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GUIDELINES

The EANM clinical and technical guidelines for lymphoscintigraphy and sentinel node localization in gynaecological cancers

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Abstract The accurate harvesting of a sentinel node in gynaecological cancer (i.e. vaginal, vulvar, cervical, endometrial or ovarian cancer) includes a sequence of procedures with components from different medical specialities (nuclear medicine, radiology, surgical oncology and pathology). These guidelines are divided into sectione entitled: Purpose, Background information and definitions, Clinical indications and contraindications for SLN detection, Procedures (in the nuclear medicine department, in the surgical suite, and for radiation dosimetry), and Issues requiring further clarification. The guidelines were prepared for nuclear medicine physicians. The intention is to offer assistance in optimizing the diagnostic information that can currently be obtained from sentinel lymph node 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 practice of referral to, and the performance, interpretation and reporting of all steps of the sentinel node procedure in the hope of setting state-of-the-art standards for high-quality evaluation of possible metastatic spread to the lymphatic system in gynaecological cancer. The final result has been discussed by a group of distinguished experts from the EANM Oncology Committee and the European Society of Gynaecological Oncology (ESGO). The document has been endorsed by the SNMMI Board.

Keywords Sentinel node · Gynaecological cancer · Lymphoscintigraphy · Blue dye · Gamma probe · Pathology

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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 these guidelines 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. They are not inflexible rules or requirements for practice and are not intended, nor should they be used, to establish a legal standard of care. For these reasons and those set out 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 out in the guidelines when, in the reasonable judgment of the practitioner, such course of action was 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.

Purpose

The aim of this document is to provide general information about sentinel lymph node (SLN) detection in patients with gynaecological cancer. These guidelines describe the protocols currently used in clinical routine (vulvar and cervical cancers) and in investigational approaches (vaginal, endometrial and ovarian cancers), 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 from one country to another and from one medical institution to another. The present guidelines for nuclear medicine physicians offer assistance in optimizing the diagnostic information from the SLN procedure. The final result has been discussed by a group of distinguished experts from the EANM Oncology Committee and the European Society of Gynaecological Oncology (ESGO). The present document was endorsed by the SNMMI Board in February 2014.

Background information and definitions

The SLN is the first regional lymph node that directly drains the lymph from the primary tumour. Thus SLNs are considered the first nodes to receive the seeding of lymph-borne metastatic cells [1]. After description of the method of SLN biopsy by Cabanas [2], SLN mapping and biopsy became a routine technique in cancer surgery (breast and melanoma), contributing to the minimization of the surgical procedure [3]. SLN detection provides prognostic information on nodal status and can help avoid morbidity from overtreatment. Furthermore, as no imaging modality is able to detect microscopic metastases, SLN biopsy is considered the only reliable method for screening lymph nodes and identifying micrometastatic disease in regional lymphatic nodes [4].

Cervical cancer

Cervical cancer is the third most frequent gynaecological cancer in developed countries but the first one in underdeveloped countries and the primary cause of death in women of child-bearing age [5]. Generally, it spreads locally to adjacent pelvic organs, but can also spread to locoregional lymph nodes, and in some rare cases lung, liver, bone and brain haematogenous metastases have been seen.

The most important prognostic factor is locoregional nodal invasion, including the pelvic and paraaortic nodes [6, 7], related to tumoral invasion of the lymphatic vascular space [8]. In stage Ia1 with lymphatic/vascular involvement nodal invasion is around 1 % [9]. Therefore hysterectomy or conization without lymphadenectomy is appropriate. In early cervical cancer there is an incidence of nodal pelvic invasion of between 11.5 % and 21 % [10, 11], which reduces to 0.5 – 7.3 % when only stage Ia2 is considered [12]. In these early stages (Ia2/Ib1, IIa1) treatment is radical hysterectomy and pelvic lymphadenectomy, to confirm nodal status and possible risk of paraaortic invasion. If there is a risk of developing nodal metastasis, generally the treatment is primary chemoradiation, avoiding surgical morbidity. There are several studies that have confirmed the orderly progression of the disease. The most frequent location of pelvic nodal metastases is the obturator group, followed by the external iliac basin [13]. Drainage will go to the pelvic nodes, the common iliac

and finally the paraaortic nodes [10]. It is infrequent to find "skip metastasis" in the paraaortic region without involvement of the pelvic lymph nodes [14–16].

Given the low rate of nodal invasion in early-stage cervical cancer (Ia2/Ib1, II1a) and the orderly progression of the spread of the disease, there is a well-established indication for SLN detection in these cases. Accurate lymph node staging is essential not only for detection, but also for both prognosis (major prognostic factor in early-stage disease) and treatment (regional control of disease) in patients with cervical cancer. Yet another important argument for SLN detection is the identification of micrometastasis by pathological ultrastaging. Significantly reduced survival associated with micrometastasis in SLN has recently been shown in patients with cervical cancer [17]. Indeed, if intraoperative pathological study shows a SLN to be positive, there is no need to continue with the hysterectomy, as the appropriate treatment would be chemoradiation. It is important to consider SLN detection in each pelvic site independently rather than doing an analysis per patient [18]. There is a decrease in the number of false-negative SLNs if lymphadenectomy is performed at a site with no drainage [19], even in more advanced stages (Ib2/IIa) [20].

