Eur J Nucl Med Mol Imaging (2007) 34:2154–2159
DOI 10.1007/s00259-007-0614-z

GUIDELINES

Sentinel node in breast cancer procedural guidelines

John Buscombe · Giovanni Paganelli · Zeynep E. Burak · Wendy Waddington · Jean Maublant · Enrique Prats · Holger Palmedo · Orazio Schillaci · Lorenzo Maffioli · M. Lassmann · Carlo Chiesa · Emilio Bombardieri · Arturo Chiti · On behalf of the European Association of Nuclear Medicine Oncology Committee and Dosimetry Committee

Published online: 18 October 2007

Abstract
Content Procedure guidelines for scintigraphic detection of sentinel node in breast cancer are presented.

Authors The paper was written by several experts in this field on behalf of the European Association of Nuclear Medicine Oncology and Dosimetry committees and approved by the Executive Committee.

Keywords Breast cancer · Axillary metastases · Lymphoscintigraphy · Sentinel node · Guidelines

An Editorial commentary on this paper is available at http://dx.doi.org/10.1007/s00259-007-0616-x-.

Disclaimer: The European Association of Nuclear Medicine has written and approved guidelines to promote the cost-effective use of high-quality nuclear medicine procedures. These generic recommendations cannot be rigidly applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures or exclusive of other procedures reasonably directed to obtaining the same results. Advances in medicine occur at a rapid rate. The date of a guideline should always be considered in determining its current applicability. All authors declare they have no conflict of interest.

J. Buscombe
Royal Free Hospital, London, UK

G. Paganelli
Istituto Europeo di Oncologia, Milano, Italy

Z. E. Burak
EGE University Faculty of Medicine, Izmir, Turkey

W. Waddington
University College Hospital, London, UK

J. Maublant
Centre Jean Perrin, Clermont Ferrand, France

E. Prats
Hospital Clinico Universitario, Zaragoza, Spain

H. Palmedo
University of Bonn, Bonn, Germany

O. Schillaci
Policlinico Tor Vergata, Roma, Italy

L. Maffioli
Ospedale Civile di Legnano, Legnano, Milan, Italy

M. Lassmann
University of Würzburg, Würzburg, Germany

C. Chiesa · E. Bombardieri
Fondazione IRCCS Istituto Nazionale per la Cura e lo Studio dei Tumori, Milano, Italy

A. Chiti
IRCCS Humanitas, Rozzano, Milan, Italy

A. Chiti (✉)
Nuclear Medicine Division, Istituto Clinico Humanitas, Via Manzoni 56, 20089 Rozzano, Milan, Italy
e-mail: arturo.chiti@humanitas.it

Background information and definitions

Sentinel lymph node is the first regional lymph node that drains the lymph from the primary tumour. It is potentially the first node to receive the seeding of lymph-borne metastatic cells [1]. Lymphoscintigraphy (LS) allows the surgeon to easily identify and biopsy the sentinel lymph node. This method identifies the sentinel node but cannot determine if it is involved with cancer. At present, this technique guides the surgeon to the sentinel node, and sentinel node biopsy has been reported as a safe and accurate method of screening axillary nodes [2, 3].

Common indications

Scintigraphic sentinel node localisation should be considered in women who have a biopsy-proven carcinoma of the breast in whom definitive surgery and axillary node clearance is planned and on whom there are no palpable axillary lymph nodes [4].

Procedures

Patient preparation

- No special preparation for the test is needed.
- The patient should remove all clothing and jewels above the waist.

Information pertinent to performing the procedure

- The time of last menses and pregnancy and lactating status of the patient should be determined.
- A breast physical examination should be performed by the nuclear medicine physician.
- Recent (not older than 1 month) mammograms should be available, as well as ultrasound, if performed

Precautions

Pregnancy is not a contraindication for LS [5–7], but only for blue dye, and it has been demonstrated that the dose to the foetus from this procedure is negligible, particularly when using activities below 10 MBq. In these cases LS is justified by the low risk of the procedure when compared to axillary dissection [8]. Nonetheless, admission of a pregnant woman in a nuclear medicine department and psychological issues must be considered before allowing the procedure. In nursing mothers, lactating should be suspended for 24 h after radiopharmaceutical administration.

