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REVIEW ARTICLE

Lymphoscintigraphy and sentinel lymph node biopsy in vulvar carcinoma: update from a European expert panel

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Abstract

Purpose This study aimed to update the clinical practice applications and technical procedures of sentinel lymph node (SLN) biopsy in vulvar cancer from European experts.

Methods A systematic data search using PubMed/MEDLINE database was performed up to May 29, 2019. Only original studies focused on SLN biopsy in vulvar cancer, published in the English language and with a minimum of nine patients were selected.

Results Among 280 citations, 65 studies fulfilled the inclusion criteria. On the basis of the published evidences and consensus of European experts, this study provides an updated overview on clinical applications and technical procedures of SLN biopsy in vulvar cancer.

Conclusions SLN biopsy is nowadays the standard treatment for well-selected women with clinically negative lymph nodes. Negative SLN is associated with a low groin recurrence rate and a good 5-year disease-specific survival rate. SLN biopsy is the most cost-effective approach than lymphadenectomy in early-stage vulvar cancer. However, future trials should focus on the safe extension of the indication of SLN biopsy in vulvar cancer. Although radiotracers and optical agents are widely used in the clinical routine, there is an increasing interest for hybrid tracers like indocyanine-^{99m}Tc-nanocolloid. Finally, it is essential to standardise the acquisition protocol including SPECT/CT images, and due to the low incidence of this type of malignancy to centralise this procedure in experienced centres for personalised approach.

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Introduction

Vulvar cancer (VC) is a rare disease, with an incidence rate of 1.5 per 100,000 women per year [1]. There are two separate pathways: human papillomavirus associated that occurs mostly in younger patients, and not human papillomavirus-induced that appears mainly in elderly women [2]. Histologically, squamous cell carcinoma is about 90% of VC [3]. The lymphatic spread of the malignancy is mainly to the inguinal lymph nodes (LNs), but clitoris and perineum cancers could spread directly to the pelvic region [4]. The most important prognostic factor is the presence of LN metastases. Indeed, the 5-year overall survival rate decreases from 95% in absence of groin metastases to 62% in presence of groin metastases [5]. Since only 25% to 35% of women with early-stage VC have groin metastases [5], inguinofemoral lymphadenectomy (IFL) is an overtreatment in the majority of these patients. Moreover, IFL is associated with a high risk of postoperative short- and long-term morbidity [6], which may impact the patient's quality of life and delay the adjuvant radiation treatment, when indicated. Sentinel lymph node biopsy (SLNB) is a minimally invasive surgical approach for LN staging. The rationale is that SLNs represent LNs with direct lymphatic drainage from the primary tumour, thus their histopathological evaluation may predict the LN status. So far, SLNB is a safe alternative to IFL in well-selected women with clinically and radiologically negative LNs [7, 8]. Negative SLN is associated with low incidence of groin relapse [9–12], less postoperative complications [9, 11] and good survival [12]. Finally, SLNB has a shorter operation time and length of hospital stay, less costs and improved pathological examination than IFL [13].

This study aims at updating the clinical practice applications and technical procedures of SLNB in VC from a European expert panel including nuclear medicine physicians and gynaecological oncologists.

Methods

We systematically reviewed the literature following the PRISMA guidelines [14]. The PubMed/MEDLINE database was searched using the MeSH terms "sentinel lymph node" AND "vulvar neoplasms" until May 29, 2019. Two reviewers independently screened the title and abstract. Original articles reporting on SLNB in VC, published in the English language, and with a minimum of nine patients were eligible for inclusion. Both reviewers independently revised the full-text version of the remaining articles to confirm their eligibility for inclusion. The references of the included articles were screened for additional relevant studies.

Results

The initial data search identified 280 citations. Screening the titles and abstracts, 218 articles were excluded. In detail, these papers included 154 off-topic studies, 28 reviews, 15 letters to the Editor, nine case reports, eight studies written in a language other than English, and four studies with less than nine patients. The full text of 62 remaining articles was reviewed. Three additional studies were found by screening the references. Finally, 65 eligible articles were included (Table 1, Fig. 1) [9–12, 15–75]. On the basis of the published evidences and consensus of European experts, an updated overview on clinical applications and technical procedures of SLNB in VC is provided.