The usefulness of SLN detection in patients with cervical cancer has been studied in a large series of 507 women [21] and in reviews that included 831 patients [22]. A detection rate of over 90 % (93.5 % and 96 %) was found using the combined technique, a high negative predictive value (94 % and 97 %) and a false-negative rate of 8 %. The most interesting result is the higher detection rate and negative predictive value in tumours less than 2 cm in size (94 % vs. 84 % and 99 % vs. 89 %).

In summary, the benefits of SLN detection are a better knowledge of nodal status – due to the detection of unusual drainage patterns (to paraaortic or presacral nodes) [23] and the possibility of ultrastaging, with the detection of micrometastases [24, 25] – and a reduction in morbidity. Morbidity is the result of unnecessary lymphadenectomy or overtreatment in patients who need chemoradiation after surgery, especially when SLN detection is performed by laparoscopy. The groups of patients that benefit most from this procedure are women with a cervical tumour less than 4 cm in size (with the best results found in tumours less than 2 cm in size [8, 21]) and in early stages (Ia2/Ib1, IIa1). Exclusion criteria are previous pelvic lymphadenectomy and nodal or parametrial invasion detected by other imaging techniques. A prior cone biopsy or previous chemotherapy treatment are not a contraindication [21]. Several authors have observed comparable detection rates of SLN as in patients with no previous history of intervention [26–29].

Despite the widespread use of SLN biopsy in cervical cancer, there is a wide variation in reported performance characteristics that are dependent on study volume, mapping technique, and the proportion of successful mappings. Thus, some aspects that have yet to be clarified are the minimum number of patients required to validate this technique, the minimum number of patients needed for a learning curve and what would be the acceptable margin of false-negative cases.

Endometrial cancer

Endometrial cancer is the most common malignancy of the female genital tract in developed countries [30]. Pelvic or paraaortic node involvement denotes a worse prognosis, with a 5-year survival rate of between 44 % and 52 % [31]. In high-risk endometrioid cancer (grade 3, >50 % myometrial involvement) or in patients with a high-risk tumour histology (clear-cell, papillary serous, carcinosarcoma) the standard of care is surgical staging, including pelvic and paraaortic lymphadenectomy. But in low-risk endometrial cancer the incidence of nodal invasion is very low and there is still no clear consensus as to management. In some patients a histological low grade is modified and increased after pathological examination of the whole tumour sample. In these patients, prior surgical staging would have been of benefit. The diagnosis of nodal invasion can modify management with the introduction of adjuvant therapy. It is important to emphasize the fact that the majority of patients with endometrial cancer are at high surgical risk due to obesity and associated comorbidities. In this setting, the SLN concept may significantly decrease postoperative morbidity if systematic lymphadenectomy could be avoided even in patients with high-risk tumours.

The use of SLN detection may provide not only surgical staging without increasing the number of complications that can result from complete lymphadenectomy, but also ultrastaging using extensive immunochemistry. Although several studies of SLN detection in patients with endometrial cancer have been carried out, there is not yet enough scientific evidence for validation (Table 1).

Vulvar cancer

Vulvar cancer is the least frequent gynaecological malignancy of the female genital tract, being responsible for only 0.3 % of all female cancer deaths [47]. Regional nodal status has an important prognostic value. The 5-year survival rate decreases from 94.7 % when the nodes are negative to 62 % when they are positive [48]. When first diagnosed, 30 % of cases show nodal invasion, with 10 – 20 % of these nodes being in the pelvic area. When a tumour is confined to one side of the vulva, more than 80 % of nodal metastases are ipsilateral. Treatment includes radical vulvectomy and inguinofemoral lymphadenectomy, both being associated with a high morbidity.

The superficial location of vulvar cancer facilitates injection and the surgical approach, as well as a fast and successful drainage to inguinofemoral nodes. Table 2 shows the most

Table 1 SLN detection in patients with endometrial cancer

Reference	Year of study	No. of patients	Injection site	Tracer	Surgery	Detection rate (%)	Lymphatic examination	False negative (%)	Negative predictive value (%)
[32]	2005	16	Myometrial and/or subserosal	Blue	Laparotomy	44			86
[33]	2006	33	Cervical	Radiotracer			Pelvic+paraaortic nodes	0	
[34]	2007	25	Subserosal	Blue		92			92.5
[35]	2007	60	Hysteroscopy	Radiotracer+blue dye	Laparotomy	82	Pelvic+paraaortic nodes	0	
[36]	2007	23	–	Radiotracer+blue dye	Laparoscopy	82.6		0	
[22]	2007	18	Subserosal (fundus)	Radiotracer+blue dye	Laparotomy	45			
[37]	2007	20	Subserosal	Blue	Laparotomy	75	Pelvic	0	
[38]	2007	40	Myometrial	Blue	Laparotomy	77.5		4	
[39]	2008	46	Cervical	Radiotracer+blue dye	Laparoscopy	87	Pelvic+paraaortic nodes	0	
[40]	2008	43	Cervical	Radiotracer+blue dye		69.8	Pelvic	0	
[41]	2008	5	Hysteroscopy	Radiotracer+blue dye	Laparoscopy	40	Pelvic+paraaortic nodes		
[42]	2008	54	Cervical vs. myometrial (hysteroscopy)	Radiotracer/radiotracer	Laparoscopy	70 vs. 65	Pelvic vs. pelvic+ paraaortic nodes		
[43]	2009	42	Cervical vs. cervical+ subserosal	Radiotracer/radiotracer+ blue dye	Laparoscopy or laparotomy	86	Pelvic+paraaortic nodes	0	
[44]	2009	33	Cervical	Radiotracer+blue dye	Laparoscopy	81.8		0	
[45]	2009	91	Subserosal vs. hysteroscopy	Radiotracer+blue dye/ radiotracer	Laparotomy	73 vs. 50	Pelvic+paraaortic nodes		
[46]	2010	34	Cervical	Blue	Laparoscopy vs. laparotomy	82 vs. 41			

