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GUIDELINES

EANM practice guidelines for lymphoscintigraphy and sentinel lymph node biopsy in melanoma

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Abstract
Purpose Sentinel lymph node biopsy is an essential staging tool in patients with clinically localized melanoma. The harvesting of a sentinel lymph node entails a sequence of procedures with participation of specialists in nuclear medicine, radiology, surgery and pathology. The aim of this document is to provide guidelines for nuclear medicine physicians performing lymphoscintigraphy for sentinel lymph node detection in patients with melanoma.
Methods These practice guidelines were written and have been approved by the European Association of Nuclear Medicine (EANM) to promote high-quality lymphoscintigraphy. The final result has been discussed by distinguished experts from the EANM Oncology Committee, national nuclear medicine societies, the European Society of Surgical Oncology (ESSO) and the European Association for Research and Treatment of Cancer (EORTC) melanoma group. The document has been endorsed by the Society of Nuclear Medicine and Molecular Imaging (SNMMI).
Conclusion The present practice guidelines will help nuclear medicine practitioners play their essential role in providing high-quality lymphatic mapping for the care of melanoma patients.

Keywords Sentinel lymph node · Melanoma · Lymphoscintigraphy · Radioguided surgery

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Preamble

These practice guidelines for sentinel lymph node biopsy (SLNB) in melanoma approved by the European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) aim to promote the use of nuclear medicine procedures of high quality. These guidelines are intended to assist practitioners in providing appropriate nuclear medicine care for patients. These guidelines 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 is below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from the one 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 these objectives.

Introduction

The accurate harvesting of a sentinel lymph node (SLN) in melanoma entails a sequence of procedures with components from different medical specialties, including nuclear medicine, radiology, surgery and pathology. The topics covered are presented under the headings:

1. Goals
2. Background and definitions
3. Indications
4. Procedure success rate, and qualifications and responsibilities of personnel
5. Procedures in nuclear medicine
6. Procedures in the surgical suite
7. Radiation dosimetry
8. Issues requiring further clarification

The present practice guidelines have been prepared for nuclear medicine practitioners. The intention is to offer assistance in optimizing the diagnostic information that can be obtained from SLN procedures. If specific recommendations cannot be based on evidence from original scientific studies, referral is made to "general opinion" and similar expressions. The recommendations are designed to assist in the referral, performance, interpretation and reporting of the SLN procedure.

Goals

The aim of these practice guidelines is to provide general information about the SLN procedure in patients with melanoma. The guidelines describe protocols currently used routinely, but do not include all existing procedures. They should therefore not be taken as excluding other nuclear medicine modalities that can be used to obtain comparable results. The present guidelines for nuclear medicine practitioners offer assistance in optimizing nuclear medicine imaging prior to SLNB to improve the diagnostic and staging information from the SLN procedure. The final result has been discussed by distinguished experts from the EANM Oncology Committee, national nuclear medicine societies, the European Society of Surgical Oncology (ESSO) and the European Association for Research and Treatment of Cancer (EORTC) melanoma group. The present document has been endorsed by the SNMMI board. The resources and facilities available for patient care may vary from one country to another and from one medical institution to another.

Background and definitions

Melanoma is a global health problem and the incidence is rising worldwide [1, 2]. Important risk factors for the development of melanoma are a history of sunburn, intermittent high UV exposure, red or blond hair and a family history of melanoma [3]. The prognosis of localized melanoma is generally good and worsens in the presence of regional or distant metastases [4]. The stage of the disease provides prognostic information and guides treatment. Approximately 20 % of patients with a melanoma of greater than 1 mm Breslow thickness have clinically occult lymph node metastases and the risk generally increases with increasing thickness of the melanoma. Physical examination of lymph nodes is inaccurate and small metastases elude detection with imaging modalities. Therefore, histopathological evaluation is important [5].

From the late 1800s onwards, elective lymph node dissection (ELND) was performed to detect and treat clinically occult lymph node metastases [6]. ELND became controversial when randomized studies did not show a survival benefit in patients without palpable lymph nodes, but a 20 % better survival was noted in the subgroup of patients with involved nodes [7]. In order to exploit this potential survival benefit, yet without exposing patients unnecessarily to the morbidity of ELND, a diagnostic test was needed to detect lymph node metastases at this early stage.

In 1992 Morton et al. described the concept of orderly progression of lymphatic dissemination and SLNB in 223 patients with melanoma [8]. Melanoma first drains to a

specific regional lymph node before involving other nodes. This is the SLN, which is defined as a node receiving lymphatic drainage directly from the primary tumour [9]. Tumour cells are present in the SLN before subsequent nodes in the regional basin become involved. Therefore, the tumour status of the SLN indicates the overall nodal status [10]. So, the aim of SLNB is to identify patients with lymph node metastases at an early stage. The SLN is usually located in a regional lymph node basin, but substantial interindividual differences exist [11, 12]. SLNs may also be observed between the primary lesion and the nodal basin (so-called in-transit or interval SLNs) [13–15]. A melanoma may directly drain to several lymph nodes in one or several nodal basins, which is often the case when it is located on the midline of the trunk or head and neck area [16].

Lymphoscintigraphy has been shown to be an accurate technique detecting at least one SLN in almost all patients [17, 18], and can identify the number of SLNs and determine their location [16, 19]. The lymphoscintigrams provide a roadmap for the surgeon. Blue dye injected at the melanoma site visualizes the afferent lymph channel that leads to the SLN and radionuclide-based detection using residual radioactivity from the lymphoscintigraphy and a gamma probe provides audiovisual guidance to the surgeon for identification of the SLNs. Surgeons find the SLN in almost 100 % of patients. The pathologist obtains multiple sections from the SLN and uses sensitive and specific staining techniques to identify even single-cell metastases. SLNs are found to contain metastases in about 20 % of patients [20–24].

Compared with ELND, the morbidity of SLNB is minimal and the recurrence rate has been demonstrated to be similar [18, 25, 26]. SLNB provides the nodal stage of the disease and the tumour status of the SLN has been proved to be the most important prognostic factor [27]. The Multicenter Selective Lymphadenectomy Trial 1 (MSLT-1) demonstrated that SLNB followed by completion lymph node dissection in the event of a positive SLN improves regional disease control and prolongs mean disease-free survival compared with patients who are observed [17]. The most important result of this trial is the finding of improved melanoma-specific survival in patients randomized to the SLN group with a melanoma of intermediate Breslow thickness (1.2 – 3.5 mm) and lymph node involvement. Unfortunately, the false-negative rate of SLNB was high (20 %). This may have been due to lack of experience at the beginning of this trial, which commenced in 1994.

