. With peritumoral injections, larger volumes (e.g. 0.5–1.0 mL) are used [18]. When injecting small volumes (e.g. 0.1 mL), the syringe may contain a small amount (0.1 mL) of air to clear any dead space within the tip of the syringe and the needle.

Radiolabelled colloid particles are suspended; thus, they may settle by gravity if left in a motionless syringe for more than a few minutes. A syringe with colloid should be gently rotated immediately prior to administration of the colloid to ensure good mixing of the radiolabelled particles [11]. Colloids should not be aggressively agitated.

Injection procedure

The optimal injection technique has been the subject of lively debate. Widely used techniques include peritumoral, subdermal, periareolar, intradermal, and subareolar injections. All enable axillary SLNs to be identified accurately, and satisfactory SLN detection rates have been reported for all injection approaches. Results of multiple studies have confirmed that the method of injection does not significantly affect the identification of axillary SLNs [61–63].

One major advantage of superficial injections is that they are easy to perform. A subdermal, periareolar, intradermal, or subareolar injection, however, is often more painful than a peritumoral injection. The addition of pH-balanced 1 % lidocaine to the radiopharmaceutical often improves patient comfort without compromising SLN identification [64]. The use of peritumoral injections requires careful investigation of a patient's prior imaging and medical records, particularly if the tumour is nonpalpable. If available, ultrasound guidance to assist with placement of peritumoral injections can be helpful. If a tumour is in the upper outer quadrant, the relatively intense activity at the injection site may make localization of a less-intense nearby SLN difficult [65, 66].

Important advantages of deep injections are improved detection of extra-axillary SLNs and the possibility of using a larger injection volume. When administering deep injections, care should be exercised to avoid injection into the dead space of a seroma resulting from a previous excisional biopsy or into a breast prosthesis.

After almost 20 years of experience, it is generally accepted that both deep and superficial injection approaches are valid and that they are often complementary. The combination of both injection techniques (deep and superficial) may even improve SLN detection and decrease false-negative findings [46]. Although the majority of superficial lymph vessels of the breast drain to only one SLN, a recent anatomical study on breast lymphatics showed there are alternative lymphatic drainage pathways to primary pathways. The authors also found that separate lymphatic networks exist in the ventral and dorsal parts of the breast. These drain to the axilla and the internal mammary node (IMN) chain, respectively, without apparent connections [67]. This observation correlates with findings of a clinical study in which drainage to the IMN chain and other lymph node stations outside the axilla was seen for tumours no matter in which quadrant of the breast they were located [68].

The site of injection can be gently massaged after tracer administration to improve drainage of the tracer. Massage can also be employed if passage of activity from the injection site is delayed at any time during the study [61, 62].

Imaging procedure

Quality control

Quality control should be routinely performed on the imaging system and image display used in SLN procedures [69, 70]. Quality control should be routinely performed on the gamma probe used in the nuclear medicine department and the operating theatre for SLN procedures [71]. The reader is referred to the SNM Guideline for General Imaging for additional information [72].

Imaging protocol

Imaging is recommended before any operation, as there is patient variability in breast lymphatic drainage into the axilla and extra-axillary regions. Imaging is an efficient means of determining if there is uptake of activity in any node, and it improves the likelihood of identifying all relevant node beds and thus the likelihood of locating all SLNs [73].

Imaging system 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/CT images. Low-energy, high-resolution (LEHR) or low-energy ultra-high resolution (LEUHR) collimators should be used. The energy window should be 15 % (±5 %) centred on the 140 keV photopeak of ^{99m}Tc.

Patient positions Most commonly, at each acquisition time point at least two or three images are acquired: anterior, lateral, and 45° anterior oblique. Anterior images are acquired with the patient lying supine on the bed of the imaging system. In the operating room, the patient most often lies supine with her/his arm on the side with cancer, extended perpendicular to her/his body. It is recommended the patient extend her/his arm as for the anterior images. Lateral images are also acquired with the patient lying supine, with her/his arm on the side with cancer (R/L) extended.