Table 2 SLN detection in patients with vulvar cancer

Reference	Year of study	No. of patients	Tracer	Stage	Unilateral (%)	Lymphadenectomy	Detection (%)	False negative (%)	Negative predictive value (%)
[49]	2000	44	Radiotracer	T1, T2	25	SLN+lymphadenectomy	100		100
[50]	2001	52	Blue	T1, T2 (87 %)	–	SLN+lymphadenectomy	88		100
[51]	2002	26	Radiotracer+blue dye	Early stage	77	SLN+lymphadenectomy	100	0	
[19]	2007	41	Radiotracer+blue dye	I, II	54	SLN+lymphadenectomy	95	0	
[52]	2007	70	Radiotracer+blue dye	Ib1/III (validation group), Ib1/II (application group)	60	SLN+lymphadenectomy (50), lymphadenectomy when SLN+ (20)	97		100
[53]	2008	45	Not reported	T1, T2	Not reported	Lymphadenectomy when SLN+	95	2.2	
[54]	2008	127	Radiotracer+blue dye	T1–T3	16	SLN+lymphadenectomy	98	7.7	
[55]	2008	36	Radiotracer+blue dye	I–IV		Lymphadenectomy when SLN+			
[56]	2008	403	Radiotracer+blue dye	T1, T2 (<4 cm)	45	Lymphadenectomy when SLN+	–		
[57]	2010	77	Radiotracer+blue dye	–	–	SLN+lymphadenectomy	98	2.7	
[58]	2010	62	Radiotracer+blue dye	I, II	Not reported	SLN+lymphadenectomy	99	6	
[59]	2012	418	Radiotracer+blue dye	I, II	31.5	SLN+lymphadenectomy		3.7	

relevant studies reported in the last decade. The largest series is that of Van der Zee [56] with 403 patients. Inguinofemoral lymphadenectomy was performed only when SLN invasion was confirmed. The results show a decrease in morbidity in the short term (wound breakdown, cellulitis) and long term (lymphoedema) in patients who underwent SLN biopsy versus patients with lymphadenectomy.

Although the vulva is a central organ, the rate of unilateral drainage is quite high [51, 52, 57]. Several groups avoid bilateral lymphadenectomy when the tumour and its drainage are unilateral [52], but other groups prefer to perform a complete contralateral lymphadenectomy to avoid possible metastatic blockage due to nodal invasion. The advantages of performing SLN biopsy over lymphadenectomy are a reduction in morbidity [56], an upstaging and, according to some authors, a reduction in surgical time [60]. Moreover, the GROINSS-V study demonstrated that non-SLN metastases occur more often as the size of SLN metastasis increases. Therefore, all patients with SLN metastasis require additional groin treatment [61].

Vaginal cancer

There are very few studies regarding SLN in vaginal cancer, which have all shown successful SLN detection in isolated cases [62–64]. Frumovitz et al. [22] performed lymphatic mapping with lymphoscintigraphy for radiotherapy planning in 14 patients. They found drainage in 79 % of patients, with bilateral lymph nodes in 55 %. The most frequent location was the inguinal basin (45 %). At present, SLN detection in patients with vaginal cancer is considered investigational. There is insufficient evidence to include SLN detection in the clinical management of patients with vaginal cancer.

Ovarian cancer

The incidence of positive lymph nodes in early-stage ovarian cancer is low, ranging from 5.1 % to 15 % [65]. Pelvic and paraaortic lymphadenectomy involves an increase in surgical time and is associated with possible morbidity. However, SLN detection in patients with ovarian cancer should be considered.

Capsular rupture during surgery possibly leading to tumour spread in the abdominal cavity is a known risk, and this can make the injection of a tracer around the tumour more difficult. Lymphatic mapping of epithelial ovarian tumours has been described by Negishi et al. [66]. To avoid tumour spread, they injected carbon particles in 11 patients diagnosed with endometrial or fallopian tubal cancer who were undergoing pelvic and paraaortic lymphadenectomy. Bilateral drainage was seen in 64 % of patients. All the lymphatic channels drained to the paraaortic nodes, and SLNs were located in the common iliac chain (26 %) and the external iliac chain (9 %).