Discussion

Validation studies

The GROINSS-V study (GRoningen INternational Study on Sentinel nodes in Vulvar cancer) was the first prospective multicentre trial published by Van der Zee et al. This study included 403 women with squamous cell cancer of vulva less than 4 cm, depth of invasion more than 1 mm and clinically nonsuspicious inguinofemoral LNs. In 259 patients with unifocal tumour and negative SLN, IFL was omitted and groin recurrences occurred in 2.3% with a median follow-up time of 35 months. Short- and long-term morbidities were decreased in patients after SLNB only compared with those underwent SLNB and IFL: wound breakdown, 11.7% versus 34.0%; cellulitis, 4.5% versus 21.3%; recurrent erysipelas, 0.4% versus 16.2%; and lymphedema of the legs, 1.9% versus 25.2%, respectively [9]. Shortly after, Levenback et al. published the results of the GOG-173 trial (Gynecologic Oncology Group-173). This prospective multicentre study included 452 patients with invasive squamous cell cancer of vulva, depth of invasion of at least 1 mm, tumour size of at least 2 cm and not larger than 6 cm, and clinically nonsuspicious inguinofemoral LNs. All patients underwent SLNB and IFL. The authors showed that the SLNB had the false-negative predictive value of 2% in women with tumour less than 4 cm [35]. These results are in line with those of GROINSS-V. Recently, Te Grootenhuis et al. evaluated long-term follow-up of 377 patients included in the GROINSS-V study with unifocal squamous cell carcinoma of the vulva (T1, < 4 cm) who underwent SLNB. They reported a groin recurrence rate of 2.5% for SLN-negative patients and 8% for SLN-positive patients at 5 years. Disease-specific 10-year survival was 91% for SLN-negative patients compared with 65% for SLN-positive patients [12]. Similarly, a meta-analysis by Covens et al. provides a low recurrence rate with SLNB of 2.8% [76].

Table 1 Characteristics of included studies

Author	Study type	Patients (groins)	Mapping method	Lymphoscintigraphy	SPECT/CT	Intraoperatively	FN	Median F-UP (range)	Groin recurrence (%)	Outcome in SLN-negative patients (%; 95% CI)
Sykes 2019 [15]	Prospective	113	R + B	248/278 SLNs		111/113 (278/278 SLNs)		12	2/74 (2.7)	
Nica 2019 [16]	Retrospective	159 (245)	R or R + B			159/159 (245/245 groins)		31	6/120 (5)	1-year PFS (90); 5-year PFS (80)
Rodríguez-Trujillo 2018 [17]	Retrospective	93	R + B					60.4 (6.7–160.7)	2/42 (4.8)	5-year DSS (83.3; 74.9–91.7)
Soergel 2017 [18]	Prospective	27 (52)	R + ICG + B		25/27 (52/91 SLNs)	27/27 (52/52 groins; 91 SLNs)	1 (1 groin; 1 SLN)			
Klapdor 2017 [19]	Retrospective	30	R or R + B	28/28	26/26	139 SLNs		43.5 (4–75)	2/30 (6.6)	
Klapdor 2017 [20]	Retrospective	772	R or B					33 (0–156)	2/69 (2.9)	3-year PFS (82.7; 72.3–92.7); 3-year OS (92.7; 85.7–99.7)
Garganese 2017 [21]	Prospective	47 (73)	R + B		71/73 groins	73/73 groins; 164 SLNs	0			
Woelber 2016 [22]	Retrospective	140 (264)	R ± B			140/140 (264/264 groins)		33	1/84 (1.2)	2-year DFS (84)
van Doorn 2016 [23]	Retrospective	27 (44)	R + B			21/27 (37/44 groins)		27 (2–96)	0	
te Grootenhuis 2016 [12]	Prospective	377	R + B					105 (0–179)	6/253 (2.5) in unifocal disease	5-year DSS (93.5); 10-year DSS (90.8); 5-year OS (81.2); 10-year OS (68.6)
Collarino 2015 [24]	Retrospective	83 (144)	R + B or ICG-R	80/83 (141 groins; 192/252 SLNs)	80/83 (146 groins; 217 SLNs)	(144 groins; 252 SLNs)				
Klapdor 2015 [25]	Prospective	40	R + B	38/40 (233 SLNs)	39/40 (347 SLNs)	40/40	0			
Verbeek 2015 [26]	Prospective	12 (20)	R + ICG + B			12/12 (21 SLNs)				
Bogliolo 2015 [27]	Prospective	45 (77)	R	45/45		45/45 (100 SLNs)	1			
Robison 2014 [11]	Prospective	69 (111)	R + B			63/69 (103/111 groins)		58.3	3/57 (5.2); 4/86 groins (4.7)	
Underwood 2013 [28]	Retrospective	38 (74)	R + B				0	20.8 (3–45)	1/50 groins (2)	
Mathéron 2013 [29]	Prospective	15 (29)		39 SLNs	14/15 (28/29	(27/29 groins, 46 SLNs)				