The concept of sequential lymphatic dissemination is now widely accepted, and SLNB is also applied in other diseases such as breast cancer [28, 29]. Its success requires a dedicated and experienced team of nuclear medicine physicians, surgeons and pathologists following a standardized procedure.

Indications

Indications for SLNB in patients with melanoma include, but are not limited to, the following. SLNB should preferably be performed after diagnostic excision of the primary lesion with a narrow margin and histological confirmation of the diagnosis, and should be combined with therapeutic wide excision. SLNB can be considered in patients with a clinically localized invasive melanoma of Breslow thickness >1 mm and in selected patients with a melanoma of Breslow thickness <1 mm presenting at least one of the following characteristics: ulceration, mitotic rate >0, and regression with documented thickness of ≥1 mm or regression of more than 50 – 75 % of the whole pigmented lesion [30–33]. SLNB in patients with a melanoma of Breslow thickness between 0.75 and 1 mm is also accepted in some institutions.

Breslow thickness is the most important factor determining the indication for SLNB. Based on the survival benefit that MSLT-1 revealed, the procedure is recommended in patients with a melanoma of intermediate Breslow thickness, defined here as 1.2 – 3.5 mm [34]. National societies differ slightly in their recommendations and the appropriate course of action in the case of melanomas of <1 mm Breslow thickness remains a matter of controversy [35–38].

On the contrary, SLNB should not be performed in patients presenting with primary melanoma and satellitosis or in-transit metastases. These patients are already stage III and the information offered by SLNB will not change prognosis or treatment approach.

Patients with a thick melanoma have generally a poorer prognosis of a higher risk of subclinical distant dissemination at the time of diagnosis. Early treatment of their lymph node metastases was not shown to improve survival rate in MSLT-I. However, SLNB may be recommended as the risk of lymph node metastases exceeds 40 % and it will reduce the nodal recurrence rate [39]. In patients with thin melanoma, the risk of nodal involvement is generally found to be less than 5 % and a survival benefit has not been adequately studied. SLNB can be discussed with patients with thin or thick melanomas for the purposes of staging or provision of prognostic information if the potential benefits outweigh the associated risks [4, 37, 40].

SLNB can be performed easily in melanoma of the extremities or trunk. In the head and neck area, the procedure is more challenging because of the intricacy of lymphatic drainage patterns, the complexity of the local anatomy and the shine-through phenomenon [41, 42]. However, an SLN detection rate of 95.2 % has been reported [43], which can be improved by additional dynamic lymphoscintigraphy [44] preoperative SPECT/CT and the intraoperative use of the gamma probe [45].

In pure desmoplastic melanoma, the SLN is generally reported to be involved in less than 5 % of patients. The SLN

procedure can be indicated, even though it is a rare situation and the bibliography is not so large (one investigator found positive SLNs in 9 % of patients) [46–49]. The incidence of lymph node metastases in patients with mixed-type desmoplastic melanoma appears to be the same as in those with non-desmoplastic melanoma [48].

SLNB can be considered in patients in whom an intermediate thickness tumour is suspected but cannot be reliably assessed for reasons such as shave biopsy, or when cryotherapy, laser or cauterization has been performed on the same lesion before the diagnosis of melanoma. It may also be contemplated in patients with atypical melanocytic lesions where the pathological diagnosis of melanoma cannot be excluded after expert histological review of the specimen. Whether there is a benefit from SLNB in patients with a single local recurrence or satellite or in-transit lesions after at least 1 year disease-free survival is unclear [50–52]. In patients with multiple in-transit metastases there is no possibility of performing a SLNB following all potential lymphatic drainages, and from an oncological point of view this diagnostic procedure loses any significance.

Extracutaneous melanoma is rare and associated with a high incidence of blood-borne metastases. The feasibility of SLNB has been demonstrated but a worthwhile benefit is difficult to scientifically assess due to the limited number of cases [53–55]. The most frequent finding is a dermal location of melanoma with no signs of epidermotropism. If there is no sign of metastasis or confirmed lymph node metastasis SLNB can be considered. In other melanocytic lesions such as atypical Spitz naevi (or Spitz tumours) or blue naevi, SLNB may be indicated in selected patients.

Cutaneous squamous cell carcinoma is known to spread to lymph nodes, increasing the risk of subsequent development of distant metastases. Therefore, lymph node status is the most important prognostic factor [56]. SLNB is feasible and reliable and this tumour therefore appears to be a good indication for SLNB [57], especially lesions with moderate or scarce differentiation. SLNB can be indicated in Merkel cell carcinoma as the lymphatic mapping certainly aids in staging and treatment decision-making in these patients [58].

Precautions and potential contraindications

Contraindications include poor general health status, grave concurrent disease, poor patient compliance and known systemic spread of disease. If poor general health causes the risks of SLNB to exceed the benefits, lymphoscintigraphy can be performed with tattooing of the SLN site(s). Regular ultrasonography may then be performed to detect nodal recurrence at an early stage.

If a lymph node is suspicious for metastasis on physical examination or when imaged, fine-needle aspiration cytology should be attempted to pursue a pathological diagnosis. If fine-needle aspiration cytology does not provide a diagnosis and SLNB is otherwise appropriate, the procedure should be performed and the suspicious node should be removed even if not a demonstrable SLN. However, apparent lymph node metastases are a contraindication, because false-negative results may occur due to inhibited tracer accumulation in the SLN and altered lymphatic drainage pattern. SLNB is less sensitive in patients with surgery or trauma in the preceding years who may have altered lymphatic drainage pathways, but a positive biopsy does have the normal implications. This is equally true after wide local excision of the primary tumour, and SLNB may be contraindicated because it may not provide a reliable result [59, 60].

SLNB is a safe procedure without known adverse effects, even during pregnancy [61]. Nevertheless, the time point of SLNB in pregnant women should be carefully discussed with the gynaecologist considering the risks and benefits of SLNB during pregnancy [62] in relation to melanoma prognosis. The nuclear physician should be aware that most of the injected radiotracer stays at the injection site, which may be of interest when a melanoma is near the foetus. The radiation exposure can be reduced using a 1-day protocol (see also section Radiation dosimetry).