Studies should only be performed by a surgeon and a nuclear medicine specialist who have undergone specific training in this technique [9]. At this time, no definition of the required training has been validated for the surgeon or the nuclear physician, although a minimum of 30 procedures has been proposed for the surgeon [10].

Quality control

Quality control for the gamma camera and image display should be routinely performed, according to published protocols [11, 12]. Demonstration of spatial registration in multiple energy windows may be required to optimise image quality. Quality control of the gamma probe used to detect the sentinel node in the operating theatre should also be performed according to published protocols [13].

Radiopharmaceuticals

A variety of colloids have been used in this technique. The radiopharmaceuticals commonly employed for LS are ^{99m}Tc-sulphur colloid (particles' size: 15–5,000 nm), ^{99m}Tc-nanocolloid (5–100 nm), ^{99m}Tc-antimony trisulphide (3–30 nm). The choice of the radiopharmaceutical depends on the geographic area: in Europe, ^{99m}Tc-nanocolloid; in USA, ^{99m}Tc-sulphur colloid; and in Canada and Australia, ^{99m}Tc-antimony trisulphide.

There is a general agreement that a radiocolloid with the majority of particles ranging between 100 and 200 nm in size can be considered the best compromise between fast lymphatic drainage and optimal retention in the sentinel lymph node [14, 15].

If a single node wishes to be seen and imaging times cannot be coordinated with the operating theatre time, a large colloid with a size of 200–1,000 nm is recommended [4]. It has been found that these larger colloids tend to "stick" in the sentinel node and allow imaging for up to 20 h post injection.

The SN is, generally, visualised in 2 h, and the patient should be in the operating theatre within about 16–20 h after the injection of the colloid [1, 4, 16]. The colloid must be labelled with technetium pertechnetate using manufacturer's instructions. A labelling yield greater than 95% must be assessed before injecting the radiopharmaceutical. General radiopharmaceutical requirements for quality control must be used.

Volume and activity

Large volumes of colloid may disrupt local lymphatics; therefore, small volumes should be injected [4]. A single aliquot of 5–20 MBq (depending on the elapsed time between scintigraphy and surgery) of colloid in 0.2 ml is considered sufficient. A higher activity can be used for late procedures. The syringe should also contain a similar amount of air to clear any dead space within the syringe and the needle. In deep lesions, a slightly larger volume (0.5 ml) may be used.

Radiation dosimetry

Radiation dosimetry for the patient has been measured and published data are summarised in the table from Law et al. [17], which gives the $S_{organ \leftarrow source}$ as experimentally determined using an anthropomorphic Alderson-Rando phantom with four peritumoural injection sites as sources and thermoluminescent dosimeter detectors positioned in target organs. The upper limit to an organ dose can be computed in the hypothesis of complete decay in the injection site without surgical removal. Using a simple equation and an average value taken from the last row of the table below (Table 1), we can calculate an effective dose of 2.6 μSv/MBq, which is significantly lower than the 21 μSv/MBq reported by Waddington et al. [18]. Values from this paper are systematically higher with respect to the upper limit obtained from Law et al. [17]: 7.8 vs 1.7 μGy/MBq for the lung and 720 vs 35 μGy for the injected breast. Data by Cremonesi et al. [19] estimated a mean of 780 μSv/MBq at the injection site, with a range of 72 to 2,700 μSv/MBq. Using these data, it can be concluded, even considering the highest values, that "radiation risk to the patient is consequently low relative to that from many other medical exposures" [18].

Table 1 Normalised absorbed doses ($D_{T,R}$) received by various organs of interest by internal emission from each breast injection and the calculated normalised effective dose [17]

Organ	Normalized $D_{T,R}$ [μGy (MBq·h)$^{-1}$]	
	Left breast injection	Right breast injection
Ovary	0.021	0.016
Bone marrow	0.095	0.104
Colon	0.043	0.044
Lung	0.197	0.230
Stomach	0.271	0.163
Bladder	0.011	0.012
Breast	4.077	3.755
Liver	0.074	0.236
Oesophagus	0.108	0.122
Thyroid	0.156	0.183
Skin	0.329	0.258
Bone surface	0.062	0.041
Remainder	0.191	0.087
Normalized ED [μSv(MBq·h)$^{-1}$]	0.312	0.291

ED effective dose

Normal distribution

- Injection site in the breast
- Lymph-node(s).