Table 1 (continued)

Author	Study type	Patients (groins)	Mapping method	Lymphoscintigraphy	SPECT/CT	Intraoperatively	FN	Median F-UP (range)	Groin recurrence (%)	Outcome in SLN-negative patients (%; 95% CI)
			R + ICG or R + B + I-CG			groins; 39 SLNs)				
Coleman 2013 [30]	Prospective	234	R + B	234/234		64/64; 101/105; 64/65	9			
Woelber 2013 [31]	Retrospective	74/106 primary-SLN group; 32/106 secondary-SLN group	R	32/32		117 SLNs in primary-SLN group; 103 SLNs in secondary-SLN group		33 (3–118)	4/74 (5.4) in primary-SLN group; 0% in secondary-SLN group	3-year DFS in primary-SLN group (72.5); 3-year DFS in secondary-SLN group (92.5)
Schaafsma 2013 [32]	Prospective	24 (34)	R + B + ICG			19/24 (25/34 groins; 35 SLNs)	0			
García-Iglesias 2012 [33]	Retrospective	76	R + B			76/76 (90 SLNs)	0	36	1/76 (1.3)	
Hutteman 2012 [34]	Prospective	9	R + B + ICG			14 SLNs				
Levenback 2012 [35]	Prospective	452 (772)	R + B			418/452 (593/772 groins)	11 (12 groins)			
Zekan 2012 [36]	Prospective	25 (50)	R			25/25 (36 SLNs)	1			
Devaja 2011 [37]	Prospective	60	R + B			59/60	0	24 (2–66)	0	
Klar 2011 [38]	Prospective	16 (29)	R			12/16 (25/29 groins)	0			
Akrivos 2011 [39]	Prospective	34 (64)	R + B or B			34/34 (52/64 groins, 80 SLNs)	3 (4 groins)			
Ennik 2011 [40]	Retrospective	64	R or B or both	60/63		61/64 (80% groins; 102 SLNs)	5			
Crane 2011 [41]	Prospective	10 (16)	R + B + ICG			10/10 (16/16 groins; 29 SLNs)				
Lindell 2010 [42]	Retrospective	77 (126)	R + B or B	58/60		75/77 (94/126 groins)	2			
Sawicki 2010 [43]	Prospective	24 (39)	R + B or B			34/39 groins; 63 SLNs	0			
Radziszewski 2010 [44]	Prospective	56 (109)	R + B	107 groins		106/107 groins	7			
Crosbie 2010 [45]	Prospective	32 (45)	R + B	32/32		31/32 (45/45 groins)	1 (1 groin)	62 (33–84)	0	
Achimas-Cadariu 2009 [46]	Prospective	46 (86)	R + B			94% patients	0	25	0	
Klát 2009 [47]	Prospective	23 (41)	R + B				1	(8–46)	0	

Table 1 (continued)