Melanoma is rare in children, but the prevalence of lymph node metastases is generally higher at a younger age. SLNB is also an accurate technique in children and adolescents [63, 64]. Tumour thickness correlates with positive SLNs [65]. Furthermore, a positive SLNB seems to be a predictor of a poor outcome [63]. SLNB should be offered according to the recommendations in adults.

Procedure success rate, and qualifications and responsibilities of personnel

Nuclear medicine physicians can almost always visualize the SLN and surgeons can almost always harvest the node. Despite the identification rate being close to 100 %, the false-negative rate is substantial. MSLT-1 was carried out at 17 specialized melanoma centres and the false-negative rate after all patients had been followed for 10 years was more than 20 % [17]. There is a learning phase for a lymphatic mapping team. A recent study at a specialized melanoma centre showed a 5.7 % false-negative rate over a 15-year period, but the rate was 29.4 % in the first year [66]. Various durations of learning phases have been recommended but none has been based on sound scientific data [67]. This is currently less of an issue because now that the procedure is done around the world and young doctors learn it during their specialist training, reductions in the high false-negative rates are being observed. SLNB should be performed by a qualified team of nuclear medicine specialists, surgeons and pathologists acting in close

collaboration. The success of SLNB continues to increase as a centre gains experience [26, 66, 68, 69].

Causes of false-negative procedures

Analysis of false-negative procedures has revealed that the cause may lie with each of its three elements [66, 70, 71]. Causative factors in lymphoscintigraphy may be imaging of the wrong nodal basin, or failure to depict all potential drainage basins, failure to visualize the afferent lymph vessel, or failure to detect an SLN in an unusual location. Furthermore, large metastases in the SLN inhibit tracer accumulation in these nodes. This is the reason why preoperative ultrasonography should be performed as a staging procedure of the nodal basin most likely to be the drainage site of the primary melanoma. Sometimes the time between lymphoscintigraphy and the operation is so long that the radioactive node can no longer be traced. If this occurs, the patient can be reinjected before the surgical procedure is started. Surgeons sometimes fail to remove an SLN in a difficult position even though it has been pointed out by the nuclear medicine physician. Also, not all SLNs accumulate the radiopharmaceutical and surgeons sometimes fail to dissect a blue lymph vessel that leads to such a nonradioactive node. Seeing all cells in an SLN requires slicing the whole node, which yields some 2,500 pathology slides. This is obviously not practical and the pathologist usually samples some ten slides from different levels. As a result, a small metastasis between two levels will be overlooked.

Procedures in nuclear medicine

Patient preparation

No special preparation is necessary prior to the SLN procedure. The nuclear medicine physician should carefully obtain a history including diagnosis, prior treatment (especially primary resection, including histopathological results), prior surgery or trauma of the affected region, comorbidities, pregnancy/nursing or prior administration of radiopharmaceuticals. Results of preoperatively performed imaging examinations should be delivered to the responsible nuclear physician. The history should be followed by physical examination of the affected body region. Every suspicion of lymph node metastases has to be excluded before SLNB. In the event of any uncertainty, the responsible nuclear physician should not hesitate to contact the responsible surgeon for further information.

To avoid constriction and occlusion of lymphatic channels, all clothes and jewellery in the region of interest and along the lymphatic vessels should be removed before injecting the radiotracer.

Administration of radiopharmaceutical

The tracer is usually injected 1 day before surgery or alternatively on the same day. For scheduling of the injection the half-life time of the radiotracer and the different speeds of distribution of the tracer from the primary site to the lymph nodes according to the body regions should be considered. No difference in SLN detection rate or false-negative rate has been found between the two protocols [72]. The 2-day protocol may have logistical advantages with flexibility in timing of lymphoscintigraphy and surgery. The 1-day protocol requires close cooperation between nuclear physicians and surgeons with respect to the estimated speed of lymphatic drainage in the affected region. Intraoperative injection is to be avoided because lymphatic drainage in melanoma may be aberrant, delayed or to more than one nodal basin or the radiopharmaceutical may have moved on to non-SLNs downstream that need not be removed.

The injection should be done under sterile conditions with disinfection of the injection site to avoid wound infection. Furthermore, topical anaesthetic cream may be used to reduce the pain, especially when the primary melanoma is in a sensitive location. To avoid contamination, a sheet should be placed over the skin next to the injection site. After every injection the punctured skin should also be covered with a swab before the needle is removed to avoid contamination of the surrounding skin.

The radiotracer is injected around the primary tumour or on each side of the centre of the excision biopsy scar, usually in four or more aliquots. Fewer deposits may be injected if appropriate [73]. In head and neck melanoma, the radiopharmaceutical should be injected in four equal deposits (3, 6, 9, 12 h) around a primary lesion because of the often complex lymphatic drainage to multiple lymph nodes. However, some centres spare the caudal injection deposit to avoid masking of nearby lymph nodes by the injection site. Also in trunk melanoma, at least four separate tracer injections might be preferred. In melanoma of an extremity, at least an injection medial and lateral to the tumour has to be performed to mimic lymphatic drainage from the tumour. The radiotracer should be injected in wheals. The injected volume is 0.1 – 0.2 ml per aliquot, depending on the location of the primary tumour. The volume needs to be small because of the intradermal injection of radiocolloid. If the volume is too large, lymphatics may collapse or the wheal on the skin surface may rupture. Subcutaneous injection should be avoided because it may not reflect the lymphatic drainage from the cutaneous melanoma. Tuberculin syringes without a dead space and a 25G or 27G needle are used. If a tuberculin syringe is not available, the needle can be cleared with air following the tracer during injection. The distance from the injection site to the scar or tumour should not exceed 1 cm. The injected dose depends on the injected radiopharmaceutical (Table 1).