Techniques

Administration

Site of injection

A sub-dermal injection over the tumour site is sufficient for all but the deepest tumours [4, 16]. The site of injection can be gently massaged after the administration or if passage of activity from the injection site is delayed at any time during the study. A peri-tumoural injection of 0.5 ml is recommended in all deep tumours [4, 20]. If the lump is not palpable, ultrasound can be used to guide the injection.

Peri-areolar injection can be used particularly in upper-quadrant tumours to avoid possible cross-talk due to short distance between peri-tumoural depot and the axillary sentinel node [21, 22]. This technique has the advantage of demanding less experience, particularly in non-palpable lesions. At present there is no evidence to justify intra-tumoural injections of colloids.

Image acquisition

Imaging is strongly recommended before any operative procedure, as there is some variability in breast lymphatic drainage into the axilla and more than one sentinel node can be visualised in up to 20% of patients.

Gamma camera

The gamma camera should be equipped with a low-energy, high-resolution collimator.

Energy window

The energy window should be 15% (±5%) centred over the 140 keV photopeak of ^{99m}Tc.

Patient position

The patient lies supine for imaging on the gamma-camera bed. Anterior and 45° anterior oblique imaging should be obtained. It is useful if the arm on the side of the cancer is extended laterally to 90°, as this will be the position during surgery.

Image collection

1. Images should be performed within 15 min after the injection, but, if required, they can be performed 2–3 h or up to 16–18 h after.
2. Planar images are acquired for 3–5 min using a 64×64 matrix, zoom 1.
3. The site of any suspected sentinel node can be localised on overlying skin on the 45° anterior oblique image using a ^{57}Co source and the skin marked with a small spot of indelible ink. If a ^{57}Co is not available, ^{99m}Tc sources using syringe needles can be employed as well.

Optional images and techniques

- If multiple sites of drainage are seen, particularly to the internal mammary lymph node chain or the contralateral axilla, further evaluation by appropriate procedures is recommended [9].
- All images obtained should be stored in a permanent form, according to national regulations.

Processing

Truncation of the high-activities (injection site) will improve visualisation of the sentinel node. A logarithmic scale to enhance low-count areas instead of a linear scale is preferable for image display.

Procedures in surgical room

Blue dye lymph node localisation

Scintigraphic sentinel node localisation does not prevent other methods such as peri-tumoural blue dye from being administered in the peri-operative setting.

Radioguided surgery

Detection probes must be able to detect the sentinel lymph node from outside the skin surface and within the exposed surgical cavity as well. The first task implies that the sensitivity of the detector is sufficient to identify a weakly active sentinel node when attenuated by, typically, up to 5 cm of soft tissue. However, strong sources of extraneous radioactivity are frequently located close to the lymph node basin under investigation, mainly arising from tracer activity retained at the injection site. Discriminating activity within the sentinel node from that originating from these sites requires the probe to also be well collimated for a small angle view, and it is advisable that the major component of this collimation be supplied to the probe 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, restoring sensitivity, and improving ease of use. The detector should also be constructed to offer a high level of shielding against radiation hitting the side face of the probe assembly.

The whole system must be designed and constructed to be suitable for intra-operative use [1]. The detector itself should be ergonomically designed for easy manoeuverability, and constructed to be suitable for sterilisation. A clear visual display capable of indicating instantaneous and cumulative counts is a major requirement. It is essential that the instantaneous count-rate be fed to an audio signal able to vary from the frequency of a continuous signal to a pulsed signal. Many commercial models are available, and their physical properties show remarkable differences [13, 23].

In the European Union, it is a requirement that all medical equipment obtain CE certification, and medical devices marketed in the USA must be registered with the FDA. However, whilst encouraged, neither body enforces mandatory compliance with the most widely recognised international electro-medical safety standard IEC 60101 [24]; and so, information regarding compatibility with its requirements should be separately sought from the manufacturer.