For acquisition of the 45° anterior oblique images, the patient (not the camera) should be rotated from supine to 45°, the patient's arm on the side with cancer should be positioned above the head, and the camera should be positioned directly above the patient. Rotation of the patient places the breast with cancer dependent toward the patient's midline. This reduces attenuation of uptake in axillary nodes and

reduces the potential for projection overlap of the uptakes at the injection site and in axillary nodes.

For lateral views, the patient might be rotated 90° from supine so that she/he is lying on her/his side contralateral to the cancer. In this position, the patient's involved breast is dependent toward the patient's midline, away from the axilla to be assessed. If rotation of a patient for 45° anterior oblique imaging is not possible, the camera can be positioned to acquire the images. In this case, if possible, the breast should be held toward the midline to allow better imaging of the axilla to be assessed. If any of the above imaging is not possible, useful images with the patient in an upright position or in a prone position with breasts dependent may be possible.

Image acquisition

Dynamic (flow) imaging

Although not often used in SLN procedures for breast cancer, dynamic (flow) imaging can provide information useful for SLN localization. If dynamic imaging is to be performed, it should be started immediately after completion of all injections.

Planar (static) imaging

Planar (static) imaging should be performed 15–30 min, 1 h, and 2–4 h after injection, and as needed thereafter up to 18–24 h. At least two, preferably all three, of the following images should be acquired: anterior, 45° anterior oblique, and lateral. Each image acquisition is typically 3 to 5 min in duration. For a system with large FOV detectors, it is recommended that the pixel size be approximately 2 mm and the matrix size be 256×256 with zoom 1 or, rarely, 128×128 with zoom 2. If a 2-mm pixel size is not feasible on a system, the smallest pixel size available should be used.

Transmission imaging

The patient's body contour should be delineated for positioning and referencing foci of activity. To accomplish this, a ^{57}Co or ^{99m}Tc flood source can be appropriately positioned on the side of the body opposite the camera or a ^{57}Co or ^{99m}Tc "point" source can be used to trace the body contour.

Because the amount of tracer uptake in a node does not correlate with the likelihood of it being the SLN, quantification of tracer uptake in nodes is not necessary or helpful. In addition, removal of all axillary nodes with radioactivity leads to fewer false-negative SLN biopsies [74]. Anatomical localization of tracer uptake is therefore sufficient.

Optional/alternate imaging (SPECT or SPECT/CT)

Conventional planar imaging does not give exact preoperative anatomical localizations of detected nodes [75]. SPECT/CT provides tomographic lymphoscintigrams registered with anatomical data. For SPECT/CT acquisition, a patient is positioned only once—an advantage for patients who are difficult to position. SPECT/CT provides three-dimensional images that generally have better contrast and spatial resolution than planar images. SPECT/CT allows the possibility of correction for effects of attenuation and scatter. It provides relatively precise localization of SLNs within an anatomical landscape, thus providing a valuable road-map for surgery [76].

Based on published reports, current indications for SPECT/CT include nonvisualization of SLN on conventional planar imaging, patient obesity, and the presence of extra-axillary SLNs, or otherwise unusual difficult-to-characterize drainage (e.g. multiple sites of drainage, visualization of IMN chain, intramammary lymph node, nodes in the contralateral axilla, or previous breast surgery). SPECT/CT might also be performed if the conventional images are difficult to interpret (e.g. suspicion of contamination or a SLN near the injection area) [75–78].

SPECT acquisition for SLN detection should be performed with a dual-detector SPECT system equipped with LEHR or LEUHR collimators. Acquisition parameters should include a matrix size of 128×128 (4–5 mm pixels) and 120 or 128 projections over 360° with 20–25 s/projection. If SPECT reconstruction includes resolution recovery, the number of projections or the time per projection may be reduced as recommended by the vendor of the resolution recovery software.

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.

Image storage

All images obtained should be stored in a permanent form according to national and other relevant regulations.