Table 1 Characteristics of ^{99m}Tc-based radiopharmaceuticals

Agent	Maximum particle size (nm)	Typical particle size range (nm)
Sulphur colloid (Sulfur colloid®)	5,000 (unfiltered)	100 – 200 (filtered)
Antimony trisulphide (Lymph-Flo®)	80	5 – 30
Sulphide nanocolloid (Lymphoscint®)	100	10 – 50
Nanocolloidal albumin (Nanocoll®)	100	5 – 80
Rhenium sulphide (Nanocis®)	500	50 – 200
Tilmanocept (Lymphoseek®)	About 7 (equivalence)	About 7 (equivalence)

Radiopharmaceuticals

Various radiopharmaceuticals, primarily ^{99m}Tc-based agents ($t_{½}$=6 h), have been used for lymphatic mapping in melanoma worldwide. The radiopharmaceutical drains from the injection site via lymphatic vessels and is accumulated in the SLN by phagocytosis of macrophages or retention due to particle size. Often, a fraction of the radiopharmaceutical moves on to second- and third-echelon nodes downstream. Smaller particles are drained more quickly to the SLN but also tend to accumulate in non-SLNs. Large particles migrate more slowly and are mainly retained in the SLN. There are no documented differences in the clinical outcome with different particle sizes [34]. The choice of radiopharmaceutical is usually based on availability: ^{99m}Tc-albumin nanocolloids in Europe, ^{99m}Tc-antimony trisulphide in Australia and Canada and ^{99m}Tc-sulphur colloid in the US.

Small particles such as ^{99m}Tc-antimony trisulphide (mean size 5 – 30 nm) drain quickly, and imaging is usually completed 1 – 3 h after administration. When medium-sized particles (50 – 200 nm) are used, nodes may not be clearly visible after 1 – 2 h and additional images should be acquired after 4 – 6 h or even the next day. This has to be taken into consideration in a 1-day protocol. In Europe, small or medium-sized colloids are commonly used (Nanocoll®, human serum albumin nanocolloid, 5 – 80 nm; Nanocis®, rhenium sulphide nanocolloid, 50 – 200 nm). Particles >200 nm move slowly and remain predominantly at the injection site. Therefore, ^{99m}Tc-sulphur colloid, with a maximum size of 350 – 5,000 nm, should be filtered with a 100- to 200-nm membrane filter after preparation of the radiopharmaceutical to select smaller particles.

A further radiotracer was approved by the US Food and Drug Administration (FDA) in 2013 and received a positive statement from the European Medicines Agency in 2014: ^{99m}Tc-tilmanocept (Lymphoseek®), which is a mannosyl diethylene triamine penta-acetate (DTPA) dextran that targets the CD206 receptor. The molecular size is 7 nm, but accumulation in SLNs is not dependent on particle size as with the other colloids. Tilmanocept binds to mannose receptors expressed by reticuloendothelial tissue including macrophages and dendritic cells in lymph nodes, which present it to T-cell lymphocytes in lymph nodes. The advantages of this tracer include rapid clearance from the injection depot and low accumulation in second-echelon nodes [74, 75]. This novel radiopharmaceutical might be of particular utility in patients with head and neck melanoma.

Labelling, injected activity and volume

Labelling should be performed according to the product information provided by the manufacturer. The commonly used radiopharmaceuticals are labelled with ^{99m}Tc-pertechnetate and a radiochemical purity of ≥90 – 95 % should be confirmed before injection. ^{99m}Tc labelling of human serum albumin colloid proceeds within 10 min at room temperature while sulphide, rhenium, and antimony colloids require heating [76, 77]. It is important to pay attention to the specific activity (number of decays per second per amount of substance) and the number of particles administered. Based on the assumption of a limited clearing capacity of the macrophages in the SLN, it has been suggested that the maximum activity of ^{99m}Tc should be loaded onto the smallest number of particles [78]. Labelling at higher specific activities has been demonstrated to result in higher nodal count rate for the same administered activity [79]. Although the kit reconstitution instructions allow the addition of 185 to 5,550 MBq in a volume of 1 to 5 ml [76], it is recommended that ^{99m}Tc-human serum albumin colloid be prepared at a minimum activity concentration of 100 MBq/ml (i.e. to deliver 20 MBq in 0.2 ml) at the time of injection and, wherever possible, the maximum reconstitution volume be used (e.g. ≥500 MBq in 5 ml). More information about good manufacturing practice can be found in *Guidance on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals* [80].

Colloids are suspensions and may therefore settle by gravity if the syringe is not moved for more than a few minutes. Before injecting the radiopharmaceutical, the syringe therefore has to be tilted, but not shaken, to distribute the tracer in the suspension homogeneously. Until now, no consensus on the injected activity has been reached. The administered activity depends on the time between lymphoscintigraphy and operation (1-day or 2-day protocol) and varies among published studies (from approximately 5 MBq up to 120 MBq). The injected activity should be adjusted according to the time

point of surgery, the physical decay and the intended residual activity in the operating room, determined by results of previous studies to achieve high detection rates (>10 MBq) [72], but also legal regulations concerning radiation safety of staff.

Image acquisition

Imaging system

All possible drainage regions have to be covered during image acquisition. Therefore, a dual-head gamma camera with large field of view detectors is preferred to reduce the examination time. However, a single-head gamma camera is also suitable. Low-energy, high-resolution or ultrahigh-resolution collimators are recommended to better distinguish individual SLNs. Using ^{99m}Tc, the energy window should be 15 % or 20 % centred on the 140-keV photopeak. Technical details of gamma probes for detection of SLNs preoperatively and in the operating room can be found below.

Body contouring facilitates the localization of hot spots. Therefore, a ^{99m}Tc or ^{57}Co flood source should be positioned on the opposite side of the camera head for transmission imaging. Because faint uptake in SLNs may be missed using a ^{57}Co flood source, imaging may be repeated without body contouring. If no flood source is available, a point source can also be used to trace the outline of the body. In some gamma cameras a ^{153}Gd source is already integrated for attenuation correction of SPECT images; this enables acquisition of simultaneous emission and transmission images at any angle.

Quality control

Appropriate quality control of the imaging system should be routinely performed and image display should be used in SLN procedures. Quality control also should be routinely performed on the gamma probe used in the nuclear medicine department and the operating room for SLN procedures. The reader is referred to the EANM guidelines *Routine quality control recommendations of nuclear medicine instrumentation* for additional information [81] and the SNMMI guidelines *Procedure guideline for SPECT/CT imaging 1.0* [82].