Interpretation criteria

- The first “hot spot” detected on images has to be considered as the sentinel lymph node.
- During the operation, the surgeon guided by the skin pen mark will locate the lymph node with the highest radioactivity. If there are two or more such lymph nodes, all should be removed.
- Before sending for histological examination, any lymph node removed should be re-chequed by the probe to demonstrate that they are radioactive.
- The decision to perform “frozen section” on the removed lymph node and subsequent axillary node clearance should follow national guidelines. The radioactivity within the node is not sufficient to preclude frozen section [18].
- LS can also visualise internal mammary chain lymph node from 2 to 8% of cases, especially after a deep injection under tumour mass and in tumours located in the inner quadrant. These spots are not considered

sentinel nodes but can be a sign of a possible change in N stage [25, 26].

Reporting

The report to the referring physician should describe:

- Site of image acquisition (projections of breast and axilla)
- Radiopharmaceutical, way of administration, and amount of activity injected
- Location of the sentinel node(s) on gamma-camera images
- Any source of error or inaccuracy of the procedure

Sources of error

- With colloids of 200–1,000 nm, surgery can be any time up to 16–18 h post injection of the radioactive colloid.
- As the rate of passage of the smaller colloids is variable, it is advisable that frequent or continuous measurement is performed to identify when activity has reached the sentinel node and determine when intra-operative probing will be optimal.

Issues requiring further clarification

- Even if some authors consider that the previous breast biopsy can alter the lymphatic drainage affecting the results of sentinel node biopsy, there are other evidences that sentinel node biopsy performed in the area of previous breast biopsy do not affect the accuracy of the procedure [27].
- There is still an open discussion on the influence of neo-adjuvant chemotherapy on sentinel node identification and removal [28].
- Multiple foci of carcinoma, particularly when located in different quadrants, have been considered a relative contraindication for sentinel lymph node biopsy because of concerns that these tumours involve more than one lymphatic vessel. Recent studies report that sentinel node localisation maintain its negative predictive value also in patients with multicentric and multifocal breast carcinoma [29, 30].
- Though there is some evidence that peri-areolar injection will be effective in patients with suspected multifocal or multicentric lesions, this must be confirmed by larger trials [29].
- There is no definitive consensus on what to do if the sentinel node cannot be visualised.

References

1. Keshtgar MRS, Ell PJ. Sentinel lymph node detection and imaging. Eur J Nucl Med 1999;26:57–67.
2. Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med 2003;349:546–53.
3. Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, et al. Sentinel-lymph-node biopsy as a staging procedure in breast cancer: update of a randomized controlled study. Lancet Oncol 2006;7:983–90.
4. De Cicco C, Cremonesi M, Luini A, Bartolomei M, Grana C, Prisco G, et al. Lymphoscintigraphy and radioguided biopsy of the sentinel axillary node in breast cancer. J Nucl Med 1998; 39:2080–4.
5. Amersi F, Hansen NM. The benefits and limitations of sentinel lymph node biopsy. Curr Treat Options Oncol 2006;7:141–51.
6. Keleher A, Wendt R 3rd, Delpassand E, Stachowiak AM, Kuerer HM. The safety of lymphatic mapping in pregnant breast cancer patients using Tc-99m sulphur colloid. Breast J 2004;10:492–5.
7. Morita ET, Chang J, Leong SP. Principles and controversies in lymphoscintigraphy with emphasis on breast cancer. Surg Clin North Am 2000;80:1721–39.
8. Gentilini O, Cremonesi M, Trifirò G, Ferrari M, Baio SM, Caracciolo M, et al. Safety of sentinel node biopsy in pregnant patients with breast cancer. Ann Oncol 2004;15:1348–51.
9. Krag D, Weaver D, Ashikaga T, Moffat F, Klimberg VS, Shriver C, et al. The sentinel node in breast cancer—a multi-center validation study. N Engl J Med 1998;339:941–6.
10. Lyman GH, Giuliano AE, Somerfield MR, Benson AB 3rd, Bodurka DC, Burstein HJ, et al. American Society of Clinical Oncology. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol 2005;23:7703–20.
11. NEMA. NU 1 2001 Performance Measurements of Scintillation Cameras. Rosslyn: National Electrotechnical Manufacturers Association; 2001 (http://www.nema.org/stds/nu1.cfm).
12. IEC. IEC/TR 61948-2 Ed. 1.0 en:2001 Nuclear medicine instrumentation—routine tests—part 2: scintillation cameras and single photon emission computed tomography imaging. Geneva: International Electrotechnical Commission; 2001.
13. NEMA. NU 3 2004 Performance measurements and quality control guidelines for non-imaging intraoperative gamma probes. Rosslyn: National Electrotechnical Manufacturers Association; 2004 (http://www.nema.org/stds/nu3.cfm).
14. Mariani G, Moresco I, Viale G, Villa G, Bagnasco M, Canavese G, et al. Radioguided sentinel lymph node biopsy in breast cancer surgery. J Nucl Med 2001;42:1198–215.
15. Bourgeois P. Scintigraphic investigations of the lymphatic system: the influence of injected volume and quantity of labeled colloidal tracer. J Nucl Med 2007;48:693–5.
16. Veronesi U, Paganelli G, Galimberti V, Viale G, Zurrida S, Bedoni M, et al. Sentinel node biopsy to avoid axillary dissection in breast cancer patients with clinically negative lymph-nodes. Lancet 1997; 349:1864–7.
17. Law M, Cheng KC, Wu PM, Ho WY, Chow LW. Patient effective dose from sentinel lymph node lymphoscintigraphy in breast cancer: a study using a female humanoid phantom and thermoluminescent dosimeters. Br J Radiol 2003;76:818–23.
18. Waddington WA, Keshtgar MRS, Taylor I, Lakhani SR, Short MD, Ell PJ. Radiation safety of the sentinel node technique in breast cancer. Eur J Nucl Med 2000;27:377–91.
19. Cremonesi M, Ferrari M, Sacco E, Rossi A, De Cicco C, Leonardi L, et al. Radiation protection in radioguided surgery of breast cancer. Nucl Med Commun 1999;20:919–24.