The new recently introduced technique of combined intraoperative injection of radioisotope and blue dye is fast enough to identify ovarian SLNs. These nodes were consistently located in a distinct lymphatic area [67]. At present, SLN detection in patients with ovarian cancer is considered investigational. There is insufficient evidence to include SLN detection in the clinical management of patients with ovarian cancer.

Clinical indications and contraindications for SLN detection

Common indications

- Early cervical cancer (Ia2/Ib1, IIa1).
- Stage I and II high-risk endometrial cancer, i.e. endometrioid cancer with the following: more than 50 % myometrial invasion or poorly differentiated (grade 3) or serous papillary, clear-cell or carcinosarcoma histological subtype.
- Squamous cell vulvar carcinoma Ib/II less than 4 cm in size, without presurgical nodal metastases.
- Although there is less reported experience, SLN biopsy in vulvar melanoma is also accepted with the same indications as in cutaneous melanoma [68].

Contraindications

- Suspected extrauterine involvement.
- Presence of pathological pelvic or paraaortic lymph nodes on radiological examination.
- Previous history of surgery or radiotherapy to nodal areas under study.
- Contraindication for surgical treatment (related to age or associated medical conditions).

Precautions

Pregnancy is not really a contraindication for SLN biopsy. In nursing mothers, breast-feeding should be suspended for 24 h after radiopharmaceutical administration.

Procedures

The procedures for SLN detection and localization involve radiopharmaceutical and/or blue dye injection, preoperative scintigraphic imaging, and intraoperative gamma probe localization followed by surgical removal of the detected lymph nodes.

There is no consensus regarding how the procedure should be performed. Controversies exist with regard to the selection of agents, the size of the particles of radiotracer, and time to scintigraphy. The need for lymphoscintigraphy has at times been called into question. However, preoperative radiotracer lymphoscintigraphic mapping should be employed whenever possible because of the potential added benefit in both improving accuracy and reducing morbidity relative to the use of a hand-held gamma probe alone [69]. Moreover, lymphoscintigraphy can detect unusual drainage patterns, such as paraaortic or presacral nodes which is useful specifically in vulvar cancer [70, 71].

Nuclear medicine procedures

Quality control

- Quality control for the gamma camera and image display should be routinely performed, according to published protocols [72, 73].
- Demonstration of spatial registration in multiple energy windows may be required to optimize image quality.
- Quality control of the gamma probe used to detect the SLN in the operating theatre should also be performed according to published protocols [74].

Patient preparation

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

Information pertinent to performing the procedure

- The time of last menses and pregnancy and lactation status of the patient should be determined.
- Other diagnostic imaging techniques, such as ultrasonography, CT or MRI should be available to the nuclear medicine physician.

Radiopharmaceuticals

Several ^{99m}Tc-based agents have been used in radioguided SLN biopsy for gynaecological cancer (Table 3) [75].

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

There is general agreement that a radiocolloid must reflect the best compromise between fast lymphatic drainage and

Table 3 ^{99m}Tc-based agents used in SLN biopsy

Agent	Particle size (nm)	
	Maximum	Average range
Sulphur colloid (USA)	350 – 5000 (see text)	100 – 220 (filtered)
Nanocolloidal albumin (Nanocoll) (Europe)	100	5 – 80
Antimony trisulphide (Canada and Australia)	80	3 – 30
Tin colloid	800	30 – 250
Labelled dextran	800	10 – 400
Hydroxyethyl starch	1,000	100 – 1,000
Stannous phytate	1,200	200 – 400
Sulphide nanocolloid (Lymphoscint)	80	10 – 50
Rhenium sulphide nanocolloid (Nanocis)	500	50 – 200

optimal retention in the SLN [76]. The particle size also determines the timing of preoperative scintigraphy and intraoperative detection of SLN, while smaller particles allow quick visualization of SLN, larger particles have the advantages of longer tracer retention in the SLN that permits intraoperative detection the following day and slow transit in the lymphatic system that minimizes visualization of non-sentinel nodes (lymph nodes downstream of the SLN). The SLN is generally visualized in 2 hours, and the patient should be in the operating theatre within about 4 – 20 hours after injection of the colloid, depending on the facility's schedule [77].

Studies have shown that the success rate in the identification of SLN is not significantly affected by the particle size of the radiotracer used [78]. The selection of the radiotracer is then based more on local availability than on differences in SLN detection. In the US, ^{99m}Tc-sulphur colloid is the radiocolloid mostly 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 range of 305 – 340 nm. After passage through a 0.22-μm filter, most of the particles are in the size range 100 – 220 nm. ^{99m}Tc-Nanocolloidal albumin (Nanocoll) is the licensed and preferred agent in Europe; it has particles in the size range 5 – 100 nm. ^{99m}Tc-Antimony trisulphide is most commonly used in Canada and Australia; it has particles in the size range 3 – 30 nm. The tracer must be labelled with ^{99m}Tc-pertechnetate using the manufacturer's instructions. A labelling yield greater than 95 % must be achieved before the radiopharmaceutical is injected. General quality control requirements for radiopharmaceuticals must be applied.