Dynamic imaging

Dynamic imaging immediately following tracer injection is important since a lymph collector directly draining to a lymph node clearly identifies this node as a sentinel node wherever it is located. For dynamic imaging the tracer is injected when the patient is already lying in a supine or prone position on the bed of the imaging system, depending on the location of the primary tumour. Starting image acquisition immediately after the injection may help to identify lymph nodes next to the injection site and to differentiate SLNs from second-echelon nodes. Lymphatic channels can be visualized in dynamic series and direct drainage pathway(s) can be identified. Furthermore, in-transit nodes can be detected reliably. Dynamic imaging (10 – 20 min, one frame per minute in a 128×128 matrix in word mode) during the first 10 min after injection is recommended for detection of SLNs in head and neck melanoma. Although dynamic images are time consuming, dynamic series should be acquired whenever possible because this facilitates image interpretation [83]. In melanoma of the hand/forearm or foot/leg, dynamic imaging should start over the injection site and follow the lymphatic drainage to the knee or elbow and axilla or groin to reveal ectopic basins and in-transit lymph nodes (popliteal, epitrochlear).

Early static images

After dynamic series, static planar 5-min images (anteroposterior and lateral) should be acquired with a 256×256 matrix over the lymph node basin in which the SLN is expected. Early images help to discriminate true SLNs from the second-echelon nodes that are often observed. In melanomas of the trunk, usually bilateral static images of the axilla, trunk and groin are necessary [84, 85]. Alternatively, body scanning from the neck to the groin can be performed.

A dual-head gamma camera is helpful because images in different views can be acquired simultaneously, facilitating differentiation of superficial and deep nodes (e.g. iliac, paravertebral, retroperitoneal).

Delayed static images

Late 3- to 5-min anteroposterior and lateral static images (1 – 3 h after tracer injection) are acquired to identify all relevant SLNs and to mark them on the skin surface. The views according to the location of melanoma are summarized in Table 2. To reduce scattering artefact from the injection site, images with lead shielding of the primary tumour can be

Table 2 Recommended regions covered by static images and/or SPECT/CT according to the location of the primary tumour

Tumour location	Static images
Trunk	Axilla + trunk + groin; or body scanning from neck to groin
Hand/forearm	Elbow + axilla + neck
Upper arm	Axilla + neck
Foot/lower leg	Knee + groin
Head neck	Neck in multiple projections
Thigh	Groin

added. This may be helpful especially if the primary tumour is located next to the nodal basin.

SPECT/CT

Often no exact localization of hot nodes is obtained by planar imaging. Hybrid imaging with SPECT and CT including anatomical information improves the localization of SLNs and reduces misinterpretation of images (see below) [83, 86]. Images obtained by SPECT/CT are three-dimensional and have better contrast and spatial resolution than planar images. For SPECT/CT, a higher overall SLN detection rate and better detection of SLNs located next to the injection site have been reported [87], and in addition there is a significant cost reduction [88]. SPECT/CT should be performed in head and neck melanoma owing to the complex anatomy [83]. Moreover, SPECT/CT is highly recommended for the groin area and recommended for the axillary area because it facilitates the detection of in-transit nodes and aberrant lymphatic drainage stasis in lymph vessels and consequently facilitates the surgical procedure [2]. In pregnant patients, SPECT without a CT scan should be performed if an inguinal or axillary nodal base is to be imaged. However, for the head and neck area a low-dose CT scan is justified because of the relative distance from the uterus and the intrinsic body shielding for scatter. The added diagnostic value in this specific area justifies the very low added dosage to the foetus contributed by the low-dose CT scan. SPECT acquisition parameters may include a 360° orbit with 180° or 90° detector geometry, 128×128 matrix size, and 3° angle step with 20 – 25 s/frame with iterative reconstruction algorithms.

CT is usually performed as a low-dose scan without contrast enhancement, which provides rough anatomical information and can be used for attenuation correction of SPECT images. For depiction of soft tissue, a corresponding CT kernel is preferred, such as a B30 kernel. Also to enable 3D viewing, transaxial, coronal and sagittal CT series with fusion series should be processed. Alternatively, one transaxial series with a small increment (1 – 2 mm) should be processed and viewed with modern 3D viewing software capable of both rendering multiplanar reconstruction views and displaying fused images with SPECT reconstruction. The small increment limits step artefacts in the *z*-axis and is also relevant for delineation of small lymph nodes. Display of high-resolution images with a 3D viewer is of great benefit, especially in the head and neck area. All acquired images should be stored in a permanent form.

Image interpretation and report

Early dynamic, static and delayed static images identify SLNs in the majority of patients. The strongest criterion for the definition of a lymph node as an SLN is the presence of a lymphatic channel from the primary tumour to the lymph node (usually visualized on dynamic images). Also, the first appearing node is rated as an SLN. The SLN is often the hottest node and the node closest to the injection site, but this is not necessarily the case. The distance from the primary may also contribute to the definition of the SLN. Nodes that appear only on late images, but in a further nodal field, are also SLNs unless dynamic images reveal that they receive lymph channels from an earlier detected node. The results of SLN mapping should be communicated directly to the surgeon, for example as a brief report in advance of the surgery, including all available and labelled images. This is of particular importance if lymphatic drainage is ambiguous.

A final report should be sent later, including the following detailed information: radiopharmaceutical used, injection technique (location, depth, number of injections), activity and volume of injected radiopharmaceutical, time point of image acquisition, orientations of images and the name of the responsible nuclear physician. The visualized structures and their location (lymphatic channels, SLNs, second- and third-echelon nodes) should be described and labelled on the images themselves. The number and location of SLNs in each basin must be carefully reported, including depth from the skin. Also, non-SLNs should be described. In particular, errors in the examination procedure (e.g. contamination), unexpected lymphatic drainage or in-transit nodes should be described in detail. Information gathered by SPECT and CT should be reported separately. Even additional findings on CT have to be mentioned (e.g. pathological lymph nodes without tracer accumulation). All acquired planar images, appropriate coregistered SPECT/CT images and the final report with a conclusion regarding the results should be available in the operating room. The nuclear physician should be contactable in case any questions arise.

Pitfalls

Some pitfalls may occur in an SLN procedure, including in patients with melanoma, and both false-positive and false-negative interpretations of lymphoscintigraphy are possible.

Sources of false-positive interpretation of images

1. Skin contamination arising from the injection or urinary contamination may be misinterpreted as a lymph node. Hot spots attributed to contamination are often very hot and focal. Planar images from different views and SPECT or SPECT/CT help to identify contamination [89].
2. Second-echelon nodes may be misinterpreted as SLNs if no early dynamic or static images are acquired. Acquiring delayed images too soon may also play a role here.

3. Lymphangioma or lymphatic lakes may be misinterpreted as lymph nodes.
4. Other tissues containing radioactivity may complicate image interpretation.