Author	Study type	Patients (groins)	Mapping method	Lymphoscintigraphy	SPECT/CT	Intraoperatively	FN	Median F-UP (range)	Groin recurrence (%)	Outcome in SLN-negative patients (%; 95% CI)
						23/23 (38/41 groins; 67 SLNs)				
Camara 2009 [48]	Not available	17	R + B			15/17 (80 SLNs)	0			
Hampl 2008 [49]	Prospective	127 (230)	R or R + B or B	125/127 (228/230 groins)		127/127	3			
Van der Zee 2008 [9]	Prospective	403 (623)	R + B					35 (2–87)	6/259 (2.3) unifocal disease; 8/276 (3) including multifocal disease	3-year DSS (97)
Moore 2008 [10]	Prospective	35 (54)	R + B			35/35 (54/54 groins)		29 (8–51)	2/31 (6.4); 2/46 groins (4.3)	
Brunner 2008 [50]	Retrospective	44 (54)	R or R + B			44/44 (54/54 groins; 120 SLNs)	3			
Johann 2008 [51]	Retrospective	First group, 23/57 (45 groins) SLNB+ IFL; second group, 34/57 (59 groins) SLNB or IFL	R + B	37/39		76 SLNs of first group; 61 SLNs of second group	1 groin of first group	Second group: 24 (6–87) for SLNB; 111 (14–209) for IFL	0	
Beneder 2008 [52]	Prospective	10	R + B	10 /10 (26 SLNs)	10/10 (38 SLNs)	38 SLNs				
Hauspy 2007 [53]	Prospective	41 (68)	R + B			39/41 (58/68 groins)	0			
Nyberg 2007 [54]	Retrospective	47	R + B or B			46/47 (46 SLNs)	0 (stage I and II 25/47 pts)			
Rob 2007 [55]	Prospective	59 (82): 16 only B and 43 B + R	B or R + B			11/16; 43/43 (82 groins; 118 SLNs)	1			
Vidal-Sicart 2007 [56]	Prospective	50/70 validation group-1; 20/70 application group-2	R + B	49/50 group-1; 19/20 group-2		49/50 group-1; 19/20 group-2		24	0	
Martínez-Palones 2006 [57]	Both	28/55 (40) SLNB group; 27/55 (49)	R + B	27/28 (44 SLNs) SLNB group		27 (62 SLNs) SLNB group	1	22.5 (0–64) SLNB group; 60 (6–110)	3/28 (10.7)	

Table 1 (continued)

Author	Study type	Patients (groins)	Mapping method	Lymphoscintigraphy	SPECT/CT	Intraoperatively	FN	Median F-UP (range)	Groin recurrence (%)	Outcome in SLN-negative patients (%; 95% CI)
		non-SLNB group						non-SLNB group		
Terada 2006 [58]	Retrospective	21 (27)	R + B			21/21 (44 SLNs)		4.6 (2–8) years	0	3-year DFS (100)
Wydra 2005 [59]	Prospective	10 (19)	R + B			14/19 groins; 25 SLNs	0			
Merisio 2005 [60]	Not available	20 (30)	R			20/20	1			
Louis-Sylvestre 2005 [61]	Prospective	17 (34)	R or R + B	17/17		17/17 (21/34 groins)	0			
Frumovitz 2004 [62]	Retrospective	14 (22 groins) with recurrence	B			13/14 (22/22 groins; 17 SLNs)	1	46 (1 week–95 months)	3 patients	
Moore 2003 [63]	Prospective	21 (31)	R + B			31 groins; 82 SLNs	0			
Puig-Tintoré 2003 [64]	Prospective	26 (31)	R + B			25/26 (46 SLNs)	0	18.5 ± 9.4	0	
Sliutz 2002 [65]	Prospective	26	R or R + B	26/26		26/26	0			
Molpus 2001 [66]	Prospective	11 (16)	R + B	10/11 (16/19 SLNs)		19 SLNs				
Levenback 2001 [67]	Prospective	52 (76)	B			46/52 (57/76 groins; 83 SLNs)	0			
Sideri 2000 [68]	Not available	44 (77)	R			44/44 (77/77 groins)	0			
de Hullu 2000 [69]	Prospective	59 (107)	R + B	59		95/107 groins; 139 SLNs	0			
De Cicco 2000 [70]	Prospective	37 (55)	R	37		37 (55 groins; 736 SLNs)	0			
Ansink 1999 [71]	Prospective	51 (93)	B			52/93 groins	2			
de Hullu 1998 [72]	Prospective	10 (18)	R + B	20 SLNs		10/10 (18 SLNs)	0			
Decesare 1997 [73]	Prospective	10 (20)	R			10 (20 groins)	0			
Levenback 1995 [74]	Prospective	21 (29)	B			18/21 (19/29 groins)	0	6.9 (2.8–21.2)	0	
Levenback 1994 [75]	Prospective	9 (12)	B			7/9 (7/12 groins)	0			