Volume and activity

In cervical cancer, the most frequently used activity is about 110 MBq in a total volume of 2 mL (0.5 mL per depot) [79]. The syringe should also contain a similar amount of air to clear any dead space within the syringe and the needle [80]. The endometrial approach is more complex and several techniques have been described. Thus the total dose injected may vary from 40 to 185 MBq and the volume injected from 0.5 to 8 mL [81]. For vulvar cancer two to four injections of radiotracer are performed with a total dose ranging from 20 to 150 MBq in an approximate volume of 0.4 – 0.5 ml (0.1 ml per injection) [53, 56, 58]. The maximum activity of ^{99m}Tc should be loaded onto the smallest number of particles. Labelling at higher specific activity has been demonstrated to result in higher nodal count rates for the same administered activity [82].

Injection procedure

Cervical cancer The radiopharmaceutical is injected peritumorally/periorificially into the four quadrants of the cervix using a 20 or 22-gauge spinal needle. When previous conization has been performed pericicatricial (if possible) injection is preferred. Superficial (submucosal) instillation is preferred in small tumours, while injection into the necrotic part of the tumour should be carefully avoided in bigger ones.

Endometrial cancer There are three reported injection approaches: cervical injection, endometrial peritumoral injection assisted by hysteroscopy or myometrial/subserosal injection. Cervical injection is the easiest approach. It can be performed the day prior to surgery, allowing the use of a radiotracer and providing a lymphatic map. Cervical injection is performed periorificially, as for cervical cancer, into the four quadrants. The detection rate obtained is the highest, ranging from 70 % to 87 % [39, 40, 44, 46]. Endometrial injection during hysteroscopy allows direct injection around the tumour. The procedure can be performed at the beginning of surgery, but if this is the case, the possibility of performing lymphoscintigraphy is lost. The detection rate obtained with this type of injection ranges between 40 % and 65 % [32, 35, 41]. Finally, injection into the corpus uteri in a myometrial or subserosal location is associated with a detection rate of between 45 % and 92 % [22, 34, 37, 45]. It is administered during surgery and usually

the only tracer injected is a blue dye. The number of injections seems to play an important role, with a minimum of three locations being required [22].

Until now, the largest series reported is that of Robova et al. [45] with 91 patients. They compared subserosal injection (with radiotracer and blue dye) with hysteroscopic injection (radiotracer only). The detection rate was better with subserosal injection (73 % vs. 50 %), but both types of injection provided results too low to consider SLN detection as an alternative to surgical staging in endometrial cancer.

A novel injection approach consists of a myometrial/subserosal injection guided by transvaginal ultrasonography, with promising results including a detection rate of 88 % when a high injected volume is achieved [81].

Vulvar cancer The superficial location of vulvar tumours makes the injection of tracer easier than in other gynaecological tumours. Three or four intradermal/intramucous peritumoral injections of radiopharmaceutical should be performed after the application of an anaesthetic cream or spray such as lidocaine or ethyl chloride.

Image acquisition

Imaging is strongly recommended before any operative procedure.

Gamma camera A gamma camera with a single or multiple heads and a large field of view is necessary to acquire planar and/or tomographic (SPECT) images. The gamma camera should be equipped with a low-energy high-resolution collimator. The energy window should be 15 ± 5 % centred over the 140-keV photopeak of ^{99m}Tc.

Patient position For imaging, the patient lies supine on the gamma camera bed.

Image collection

- For endometrial and ovarian cancers, a dynamic study is not used. Most medical centres obtain images at 30 and 60 – 120 min after injection. The injection and images can be carried out the day before surgery or on the day of surgery. Delayed images are helpful for detecting drainage to multiple nodal basins.
- Planar images are acquired for 3 – 5 min in anterior and lateral views. A 256 × 256 or a 128 × 128 matrix with zoom 1 are the most commonly used options, although each facility can use its own protocol.
- A ^{57}Co or ^{99m}Tc flood source can be used for better delineation of the patient's body contour. Otherwise, this contour can be achieved by drawing it with a ^{57}Co or ^{99m}Tc source (pointer or syringe needle).
- The site of any suspected SLN can be localized on overlying skin using a pointer and the skin marked with a small spot of indelible ink.

Optional images Conventional planar imaging helps but does not give an exact preoperative anatomical location of the detected nodes [83]. The recently introduced hybrid systems with a SPECT gamma camera and an integrated CT scanner (SPECT/CT) fuse tomographic lymphoscintigrams with anatomical data. SPECT/CT systems consist of a dual-head variable-angle gamma camera equipped with low-energy high-resolution collimators and a low-intensity CT scanner. The patient can stay in the same position during imaging and the two images are easily fused. SPECT/CT provides a three-dimensional image with better contrast and spatial resolution than planar imaging and has the possibility to correct for attenuation and scatter. This combination of imaging properties results in precise localization of the SLN within an anatomical landscape, providing a valuable surgical road-map [84].

Application in the field of SLN mapping has been widely developed in breast cancer, melanoma and head and neck tumours. However, the deep drainage observed in gynaecological tumours, specially cervical and uterine, can be difficult to localize. The information from flat-plane images, with only anterior and lateral views of the pelvis, is limited and cross-sectional SPECT/CT slices could provide better orientation. Nevertheless, there are very few studies investigating SPECT/CT in gynaecological cancer, and the series are small [23].