Sources of false-negative interpretation of images

1. Adjacent nodes may be misinterpreted as one SLN.
2. The SLN may be masked by the injection site, especially in head and neck cutaneous cancer [90].
3. Only a small amount of the radiotracer drains from the injection site. In the event of any alteration in the lymphatic drainage, the SLN may contain little radioactivity. Imaging without a transmission source for body contouring or lead shielding of the injection site may help.

In summary, these pitfalls occur more often if only a single view and late static images are acquired. Images in multiple projections (ventral, dorsal, lateral, oblique) and SPECT or SPECT/CT can improve image interpretation and overcome some limitations [87].

In some patients lymphatic drainage is slow. If no tracer drainage is observed in dynamic or early static images, massage of the injection site or along the lymphatic vessels can be helpful. To avoid contamination, the patient or nuclear technologist should wear gloves. Furthermore, the injection site may be warmed with a hot-water bag to improve drainage of tracer. Constriction of the lymphatic vessels should also be excluded. Slow lymphatic flow is observed in older patients (>50 years). In extremity melanoma, passive exercise of the limb may be helpful [91]. In some cases, repeated imaging (delayed images up to 24 h) or reinjection of radiotracer, if there is any suspicion of false injection, may also be helpful.

Skin marking

A skin mark directly over the location of the SLN is helpful to define the region of interest in the operating room and to assist the surgeon in intraoperative localization of SLNs. The SLN in each basin should be marked accurately on the skin using indelible ink or tattoo since this is valuable information for follow up if the SLN is not removed for some unexpected reason. In some patients a pair of skin marks from an anterior and a lateral view may be helpful. Good communication between the surgeon and the nuclear medicine imaging team is important here to ensure that the operating position for the surgical procedure is known before imaging is performed, otherwise the skin marks could be misleading. The patient positioning has to be noted and if possible the patient should lie in the same position as in the operating room. In order to define the surface location of the SLN, a gamma probe, a syringe with a small amount of radiopharmaceutical in the tip or a tracer source (e.g. a ^{57}Co 'pencil' marker source) can be used. The depth of the node should be described or indicated using SPECT/CT or an orthogonal view. To allow for orthogonal depth measurements using electronic callipers a small amount of tracer in the needle hub or tracer source can be placed on the skin mark.

To avoid confusion it is recommended that lymph nodes that can be clearly identified as second-echelon nodes should not be marked, otherwise unnecessary resection of second-tier nodes may be performed, increasing the risk of morbidity [92]. The presence of more than one SLN within a nodal basin should be described in detail in the report. In the operating room, the surgeon should not only rely on skin marking but read the images acquired prior to the operation carefully. Especially in cases of aberrant lymphatic drainage, the responsible nuclear physician and surgeon should discuss the results of lymphoscintigraphy.

Procedures in the surgical suite

For correct intraoperative localization of the SLN, the acquired images should be available in the operating room either as hard copy or in electronic form, depending on local conditions.

The operation

The operation is typically performed as a 1-day admission procedure under general anaesthesia but can if necessary be performed under local anaesthesia. The surgeon's repertoire includes both detection techniques; 13 % of the SLNs are only radioactive, 1 % are only blue, while the remaining 86 % are both radioactive and blue [93]. If a blue dye procedure is performed in addition to radioguided surgery, 0.5 – 1 ml patent blue V or isosulfan blue is injected intradermally around the melanoma or the biopsy site at the beginning of the operation [94]. Massage of the injection site will accelerate lymphatic drainage. The dynamic lymphoscintigrams indicate where the afferent lymph vessel is to be found and guide, in combination with the skin marking, the site of the incision. This vessel is typically identified underneath the subcutaneous fascia. The blue vessel is dissected until it drains into the SLN. The node is freed from the surrounding tissue and afferent and efferent blood and lymph vessels are ligated and divided. The basin is examined for other afferent lymph vessels and scanned for additional radioactive SLNs.

Using only radionuclides, preoperative lymphoscintigraphy and skin marks are used as a "road map" for moving the gamma probe and identifying the region with the highest count rate. To reduce scattering artefacts, the probe has to be pointed away from the injection site. The probe is then used for guidance in an iterative process, as the surgeon

proceeds to progressively expose the overlying tissue in order to identify precisely the location of the radioactive nodes in the surgical bed (in vivo measurement). After excision, the probe is placed over the resected tissue to confirm the successful dissection of the SLN (ex vivo measurement). Subsequently, the surgical bed is measured again and checked for remaining activity, which may be present especially in cluster nodes. The information from preoperative SPECT/CT is helpful in identifying these cluster nodes. The surgeon should also palpate the region of interest to identify enlarged hard nonradioactive or nonblue nodes full of metastases and no longer receiving lymphatic drainage. These nodes should also be removed.

The advantage of the blue dye technique is that identification of the node on a direct lymphatic drainage pathway is certain, but this approach requires finesse and a delicate surgical technique. The probe-guided operation is more straightforward but it can be difficult to identify the correct node when multiple nodes have accumulated the radiopharmaceutical. Allergic reactions to the blue dye are rare and usually mild but anaphylactic shock has been described [95]. Pregnancy is listed as a contraindication to blue dye due to the risk of anaphylaxis [29, 61, 96]; however, specific adverse events due to the radioactive and blue tracers in pregnant women are not known to have been reported.

Gamma probe

The gamma probe used should be designed for intraoperative application. The probe should be placed in a sterile sheet. The probe should provide instantaneous and cumulative counts. Conversion of count rate into an acoustic signal with a variable pitch facilitates SLN localization. Many different systems are commercially available, and users are advised to evaluate a number of probe systems prior to purchase to ensure their suitability. All medical devices used need CE certification. Quality control should be routinely performed on the probe used in the nuclear medicine department and the operating room for SLN procedures [81].

Gamma cameras

The resolution of a hand-held gamma probe is lower than that of conventional gamma cameras. Deeply located SLNs may be difficult to localize because of attenuation due to overlying tissue. Also, SLNs may be hidden by the injection site, as is often observed in malignancies in the head and neck region (shine-through phenomenon). In these challenging settings, using three-dimensional imaging and navigation [97–99] or a portable gamma camera [100–102] may improve intraoperative detection of SLNs.