B blue dye, *DSS* disease-specific survival, *DFS* disease free survival, *ICG* indocyanine green, *FN* false negative, *PFS* progression free survival, *R* radiotracer, *SLN* sentinel lymph node

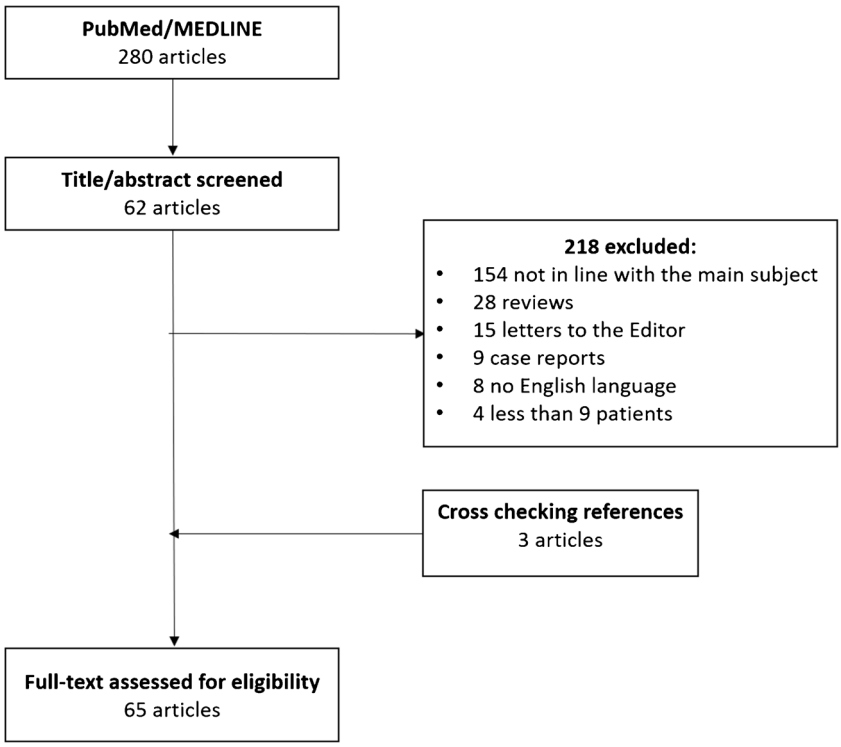

Fig. 1 Flow chart showing search strategy

Indications and contraindications

On the basis of both GROINSS-V and GOG-173 trials [9, 35], SLNB is currently the standard of care for early-stage patients with unifocal primary tumour smaller than 4 cm in diameter, with more than 1mm depth of stroma invasion and clinically at N0 stage (Table 2) [7, 8]. Lateral tumours (more than 1–2 cm from midline structures) mainly spread to the ipsilateral LNs, thus are scheduled to the ipsilateral SLNB [7, 8]. Conversely, midline tumours may drain to both groins [4], so bilateral SLNB is advised. In this case, when SLN is detected only unilaterally, contralateral IFL is recommended to avoid possible false negatives of the method [7, 8]. Indeed, Louis-Sylvestre et al. described that 3/13 patients with midline lesions but unilateral drainage at lymphoscintigraphy had contralateral groin node metastasis [61]. Similar results have been reported by Coleman et al. [30]. Besides, large midline tumours (≥ 2 cm in diameter) have high risk of groin recurrences after negative SLNB [11, 19]. Hence, we conclude that midline tumours should be treated with caution and LN assessment should be bilateral even though lymphoscintigraphy shows unilateral SLNs.

Patients with multifocal disease are not suitable for SLNB due to a higher groin recurrence rate (10.5%) compared with groin recurrence rate in patients with unifocal disease (2.3%) as described by Van der Zee et al. They hypothesised that the peritumoural injection may not be representative for the extension of the multifocal tumours [9].

When the procedure shows metastatic unilateral SLN, contralateral groin dissection and/or radiation should be performed [7]. However, Woelber et al. showed that none of the patients with metastatic unilateral SLN had a contralateral non-SLN metastasis, so they concluded that contralateral

Table 2 Indications and contraindications for sentinel lymph node biopsy in vulvar cancer

Indications	Contraindications
Histologically proven VSCC	T > 4 cm multifocal disease
> 1mm depth of stromal invasion	Prior excision of the primary tumour
Unifocal primary tumour	Vulvar recurrence
T < 4 cm, not involving anus, vagina, urethra	cN+
cN0	Prior radiotherapy of inguinal-pelvic area
	Contraindication to surgical treatment

VSCC vulvar squamous cell carcinoma, *cN0* clinically negative nodes, *cN+* clinically positive nodes

IFL, especially in multimorbid or obese patients, could be avoided for reducing surgical morbidity [22].