Skin marking

Surface marks that provide a means to triangulate SLNs and a means to estimate their depths are desired by some surgeons. Imaging from at least two projections should be performed. Surface locations should be marked on the skin with a small spot of indelible ink, and the depth of the node should be noted. When marking the skin in the imaging process, an attempt should be made to position the patient as she/he would be positioned for surgery. If more than one node is found in the same region, some practitioners prefer to mark just the hottest node(s) and describe and display the other nodes on accompanying reports and images. If SPECT/CT imaging is available, appropriate coregistered images should be made available at the time of surgery.

Image processing

No particular processing procedures are needed for planar images. Truncation of high activities (the injection sites) will improve visualization of the SLN. A logarithmic scale to enhance low-count areas instead of a linear scale is preferable for image display. Processing parameters should be carefully chosen so as to optimize image quality (see SNM Guideline for General Imaging [72]).

Interpretation

Early and delayed lymphoscintigraphic planar images identify SLNs in the majority of patients. Major criteria to identify lymph nodes 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 lymph nodes. The SLN is not necessarily the hottest node, although that is often the case. Separate lymphatic channels that drain to different lymph nodes identify each of these as distinct SLNs, even though they may be located in the same anatomical region. When drainage to more than one anatomical region is seen, each of these regions has at least one SLN.

The report to the referring physician should describe the orientations of the images acquired, the radiopharmaceutical, the method of administration, the dose 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 are critical for accurate dissemination of information regarding numbers and locations of nodes.

Procedures in the surgical suite

Blue-dye node localization

Most breast cancer surgeons combine LS/probe information with information obtained using blue dye injected during surgery. This combining of information is an excellent method for decreasing false-negative findings and increasing sensitivity [45, 62].

Currently, the commonly used dyes are patent blue V, isosulfan blue, and methylene blue. Blue dye can be injected around the primary tumour in a manner similar to that for radiopharmaceutical injections, 10–20 min prior to surgery in a volume of 2–5 mL. Care should be exercised to avoid injection into the dead space of a seroma [34]. The injection should be performed after the patient is anaesthetized to avoid painful injection. If local anaesthesia is to be used, the local anaesthetic should be administered using a separate syringe (e.g. lidocaine) since the admixture of isosulfan blue with local anaesthetics in the same syringe results in immediate precipitation of 4–9 % drug complex. Five minutes of massage of the injection site enhances movement of the dye through the lymphatics to the SLN. Within 5–15 min the SLNs are coloured. Washout is evident after approximately 45 min.

Multiple studies have established the validity of blue dyes as markers for SLNs. The study results include reasonably high detection rates (ranging from 75 % to 95 %) [79], although they are slightly lower than those achieved when radiopharmaceuticals are used. In most cases, the same SLNs are detected by the two methods. A notable disadvantage of using blue dyes is that blue dyes are not helpful if extra-axillary nodes (IMN or supraclavicular nodes) are to be evaluated [80, 81]. Another disadvantage in patients who are having breast-conserving surgery is the temporary blue tattooing of the skin or areola when the dye is injected superficially.

It is important to be aware of contraindications for the use of blue dyes. Blue dyes may interfere with pulse oximetry readings, so in certain patients they should be used with caution. Blue dye can induce anaphylactic reactions that require resuscitation in 0.5 to 1.0 % of patients. Hypersensitivity to the product is the only contraindication. Blue dye should not be used in pregnant women because of the risk of anaphylactic reaction. Blue dye should also not be used if there is prior evidence of a patient having had an allergic reaction to this type of agent or of a patient having severe renal impairment [79–85].

Radioguided surgery

Detection probes must be able to detect SLNs from the skin surface as well as within exposed surgical cavities. The first task requires that the sensitivity of the detector is sufficient to identify a weakly active SLN when attenuated by up to 5 cm of soft tissue. Discriminating activity within a SLN also requires that the probe be well collimated for a small angle view. It is thus advisable that the major component of collimation be in the form of a detachable collimator of suitable construction. This allows it to be removed when it is not required, rendering the probe more compact and more sensitive. The detector should be constructed to offer a high level of shielding against radiation hitting the side of the probe assembly. The whole system should be designed and constructed to be suitable for intraoperative use [2]. The detector itself should be ergonomically designed for easy manoeuvrability and constructed so as to be suitable for sterilization.