Radioactive waste

The radioactive waste should be collected according to local conditions. Personnel working with radioactive material should be trained. The staff of the surgical department and the institute of pathology involved in SLNB should be educated in safe handling of contaminated material.

Histopathology

Histopathological assessment of SLNs is the "gold standard" to determine the presence of lymph node metastases. Procedures for pathological examination vary among centres and countries. Frozen sections have a poor (47 %) sensitivity and are no longer used [103]. Serial sections are obtained and stained with haematoxylin and eosin and immunohistochemical stains, usually S-100 antibodies, MART-1/Melan-A and HMB-45 [104, 105]. The EORTC Melanoma Group has provided dedicated guidelines on how the SLN should be divided and analysed (e.g. [106–108]).

Completion lymph node dissection

Patients with a positive SLN are offered completion lymph node dissection and 12 – 25 % of them are found to have involvement of additional lymph nodes [109–112]. The results of the MSLT-1 study show that this management prolongs disease-free survival in patients with tumours thicker than 1.2 mm and improves melanoma-specific survival in patients with nodal metastases from tumours of intermediate Breslow thickness [17]. The ongoing MSLT-2 and EORTC Minitub trial have been designed to assess the role of completion lymph node dissection in patients with a positive SLN [113, 114].

Radiation dosimetry

The use of radioactive colloids for SLNB requires the optimization of radiation safety issues, including issues regarding patients, staff in nuclear medicine departments, the operating room, pathology laboratories and the disposal of radioactive waste. The following sections on patient and staff dosimetry were taken almost entirely from the previous *EANM-EORTC general recommendations for sentinel node diagnostics in melanoma*, which were published in 2009 [115].

Patients

For a regular nuclear medicine department, lymphoscintigraphy is a procedure involving low activities. The estimated local radiation dose varies depending on the administered activity,

injection site, volume of tracer, the use of multiple injections, and retention time [116]. However, melanoma originates from skin tissue that is relatively less radiosensitive than many other tissues. The tissue weighting factor defined by the International Committee of Radiation Protection (ICRP) for the determination of effective dose is 0.01 for skin compared with 0.12 for breast. Therefore, in patients with melanoma the local radiation dose contributes little to the effective dose [117].

The different radiopharmaceuticals used for SLN imaging show minor differences in dosimetry. The local absorbed dose at the injection site with respect to the most common radiocolloids is less than 50 mGy/MBq [116, 118, 119]. In determining the effective dose, it should be taken into account that the radiolabelled colloid migrates minimally throughout the bloodstream or reticuloendothelial system (RES) or beyond the SLN and second-echelon lymph nodes. Assuming that 20 % of the administered activity is absorbed in the RES systemically, the effective dose is calculated as 2 μSv/MBq in a 'worst-case' calculation for melanoma [120]. This corresponds to 0.04 mSv after an injection of 20 MBq of ^{99m}Tc-labelled small colloid.

It should be noted that adoption of SPECT/CT imaging protocols for SLN in melanoma will increase both local radiation dose and effective dose due to inclusion of the CT procedure, the dosimetry being dependent upon both the site of the melanoma and the CT acquisition parameters selected. A low-dose CT scan with a field of view limited to avoid radiosensitive tissues can help to keep the effective dose to a minimum. For a low-dose CT scan for attenuation correction, an effective dose of 2.4 mSv has been reported [121]. The total exposure in such cases is the emission-generated dose plus the transmission-generated dose.

Pregnancy

Pregnant patients may be offered SLNB after careful counselling regarding the safety and efficacy of the procedure. According to ICRP publications, the risk to the foetus is considered negligible for investigations exposing a foetus to <1 mSv [122]. The dose from the radiopharmaceutical is low (120 MBq administered activity in the breast area results in an effective dose of 0.0085 mSv according to ICRP publication 106 for ^{99m}Tc-labelled small colloids) [123]. For a low-dose CT scan of the neck area, the dose is higher than from the radiopharmaceutical, but again very low. The estimated dose to the foetus is less than 0.1 mSv for full-dose diagnostic CT protocols of the head (using higher current because of the skull) [124]. Only in a melanoma located rather close to the foetus (over the lower abdomen or back) is the theoretical risk of exceeding 1 mSv a relevant question. In such a case, the most important modification that may reduce foetal radiation exposure will be reduction of the injected activity and a 1-day protocol should be used, with a short interval from injection to operation to minimize decay [116, 125, 126]. To compensate for this lower injected dose, image acquisition should be twice the normal duration [127]. In pregnant women, SPECT/CT of the thorax and the abdomen/pelvis is contraindicated – in the former because too little diagnostic gain is to be expected for axillary nodal basins and in the latter because of the significant foetal dose associated with these scan areas. In these cases SPECT alone is preferred. However, in single cases a low-dose CT scan in addition to SPECT might be performed after interdisciplinary discussion of risks versus benefits.

Lactating women

The presence of ^{99m}Tc in breast milk has not been reported, but it has been recommended that breast feeding should be suspended in nursing mothers for at least 4 h [123] and preferably for 24 h after radiopharmaceutical administration [125], since the radiopharmaceutical will be excreted from the breast milk during this period.

Staff dosimetry

Within the EU, national implementations of EU Directives apply with respect to radiation protection aspects of the clinical practice of nuclear medicine. In applying the 1990 recommendations of the ICRP [128], the Basic Safety Standards Directive enforces [129] a general radiation protection framework to ensure the safety of employees and the public. The Medical Exposures Directive reinforces [130] the need for justification, optimization and limitation of all exposures, and places additional specific requirements on stated duty holders, especially with respect to the practical aspects of a medical exposure – referral, individual justification and execution – including the training and competence of all staff whose actions contribute to the procedure(s) performed.

Staff in the nuclear medicine department

To comply with regulatory requirements, including those mandated by the Medical Exposures Directive within the EU and those in force elsewhere [131], radiocolloid administration and preoperative diagnosis must be performed by trained nuclear medicine personnel working in controlled environments. The administered activities in lymphoscintigraphy are low compared with those used in most other nuclear medicine procedures. Any increase in the occupational exposure of nuclear medicine staff due to an SLN procedure will be minimal compared with the exposure allowed by legislation as they are already categorized as radiation workers. The highest doses received by the hands of the staff have been recorded for the

physician who administers the tracer [132]; however, this dose is far below the ICRP annual dose limits for the extremities of a radiation worker [128]. One potential cause of significant exposure exists, however: if transmission imaging using a radioactive ^{57}Co flood source is performed, the source must not be held directly during image acquisition.