20. Pijpers R, Meijer S, Hoekstra OS, Collet GJ, Comans EF, Boom RP, et al. Impact of lymphoscintigraphy on sentinel node identification with technetium-99m-colloid albumin in breast cancer. J Nucl Med 1997;38:366–8.
21. Pelosi E, Bello M, Griors M, Ala A, Giani R, Bussone R, et al. Sentinel lymph node detection in patients with early-stage breast cancer: comparison of periareolar and subdermal/peritumoral injection techniques. J Nucl Med 2004;45:220–5.
22. Chakera AH, Friis E, Hesse U, Al-Suliman N, Zerahn B, Hesse B. Factors of importance for scintigraphic non-visualization of sentinel nodes in breast cancer. Eur J Nucl Med Mol Imaging 2005;32:286–93.
23. Zanzonico P, Heller S. The intraoperative gamma probe: basic principles and choices available. Semin Nucl Med 2000;1:33–48.
24. International Electrotechnical Commission. Medical electrical equipment—part 1: general requirements for safety. IEC 60101-1. (1988-12). Geneva: IEC; 1988.
25. Paganelli G, Galimberti V, Trifirò G, Travaini L, De Cicco C, Mazzarol G, et al. Internal mammary node lymphoscintigraphy and biopsy in breast cancer. Q J Nucl Med 2002;46:138–44.
26. Clarke D, Khoni N, Mansel ER. Sentinel node biopsy in breast cancer. ALMANAC trial. World J Surg 2001;25:819–22.
27. Luini A, Galimberti V, Gatti G, Arnone P, Vento AR, Trifiro G, et al. The sentinel node biopsy after previous breast surgery; preliminary results on 543 patients treated at EIO. Breast Cancer Res Treat 2005;89:159–63.
28. Schwartz GF, Meltzer AJ. Accuracy of sentinel node biopsy following neoadjuvant (induction) chemotherapy for carcinoma of the breast. Breast J 2003;9:374–9.
29. Kumar R, Jana S, Heiba SI, Dakhel M, Axelrod D, Siegel B, et al. Retrospective analysis of sentinel node localization in multifocal multicentric, palpable, or non palpable breast cancer. J Nucl Med 2003;44:7–10.
30. Knauer M, Konstantiniuk P, Haid A, Wenzl E, Riegler-Keil M, Postlberger S, et al. Multicentric breast cancer: a new indication for sentinel node biopsy—a multi institutional validation study. J Clin Oncol 2006;24:3374–80.