SPECT/CT is usually performed immediately after delayed planar imaging. There is no definite protocol for SPECT acquisition and different teams can adopt their own approach. In general, 120 projections (60 each detector), 3° and 15 – 25 s per projection, 128 × 128 matrix and zoom 1 are the accepted parameters. CT parameters depend on the CT device.

Cervical cancer:

SPECT/CT images are clearly useful in the detection of parametrial SLN [85, 86] and nodes that are in unusual locations. Some authors have found a higher detection rate of SLN compared with blue tracer and hand-held probe detection [86], with improvements in detection rate from 70 % to 100 %.

Endometrial cancer:

The deep location of the corpus uteri and its unique drainage lead to a lower correlation of planar lymphoscintigraphy with surgical findings than in most other tumours [39]. In these tumours, the three-dimensional information provided by SPECT/CT is more

useful in the planning of surgery and can lead to a decrease in the surgical time needed.

There is still a lack of data on the use of SPECT/CT in endometrial cancer. So far Pandit-Taskar et al. [87] have reported the largest series, with a study of 40 patients. They found a higher detection rate using SPECT/CT (100 %) than when using planar lymphoscintigraphy, a hand-held probe, or blue dye alone (75 % vs. 93 % vs. 83 %) and highlighted the benefits of a previous anatomical image in the detection of paraaortic nodes.

Vulvar cancer:

SPECT/CT is not widely used because deep drainage is less frequent than in other tumours. It may help in the three-dimensional location of the SLN, but not in the surgical management or the final number of depicted nodes. There are only three reported cases, all in vulvovaginal melanoma, in which detection was higher due to the increase in the number of SLN locations identified by SPECT/CT [88, 89].

Image storage

All images obtained should be stored in a permanent form, according to national regulations.

Image processing

No particular processing procedure is needed for planar images.

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

In the case of SPECT, one should take into account the different types of gamma camera and software available. Careful choice of processing parameters should be adopted in order to optimize the image quality. Iterative reconstruction using a low-pass post-filter often provides better images than filtered back projection. Ordered subsets expectation maximization (OSEM) with two to five iterations and 8 – 20 subsets is the preferred algorithm. Images are corrected for attenuation and scatter. The SPECT image is fused with the CT image and analysed using two- or three-dimensional orthogonal reslicing. These images must be available in the operating room for consultation.

Reporting

Early and delayed lymphoscintigraphic planar images are able to identify SLNs in the majority of cases. Major criteria for identifying lymph nodes as SLNs are the visualization of lymphatic ducts, the time of appearance, the lymph node basin, and the intensity of lymph node uptake. Sequential planar images are essential for identifying the first draining lymph nodes as SLN by visualization of lymphatic ducts or the first appearing nodes on lymphoscintigraphy. These nodes can be distinguished from secondary lymph nodes which mostly appear on delayed planar images. In some cases SPECT/CT can detect additional lymph nodes in other basins. Less frequently a radioactive lymph node may appear between the injection site and a first draining node; its increasing uptake helps differentiate this node from a lymphatic lake or a lymphatic duct. 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 must have at least one SLN.

The report to the referring physician should describe:

- The radiopharmaceutical, the method of administration, and the amount of activity injected
- The imaging protocol
- The location of the sentinel node(s) on gamma-camera images
- Any source of error or inaccuracy of the procedure

Procedures in the surgical room

Blue dye lymph node localization

Scintigraphic SLN localization does not prevent other methods such as peritumoral blue dye from being administered in the perioperative setting.

Currently, commonly used dyes are patent blue V, isosulfan blue, and methylene blue. Blue dye can be injected around the primary tumour, in a similar way to a radiopharmaceutical, 10 – 20 min before surgery in a volume of 0.5 – 1 mL in vulvar cancer. Larger volumes (2 – 4 mL) may be needed for cervical and endometrial cancer. The injection should be performed after the patient is anaesthetized to avoid pain on injection. Within 5 – 15 min the SLN is coloured. Washout is evident after approximately 45 min. Multiple studies have established the validity of blue dyes as markers for SLN with high detection rates (ranging from 75 % to 95 %), although slightly lower than those achieved by radiopharmaceuticals. In most cases, the same SLNs are detected by the two methods.

It is important to be aware of contraindications to 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 presents the risk for an anaphylactic reaction, in earlier allergic reaction to blue dye and in severe renal impairment (methylene blue) [90]. Hypersensitivity reactions to

radiopharmaceuticals are rare but have also been reported. Blue dye may also cause discoloration of urine 24 – 48 h after administration and it is contraindicated in pregnant women.

Cervical cancer The best detection rate is achieved using the combined technique (blue dye and radiolabelled colloid), with a success rate of over 90 % [21, 91]. This combination technique can detect SLNs more frequently in the paraaortic region than a single marker [92].

Endometrial cancer As shown in Table 1, the majority of studies have used the combination approach. The SLN identification rate using only blue dye ranges from 44 % to 92 %. The average identification rate using the combination of dye and radiotracer is 83 %.

Vulvar cancer Early studies in vulvar cancer were performed with blue dye as the sole tracer, with a detection rate approaching 90 % (86 % – 88 %) [49]. The introduction of radiotracers improved the detection rate to 95 – 100 % [18, 49, 52, 53, 58]. Nowadays, the accepted methodology includes the injection of both tracers (radiotracers and blue dye).