When used intraoperatively, a probe is placed in a sterile bag so that it can 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. Many commercial models are available with discernible differences [69, 86]. In the European Union, it is a requirement that all medical equipment have CE certification. Medical devices marketed in the USA must be approved by the FDA. Neither body, however, enforces mandatory compliance with the most widely recognized international electromedical safety standard IEC 60601 [87]. Thus, information regarding compatibility with regional requirements should be separately sought from the manufacturer of a device.

Using the images and skin markings as guides, the probe (placed over the regions of highest counts) can be used to select the optimum location for incision. The surgeon uses the probe to guide dissection to the hot node(s) and places the probe in the surgical bed after node excision to confirm removal of the hot node(s). In working with the probe, it is important to direct the probe away from activity at the injection sites. Counts are recorded per unit time with the probe in the operative 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 accumulations (e.g. liver).

The identified SLNs are removed by the surgeon. When a hot node has been removed, the wound site should be checked for remaining activity. Due to the limited spatial resolution of gamma cameras, nodes closer than about 15–20 mm may appear as one spot. Thus, after removal of one node, another hot node may still be present. The current use of SPECT/CT may reveal the presence of a cluster of lymph nodes on CT images. The number of nodes to remove from any one basin will depend on the report from LS and local practice [88, 89].

Deeply located SLNs are difficult to detect because of attenuation and radioactivity at the injection site that may cause nearby SLNs to be hidden. This situation is observed mostly when tumours are in the superior outer quadrant and when tumours are located in inner quadrants and SLNs are in the IMN. It is advisable to use smaller diameter probes (e.g. 10 mm diameter probes) in intercostal areas as they generally allow focal activity in limited surgical spaces to be localized more easily [90]. The use of SPECT/CT images can help localize focal activity as can the use of intraoperative imaging with portable gamma cameras [91, 92].

Patients who have undergone previous breast surgery or received 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 tumour 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. To minimize false-negative results, the open axilla should be palpated and suspicious lymph nodes harvested, even if these are neither hot nor blue. In cases of nonvisualization or if the SLN is located outside the lower medial part of the axilla, palpation of the typical SLN area is particularly important [93].

Radioactive waste in the operating room (sponges, etc.) and in pathology should be collected according to institutional radiation safety procedures. This waste will also be a biohazard and should be handled accordingly. Personnel not accustomed to dealing with radioactive materials should be educated as to their safe handling and disposal. Appropriate education of surgical suite personnel and pathologists will often be very valuable for the establishment of appropriate handling of radioactive materials, reassurance of concerned individuals and expedient processing of tissues.

SLN nonvisualization

The majority of patients with preoperative lymphoscintigraphic SLN nonvisualization will have at least one SLN detected intraoperatively, either by gamma probe alone or by gamma probe combined with blue dye. While logistically difficult in most centres, a second radiotracer injection, at perhaps a different injection site, may be useful to visualize previously nonvisualized SLNs.

In approximately 1 to 2 % of patients, SLNs will not be detected preoperatively or intraoperatively and the status of the axillary nodes cannot be determined. Old age, obesity, tumour location other than the upper outer quadrant, and nonvisualization of SLNs on preoperative LS may be associated with failed SLN localization [94]. The significance of preoperative scintigraphic nonvisualization is not yet known. Some studies have suggested that patients with unsuccessful axillary mapping may have an increased risk of positive axillary involvement [95]. There is no definitive consensus on what to do if a SLN cannot be visualized. However, current standards of care recommend ALND when intraoperative SLN identification is not achieved [96].

Multiple SLNs

In principle, SLN biopsy requires the removal of all SLNs receiving direct lymphatic drainage from the site of the primary tumour. In practice, this is not always achieved. The question remains as to how many SLNs should be biopsied when multiple nodes are found. In patients with multiple radiolabelled nodes, it is often difficult to distinguish between SLNs and second tier nodes. However, removing more than five nodes from the axilla does not result in marked improvement in the sensitivity of axillary SLN biopsy [90–100].