Patients with prior excision of the primary tumour are not eligible for SLNB due to possible disruption of lymphatic vessels causing a misidentification of SLN [7]. Levenback et al. showed that the intraoperative identification of SLNs was hampered in patients with prior excisional biopsy (44%) versus punch biopsy (16%) [67]. Similar findings have been described by Crosbie et al. [45]. Conversely, Ennik et al. described that SLN detection rate was not significantly lower in 27 cases with prior tumour excision compared with 38 cases without previous surgery or just previous incisional biopsy [40]. This result is in line with the results of Woelber et al. [31].

For patients with vulvar recurrence and previous SLNB, the standard treatment is IFL [8]. In 27 patients with recurrent VC who were not suitable for, or refused standard IFL, van Doorn et al. found feasible to repeat SLNB, but technically more challenging with a lower SLN identification rate (77%) [23].

Recently, Garganese and co-workers showed that SLNB seems to be safe (none false negative) in clinically/radiologically node-negative groins in case of: (a) T > 4 cm or multifocal, (b) after a complete tumour diagnostic excision, (c) contralateral nodal involvement and (d) local recurrence [21], providing that the preoperative work-up (by ultrasound and PET/CT) is very accurate in the selection of patients with negative LNs [21, 77]. Despite these promising results, we underline that further multicentre trials are warranted in order to obtain a higher level of evidence to extend the indication of SLNB.

Preoperative procedures

Patient preparation

No specific patient preparation is required for SLN mapping.

Radiopharmaceuticals

Technetium (^{99m}Tc)-radiolabelled colloids are lymphatic radiotracers commonly used for SLN mapping. ^{99m}Tc is a gamma emitting radionuclide with a relatively short half-life, thus low radiation burden for both patients and medical staff. In Europe, the most commonly used colloid is nanocolloidal albumin [78]. In 1997, Decesare and colleagues published the first clinical application of this radiotracer in VC [73], and since then it was validated in several studies [79]. Compared with optical tracer, the radiotracer has the ability to visualise the preoperative lymphatic mapping.

Nowadays, there is a trend towards the use of a hybrid tracer, indocyanine (ICG)-^{99m}Tc-nanocolloid, that combines radioactive and fluorescent guidance in a single injection, thereby allowing a preoperative lymphatic mapping and a better intraoperative visualisation of SLNs with ICG compared with blue dye [26, 29]. In fact, Mathéron et al. found that 96% of SLNs were intraoperatively visualised with ICG, whereas only 65% of SLNs were stained blue [29]. This result is in line with the study of Verbeek et al. [26]. In our opinion, ICG-^{99m}Tc-nanocolloid seems to be a promising radiotracer for pre- and intraoperative SLN identification.

Dose and administration

An anaesthetic cream or spray is applied around the primary tumour for pain relief about 5–10 min before the radiotracer injection. ^{99m}Tc-nanocolloid or ICG-^{99m}Tc-nanocolloid is then injected intradermally into four quadrants around the tumour-edge using a 25-gauge needle. Usually, 4 aliquots of 37 MBq in 0.1 mL of radiotracer are used in 1-day protocol and 4 aliquots of 74 MBq in 0.2 mL in 2-day protocols (injection 1 day prior to surgery) [78].

Acquisition protocol

Five minutes after injection, pelvic dynamic images of 15–30 min are acquired in anterior and posterior projections using 60 s per frame, matrix 64 × 64 and zoom 1. Then, anterior and lateral static images of 3–5 min, with a 256 × 256 or 128 × 128 matrix and zoom 1, are obtained at 20–30 min (early images) and at 60–120 min (late images) post injection. Afterwards, a reference source such as ^{57}Co-penmarker can be used for location of SLNs on overlying groin skin. The SLN site is then skin-marked with indelible ink in the anterior and lateral projections, allowing a more selective incision. Finally, single photon emission computed tomography with low-dose computed tomography (SPECT/CT) images are obtained using 15–25 s per frame, 3°, a 128 × 128 matrix and zoom 1 [78].