Radioguided surgery

Detection probes must be able to detect the SLN 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 SLN when attenuated by, typically, up to 5 cm of soft tissue. Discriminating activity within the SLN requires the probe also to be well collimated for a small angle view. It is thus advisable that the major component of this collimation is applied 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 intraoperative use [1]. The detector itself should be ergonomically designed for easy manoeuvrability, and constructed to be suitable for sterilization. The probe is placed in a sterile bag for intraoperative use in the surgical field. 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 [74, 93]. In the European Union, it is a requirement that all medical equipment obtains 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 recognized international electromedical safety standard IEC 60101 [94]. Therefore, information regarding compatibility with its requirements should be separately sought from the manufacturer.

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). For vulvar cancer a conventional gamma probe is normally used. In cervical and endometrial cancer surgery laparoscopy-adapted probes have been introduced during the last decade. Generally, this kind of gamma probe consists of a stainless steel outer tube of length 30 – 35 cm. In this tube a CdTe semiconductor is mounted at the tip of a stainless steel shaft. The tip is shielded with a tungsten layer. The tungsten cover shields radiation sources outside the field of view with an efficiency of >99.9 %. The detection probe is connected to a readout unit. During laparoscopy the steel probe is put into a disposable laparoscope cover or some models can be sterilized and can be operated without any cover.

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 (i.e. liver). Lymph nodes recognized by the nuclear physician as SLN must be removed in the operation room by the surgeon. Other nodes may sometimes be removed depending on the degree of remaining radioactivity measured by the gamma probe. A SLN usually has at least ten times the background counts, taken at a location remote from the injection site. When a hot node has been removed, the wound site should be checked for remaining activity. Due to the limited spatial resolution of the gamma camera, nodes closer than about 15 – 20 mm may appear as one spot, so after removal of one node in a limited number of cases another hot node may still be present in a close location. The CT part of currently used SPECT/CT images may provide information about the presence of a cluster of lymph nodes. This preoperative information may lead to strong post-excision control after removal of the first radioactive node by the surgeon. When other sources of activity are found in the lymphatic basin, the decision as to whether to remove them will depend upon the report from lymphoscintigraphy, and the working definition of “nodes to remove” (e.g. nodes with counts per second higher than 10 % of the counts of the hottest node; 10 % rule).

If blue dye is used, it can be a useful adjunct to aid SLN localization and harvest. Following injection, blue dye drains

to the SLNs staining the channels, which can be followed to the first-echelon nodes. Direct visualization and dissection of these channels facilitates SLN localization.

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. In patients with vulvar cancer, a second radiotracer injection may eventually be performed to depict the previous nonvisualized SLN. In patients with cervical and endometrial cancer and SLN not visualized on lymphoscintigraphy, there are no data about second injections. In approximately 1 – 3 % of all patients with vulvar cancer, SLN will not be detected intraoperatively, and the status of the lymphatic basin cannot be determined. This percentage increases to 10 – 15 % of patients with cervical and endometrial cancers. In general, if the SLN is not detected, systematic lymphadenectomy in standardized anatomical regions should be performed instead. In patients with cervical cancer lymph node staging must be performed on both sites separately – if the SLN is detected only on one side, systematic lymphadenectomy should be performed on the other side.

Interpretation criteria

In practice, any lymph nodes that have increased radioactive uptake or vital dye uptake are localized, and more often than not, multiple nodes are detected. The question remains as to how many SLNs should be biopsied when multiple nodes are found. While removing too few nodes may miss potential metastasis in regional lymph nodes, indiscriminate removal of axillary nodes may cause morbidity similar to that in axillary lymphadenectomy.

Radiation dosimetry

The use of radiocolloids for SLN detection in patients with gynaecological tumours should be optimized with respect to radiation safety issues for the patient and for the staff of nuclear medicine, surgery and pathology departments, and also for radioactive waste disposal. SLN detection is a nuclear medicine procedure in which low activities are used.

Radiation dosimetry for patients

The amount of injected activity ranges from 10 to 150 MBq depending on the study and on the time to surgery. Estimation of the patient's dosimetry after injection is difficult. Because only a reduced fraction of the tracer is transported, the effective dose is mainly determined by the amount of tracer retained at the injection site. Because the injection depot is usually excised during surgery, shortening the interval to the operation will further decrease the local radiation. In patients the estimated radiation exposure depends on some variables such as injected activity, the retention time and the administration of multiple injections. There are minor differences in radiation dosimetry of different radiopharmaceuticals used for SLN detection. Locally absorbed radiation doses at the injection site for two of the most commonly used radiocolloids are shown at Table 4 [95].

The absorbed doses are far below the thresholds for deterministic radiation effects [96]. In SLN procedures, the locally injected radiocolloid migrates minimally into the bloodstream or reticuloendothelial system further than the sentinel and second-echelon lymph nodes. Therefore the equivalent radiation doses may be expected to be negligible. The effective doses for SLN detection in patients with breast cancer have been reported to be about 0.32 mSv and in patients with malignant melanoma to be 0.0019 mSv/MBq for the worst case scenario where 20 % of injected activity is assumed to be absorbed systemically [95, 97]. Similar calculations should be extrapolated to SLN detection in patients with gynaecological cancer.