Histopathology

Before specimens are sent for histological examination, they should be evaluated ex vivo using the probe to demonstrate that they are radioactive [101]. This evaluation should be performed on all nodal specimens and all tumour specimens.

Histopathological assessment of SLNs is the "gold standard" procedure for the subsequent surgical management of breast cancer patients. However, this gold standard is highly variable among centres. In many institutions, SLNs are assessed intraoperatively using imprint cytology, frozen sectioning, or both, and more thoroughly after the operation. The sensitivity of the intraoperative diagnosis is variable and many facilities do not adopt it at all [102]. Some molecular methods have been used previously for SLN diagnosis, but have shown a lack of reproducibility, require a longer time for the intraoperative assessment, and provide no means to study the whole lymph node. A new molecular method has been developed recently. It is based on a one-step nucleic acid amplification (OSNA) method. This procedure is in validation studies in many centres; it is in routine use in others [103].

Radiation dosimetry

Nuclear medicine, surgery, and pathology professionals are involved if a radiopharmaceutical is used in a SLN procedure. Each involved practitioner and the patients receiving such procedures are exposed to radiation. The exposures received by each, when doses standard for SLN procedures are administered, are well below recommended limits for both public and thus occupational exposures.

Estimates of exposures to patients [101, 104–110], surgeons [101, 105, 107, 111–117], and pathologists [101, 105, 112–115, 118, 119] have been reported by several investigators and are offered in relevant radiopharmaceutical package inserts [120, 121]. Table 3 is a summary and interpretation of much of the available data.

All of the published data indicate that exposures to patients and professionals from SLN procedures are minimal. Low patient effective dose and very low fetus/uterus equivalent dose [39, 40, 101, 109, 110, 123] indicate exposure to radiation is not a contraindication for a SLN procedure in any patient, including pregnant patients. However, prudence dictates that care should be exhibited when conducting a SLN procedure on any patient. In patients who are breast feeding, nursing should be suspended for 24 h following radiopharmaceutical administration. Regarding professionals, the United States Nuclear Regulatory Commission (NRC) has determined that the exposures to pathologists from radioactive SLN specimens are too small to require regulation [124]. The injection site absorbed dose can be significant (see able 3). There are no known negative consequences of this. The site is often, but not always, excised. The dose is very small relative to that received from postoperative radiation therapy. Because exposures in SLN procedures of all non-nuclear medicine personnel are low, none need be monitored routinely for radiation exposure. The decision to badge personnel involved only with SLN procedures is at the discretion of individuals and local custom.

Absorbed doses and equivalent doses to several organs have been estimated and can be found in tables in a few publications and relevant package inserts [104, 106, 110, 120, 121, 125]. The dose to a patient from a transmission source will vary. One estimate of the dose from a transmission source is 0.003 mSv [106, 107]. The dose from a CT scan also varies. One estimate of the dose from the CT element of a SPECT/CT scan is 2.4 mSv [126]. A low-dose CT scan with a field of view limited to avoid radiosensitive tissues can help

Table 3 Ranges of estimates of radiation exposures

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

[a] Estimates extracted or derived from information in the included references

[b] Assuming that SLN procedures were conducted on 100 patients in a year and assuming each patient was injected with a dose of 18.5 MBq (0.5 mCi)

[c] International Commission on Radiological Protection (ICRP) recommended limits [122]

[d] Pregnant-woman effective-dose estimate and limit are the same as those for a non-pregnant patient

keep the equivalent dose to a minimum. The estimates are dependent on various acquisition parameters. The total exposure in such cases is the emission-generated dose plus the transmission-generated dose.

Issues requiring further clarification

T3 and T4 tumours

Evidence regarding the efficacy of SLN biopsy is mainly based on studies including only T1 and small T2 tumours. A few reports suggest that false-negative rates in the case of large tumours are similar to those for small tumours; however, more evidence is needed for definitive confirmation of this [127, 128].

Multifocal and multicentric tumours

Multifocal breast cancer is defined as two or more separate foci of ductal carcinoma that are more than 2 cm apart within the same quadrant; multicentric breast cancer is the presence of separate independent foci of carcinoma in different quadrants [129]. Both types of cancer have high prevalence of axillary metastases, and both have high reported false-negative rates [130]. Despite those factors, which raise concerns, acceptable axillary recurrence rates have been reported [127–131].