Planar lymphoscintigraphy and SPECT/CT

Early images allow to detect the lymphatic routes and the first draining SLNs, whilst late images permit to differentiate SLNs from the higher-echelon nodes, i.e. the LNs draining from the SLN [78]. In particular, lymphoscintigraphy enables to visualise the vulvar lymphatic drainage. Rob et al. detected 83.9% of SLN in superficial medial and intermediate regions and 16.1% of SLN in the deep femoral groins [55]. Moreover, lymphoscintigraphy allows to identify the number of SLNs before surgery [42] and the identification of unexpected drainage patterns [30]. Regarding this, Coleman et al. showed bilateral drainage in 14/64 patients with a lateral tumour and unilateral drainage in 27/65 patients with lateral ambiguous tumour (within 2 cm, but not involving midline structures) [30].

SPECT/CT images identify more SLNs compared with planar imaging and allow an exact anatomical localisation of SLN [24, 25, 52, 80]. In detail, Beneder et al. described that 4/10 patients had iliac SLNs on SPECT and CT/MRI 3D

software image fusion images, of which 2 patients had metastatic iliac SLNs without metastatic groin SLN [52]. Collarino et al. found that 180/217 SLNs were located in the medial regions of Daseler, whilst only one SLN was identified in the lateral inferior region. They concluded that in metastatic SLN patients the IFL might be spared in the lateral inferior region of Daseler [24]. Another contribution of SPECT/CT is the identification of aberrant lymphatic drainage pathways [25]. In fact, Klapdor et al. showed that seven patients had unpredicted drainage on SPECT/CT images like paravesical, paravaginal and gluteal drainage [25]. Furthermore, SPECT/CT images decrease the false positive uptake owing to external contamination [81], or presence of radioactivity in enlarged lymphatic vessels [82]. Thus, SPECT/CT enables to personalise lymphatic mapping, providing detailed information about the number and anatomical location of SLNs for adequate surgical planning.

A novel approach is the real-time fusion of freehand SPECT and ultrasound for anatomical co-registration of preoperative SLN localisation as reported by Bluemel et al. They included 151 patients of which three patients had a squamous cell carcinoma of vulva. This study showed that the real-time co-registration and fusion of freehand SPECT and US was feasible and increased up to 75% after training by radiologists [83]. Recently, Garganese et al. have investigated the feasibility of real-time fusion of ultrasound and three-dimensional SPECT/CT images for preoperative SLN mapping in five women (10 groins) with VC. The authors showed that the fusion of images was feasible and completed successfully in all cases with a median overall time of 32 min (range 25–40 min). Despite these encouraged results, further studies are needed to investigate the role of this new technology in the clinical work-up [84].

Image interpretation and pitfalls

On dynamic and early planar images, SLNs are the first draining LNs having a persistent focal uptake with or without visualisation of afferent lymphatic vessels from the site of injection (the primary lesion). On late planar images, additional SLNs are additional hot spots detected later and closer to the site of injection, whilst those located in the same regions of the first draining SLNs are considered to be higher-echelon nodes [85].

One possible pitfall is represented by false positive SLN. In this context, de Hull et al. showed one case in which the true SLN was totally replaced by tumour cells causing a lymphatic stasis and consequently a bypass of lymphatic flow to another LN [86]. Other potential pitfalls are related to the non-visualisation of the SLN [87] due to technical problems during the injection such as too deep injections or loss of injection fluid, and in case of overweight patients. Therefore, we strongly advise a careful preoperative imaging to rule out gross nodal involvement and a re-injection of radiotracer when the SLN is not visualised on SPECT/CT.

Imaging report

Each component of the lymphatic mapping procedure needs to be described (Figs. 2 and 3).