In recent years the use of SPECT/CT imaging for SLN detection has increased. Therefore, the additional radiation dose of CT imaging to patients should also be taken into account for dosimetric purposes. The additional absorbed dose from the CT component of SPECT/CT imaging varies and depends mainly on the characteristics of the CT scan such as whether the procedure is a full-dose CT scan for diagnostic purposes or, as in most centres, a low-dose CT scan only for localization and attenuation correction [98].

Since pregnancy is not an absolute contraindication for SLN detection, pregnant women can also undergo SLN detection procedures after careful counselling related to the safety and efficacy of the procedure. According to the ICRP, the risk to the fetus can be accepted as negligible if the radiation exposure from the procedure is below 1 mSv [99]. The maximum calculated doses to the fetus from SLN detection procedures in patients with breast cancer using 92.5 MBq of radiocolloid have been reported to be about 4.3 mGy, which is far below the deterministic fetal dose threshold limit of 50 mGy [100]. The dose to the fetus from the SLN procedure in patients with melanoma has been reported to be well below 1 mSv limit for stochastic effects of radiation. In patients with gynaecological cancers, the estimated dose to the fetus may theoretically exceed 1 mSv because of the close proximity of the injection site to the fetus compared to breast cancer and melanoma elsewhere in the body. In this case, two precautions to reduce the fetal radiation dose can be offered: (1) to reduce the injected activity, preferably to 30 – 40 MBq and acquire images over twice the normal duration, and (2) to have a short time interval between injection and operation, i.e. always to perform 1-day protocol [101, 102].

Table 4 Locally absorbed radiation doses at the injection sites for two ^{99m}Tc-based radiocolloids used in SLN detection

Agent	Injection volume (mL)	Local tissue dose (mGy/MBq)
Nanocolloid	0.1	20 – 44
Antimony sulphur colloid	0.1	20 – 30

Radiation dosimetry for staff

In accordance with the regulatory requirements including those mandated by the Medical Exposures Directive within the EU and those in force elsewhere, radiocolloid preparation, administration and preoperative procedures must be performed by trained nuclear medicine personnel working in a controlled environment [96].

Staff in the nuclear medicine department The activities of radiocolloids are low compared to those of other commonly used diagnostic nuclear medicine radiopharmaceuticals. The occupational exposure to the nuclear medicine staff from the SLN procedure will be minimal as they are already categorized as radiation workers. It has been reported that the highest doses to personnel will be the hand radiation dose of the individual who does the injection [103]. However, this dose is much lower than the ICRP threshold limit of the annual hand dose for radiation workers. 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 For the radiation absorbed doses to personnel other than nuclear medicine staff, the operational dose exposures are reported to be minimal, as the mean whole-body dose to surgical staff during SLN procedures is below 1 μSv per operation with the highest occupational dose to the surgeons performing SLN biopsy and this is below 2 μSv per operation [104, 105]. The hand dose to the surgeons has been calculated as 5 – 94 μSv per operation. Therefore, the radiation monitoring of the surgical staff involved in SLN procedures is not necessary. Also no shielding devices are required in the operating rooms during a procedure. The presence of a pregnant surgeon or scrub nurse may be questioned although it has been reported that a pregnant surgeon who performs up to 100 SLN procedures per year will stay below the accepted limits of radiation exposure calculated for pregnant women [104].

Staff in the pathology department The radiation exposure of personnel in the pathology department will be much lower than that of surgical staff, because they spend less time with the specimens and there is a much longer time between injection and laboratory work. Even personnel performing an unusually high number of procedures receive radiation doses well below established limits for the general population. Therefore, monitoring radiation exposure is not required for pathology personnel who deal with SLN specimens.

Radiation dosimetry for specimens and waste materials

Outer labelling of specimens as radioactive during transport to the pathology laboratory may be considered but is generally not mandatory, since the dose rates of specimens are usually below the 5 μGy/h threshold limit of outer labelling as radioactive. Generally, surgical instruments and pathology slides stay at background radiation levels and do not need to be treated as contaminated. But measurable radioactive contamination of sponges or absorptive material may be observed especially when they are used in close vicinity to the injection site. Although this creates a negligible radiation hazard, such surgical waste may be monitored and if any measurable radiation contamination is detected, the waste can be treated as radioactive waste material for decay-in-storage before disposal [106].

In summary, SLN procedures in patients with gynaecological cancers cause low radiation exposures to both the patients and the staff. No additional shielding or monitoring is needed in the operating room or the pathology laboratory. The contamination of surgical waste material is not common but if measurable, the material should be treated as radioactive [107].

Issues requiring further clarification

- SLN detection in patients with endometrial cancer is not a standard of care. Results are promising but the lack of consensus over the best injection modality does not permit standardization of the technique, which is still in the validation phase.
- SLN detection in patients with ovarian and vaginal cancer is not standard of care and should be considered an investigational procedure
- In patients with cervical cancer, lymph node staging must be performed on both sides of the pelvis, and if SLN is detected on only one side, lymphadenectomy should be performed systematically on the other side

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