Staff in the operating room

Radiation exposure of operating room personnel arising from the handling of radioactive specimens from SLN procedures is minimal. Studies have demonstrated that the occupational doses are insignificant: the mean whole-body dose received by surgical staff has been measured at <1 μSv per operation [116, 133–135], with the maximum effective dose to the surgeons involved reported to be <2 μSv [34, 116, 136] . The radiation dose to the hands of the surgeon has been estimated to be 5 – 94 μSv per patient [120]. When the surgical procedure is performed 24 h after injection, the absorbed doses to the hands of the medical staff may potentially be minimized [132, 137]. The monitoring of operating room personnel for occupational exposure to radiation during SLNB procedures is unnecessary. Additional shielding and monitoring devices are not required in the operating room.

Pregnant staff in the operating room

One circumstance requiring specific consideration is that of the pregnant female surgeon or scrub nurse regularly performing or assisting the procedure. A pregnant surgeon who participates in up to 100 SLN operations will stay below the limit of radiation exposure as recommended for pregnant women [135]. For a scrub nurse the exposure will be even less due to the larger distance from the source.

Staff in the pathology department

The pathology staff usually spend a shorter time handling the radioactive tissue specimens than does the surgeon, and do so longer after injection; their exposure will therefore be lower. Even personnel performing an unusually high number of procedures receive radiation doses well below established limits for members of the general public [138]. Under any circumstances, radiation exposure to the pathology staff is low and should normally not require badge monitoring.

Radiation safety precautions

When labelling the pathology specimens to be transported to the laboratory, in many institutions they are sealed in suitable containers with outer labels indicating radioactive content [137]; however, labelling is not required if the surface dose rate is <5 μGy/h [139]. Even if specimens not labelled in an institution does, all personnel handling them must be properly trained and authorized and the specimens should be transferred promptly. If leakage from the container occurs, the surface contamination will in most cases be above the limits allowed by legislation. Therefore, labelling can serve as a reminder to staff handling the containers that they must enact the required decontamination protocols.

Radioactive clinical waste

While surgical instruments and pathology slides appear to stay at background radiation levels, measurable contamination of absorptive surgical sponges and other materials used in the handling of radioactive tissues does occur, especially when they are used in the vicinity of the injection site [116, 140]. Although a negligible contamination hazard, such materials constitute radioactive clinical waste. It is advisable to monitor them for contamination and, if contamination is found, to hold the waste for decay-in-storage before disposal.

In summary, radiolocalization of SLNs in patients with melanoma is associated with low levels of radiation exposure. While lymphatic mapping is not contraindicated in pregnant patients, it is common to halve the dose activity and same-day surgery is preferred. Radiation exposure monitoring, limiting the number of SLN procedures performed and additional shielding are not required for staff in the operating room or pathology department.

Issues requiring further clarification

SLNB using blue dye or radiolabelled colloids is widely accepted because of the following benefits and characteristics: acquisition of valuable staging and prognostic information, reduction in disease recurrence, improvement in survival, low morbidity and minimal invasiveness. Nevertheless, some issues have to be addressed in further trials:

- The indication for SLNB in locally recurrent melanoma has to be clarified in prospective trials. Single-centre studies have demonstrated the feasibility of SLNB in patients with in-transit melanoma or local recurrence. Optimization of regional treatment seems to be possible.
- Recommendations for SLNB in melanoma with a Breslow thickness <1 mm differ among organizations worldwide and should also be investigated in further prospective studies.
- The role of the new receptor-targeted radiotracer ^{99m}Tc-tilmanocept needs to be evaluated and compared with the current standard in Europe [141]. The first results of a nonrandomized phase III trial comparing this tracer and blue dye showed that ^{99m}Tc-tilmanocept identifies 98.7 %

of blue nodes and identifies more SLNs in more patients and more melanoma-containing nodes [75]. In particular, due to the intricate lymphatic drainage patterns in the head and neck area, the role of ^{99m}Tc-tilmanocept in head and neck melanoma needs to be defined.

– As an alternative nonisotopic and nonblue dye methodology, the fluorescent dye indocyanine green (ICG) may be administered in the operating room for detection of SLNs in melanoma. Fluorescent subcutaneous lymphatic vessels or nodes can be visualized using special cameras. One potential limitation of ICG fluorescence techniques is that the fluorescence effect is time-limited, so that effective nodal detection is confined to a 30-min period [142]. A second possible limitation is the restricted optical penetration (<10 mm). Lymph nodes with overlying structures or lying deep in adipose tissue may easily be missed [143]. Combinations of ICG and radiocolloids (hybrid tracers) also yield high identification rates and their use needs to be investigated in further studies [144, 145].

  Administration of colloidal ferumoxides in lymph nodes is another alternative method for detection of the SLNs [146]. A recent prospective, multicentre and multinational trial, the Central-European SentiMag study, compared the gold standard (^{99m}Tc-nanocolloids with or without blue dye) and lymphoscintigraphy using superparamagnetic iron oxide particles (SPIOs with a particle size of 60 nm, Sienna+®; Endomagnetics Ltd., Cambridge, UK) and a hand-held magnetometer (SentiMag®; Endomagnetics Ltd) in 150 participants undergoing breast cancer surgery and SLN sampling. Results showed an equivalent detection rate per patient of 97.3 % (146 of the 150 patients) for ^{99m}Tc-nanocolloids vs. 98.0 % (147 patients) for Sienna+® [142].

  In summary, the results of non-isotopic and non-blue dye alternatives are promising. However, their relevance for SLNB in melanoma needs to be investigated in prospective trials.

– For intraoperative detection, usually conventional acoustic gamma probes are used. However, in recent years, portable gamma cameras have been developed and have been introduced to the operating room. These enable fast and reliable detection and localization of SLNs [147, 148]. Additionally, a 3D system has been developed [98, 149] that allows the surgeon to visualize the SLN in real-time using 3D navigation. Both technical developments may simplify and speed up the SLNB procedure and also enable reliable detection of SLNs in anatomically complex regions such as the head and neck, where it is difficult to locate SLNs [97, 99, 102]. Further prospective studies are necessary to evaluate the field of indications for these novel intraoperative probes and to investigate their cost-effectiveness.

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Compliance with ethical standards

Conflicts of Interest None.

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