Ductal carcinoma in situ

Ductal carcinoma in situ (DCIS) does not metastasize to regional lymph nodes, but ductal invasion is missed in up to 40 % of patients with DCIS. Because this is the case, SLN biopsy is recommended in patients with DCIS undergoing mastectomy [132]. In patients in whom breast conservation is planned, if invasion is detected in a surgical specimen, SLN biopsy can be performed later. However, wide local excision can alter lymphatic drainage, especially to IMNs. Because local invasion can be missed on initial diagnostic biopsy, some centres choose to perform SLN biopsy in all patients with DCIS to avoid a less-accurate SLN biopsy after wide local excision [133].

Suspicious palpable nodes

Palpable axillary nodes may be tumour-negative in up to 40 % of patients [134]. One widely accepted practice for assessment of suspicious palpable nodes is preoperative axillary ultrasound scan with fine needle aspiration cytology or core needle biopsy. Another accepted practice is to perform SLN biopsy if palpable nodes are negative following preoperative evaluation. In this case, suspicious palpable nodes should be harvested for histopathological evaluation, even when neither hot nor blue.

Evaluation of internal mammary and other extra-axillary nodes

Internal mammary SLN detection rates are significantly affected by depth of radiopharmaceutical injection. It is generally recognized that mapping of IMNs requires deep injection of radiopharmaceuticals, either peritumoral or intratumoral [135–137]. In some studies, IMNs have been detected in about one-third of patients with breast cancer, of which about 63–92 % could be harvested during surgery. Of the harvested IMNs, 11–27 % had metastases [138–140]. There is no doubt that metastasis in the IMNs significantly worsens prognosis in breast cancer, and predictive models suggest that it is under-treatment of such metastases that is the cause of the poorer prognosis in medial quadrant tumours versus lateral quadrant tumours [141]. However, the significance of IMN biopsy continues to be discussed. There is evidence that mapping of IMNs leads to stage migration and to modifications of treatment planning with respect to radiotherapy and systemic therapy, but more evidence is necessary to support the idea that mapping of IMNs will improve the outcome of treatment and survival [140, 142]. If complete SLN biopsy in breast cancer is the aim, peritumoral injection of tracer is required.

Prior excisional biopsy

Lymph drainage is probably changed in patients who have undergone breast surgery. Non-axillary drainage has been identified more often in re-operative SLN biopsy than in primary SLN biopsy [133]. However, there is evidence that successful SLN biopsy can be performed in proximity to the site of a previous breast biopsy [143, 144].

Prior breast surgery other than excisional biopsy

SLN biopsy can be performed following local recurrence after breast conservation in DCIS patients. Furthermore, plastic surgery with breast augmentation or reduction does not contraindicate the SLN procedure [145].

Prior axillary surgery

A second SLN biopsy can be performed following local recurrence after breast conservation and negative axillary SLN biopsy. The success rate may be lower than with a primary SLN biopsy. Furthermore, extra-axillary SLNs are visualized more frequently in patients with prior axillary surgery. Encouraging results have been reported regarding detection of axillary recurrences, but the evidence is not conclusive [146]. On the other hand, there is no evidence that these patients benefit from diagnostic ALND.

Neoadjuvant chemotherapy

SLN biopsy gives precise axillary staging prior to neoadjuvant chemotherapy; however, prechemotherapy SLN biopsy may delay the start of treatment, and require an additional surgery. After neoadjuvant chemotherapy, SLN biopsy may lead to an underestimation of the initial stage [34, 147]. On the other hand, axillary nodal status after neoadjuvant therapy is a highly significant prognostic factor. Pathological complete response in the axilla can be achieved in up to 40 % of patients. ALND and associated morbidity are avoided in these patients. Available data show that there are, in this category of patients, no significant differences in the success rate of SLN biopsy when compared with patients not having neoadjuvant chemotherapy [148–150].

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