For dynamic images:

a. Lymphatic ducts directly draining from the injection site to LNs
b. Bilateral or unilateral drainage

For early and late images:

c. Number of the higher-echelon nodes
d. Additional LNs appearing on late images in other basins

For SPECT/CT:

a. Localisation of SLNs in the Daseler areas
b. Identification of additional SLNs
c. Localisation of non-radioactive LNs with short axis > 1 cm seen on the low-dose CT

Intraoperative procedures

Optical tracers

Blue dye has been the first optical tracer for intraoperative lymphatic mapping in VC [75]. The advantages of this tracer are the following: (a) intraoperative injection, avoiding patient discomfort, (b) intraoperatively visualisation of afferent lymphatic channels and identification of SLNs, (c) lack of ionising radiation, (d) availability and easy to handle. The disadvantages are the following: (a) very low penetration into tissue, so not applicable for obese patients and (b) contraindicated during pregnancy, lactation, or in cases of anaphylactic allergic reactions (favism).

In the last years, ICG has emerged as an interesting optical agent used for the intraoperative lymphatic mapping in VC. In detail, ICG emits a light signal in the near-infrared band after excitation, offering a real-time intraoperative guidance with higher tissue penetration compared with blue dye. The strength points are comparable with blue dye. The limitations are the following: (a) low penetration depth of near-infrared rays, (b) the necessity of intraoperative fluorescence camera and (c) the rapid diffusion through the lymphatic pathway, with the visualisation of more LNs than SLNs.

In conclusion, we emphasised that the use of optical agents is recommended preferentially in combination with a

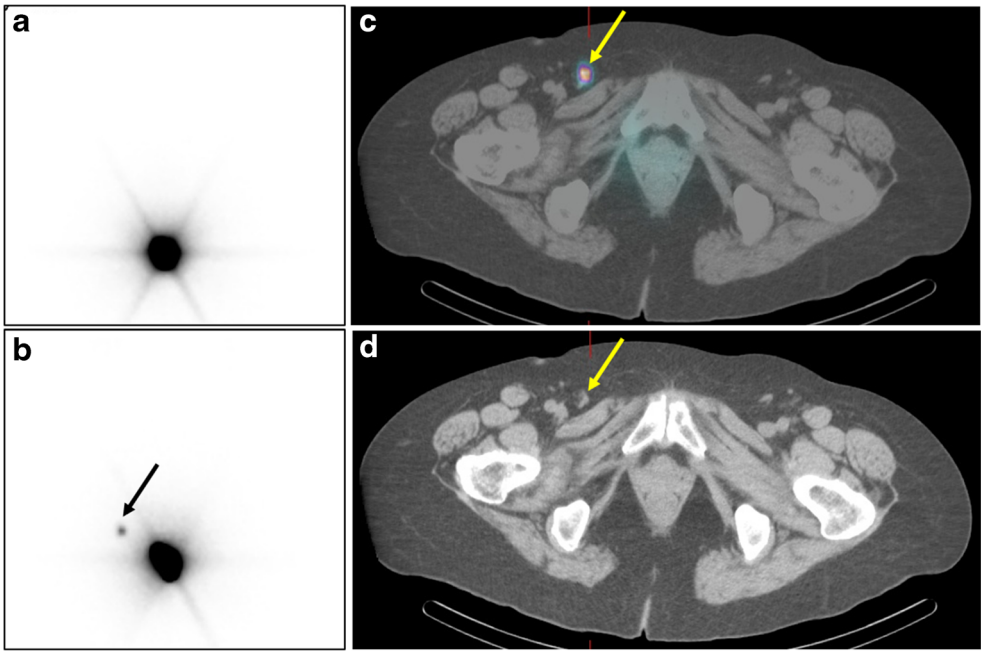

Fig. 2 A 70-year-old woman who had right lateral tumour of vulva. Anterior early image (**a**) shows no lymphatic drainage. Late planar image (**b**) shows unilateral lymphatic drainage with a single SLN (arrow) in the right groin corresponding with a focal uptake (yellow arrow) on transverse-fused SPECT/CT image (**c**) and not enlarged lymph node (yellow arrow) located the right medial superior inguinal zone on transversal low-dose CT (**d**)

radiotracer, in addition to preoperative SLN mapping with lymphoscintigraphy and SPECT/CT.

Surgical procedure and pathological analysis

Prior to groin surgery, when a double tracer procedure is chosen, blue dye or ICG should be injected around the tumour in the same location as the radiotracer injections. The handheld gamma probe is placed on the groin skin to identify the area of greatest radioactivity (preoperative counting), and thus guiding the skin incision. The probe is then used intraoperatively for localising the SLN(s) (intraoperative counting). Shortly after the excision of SLNs, the probe is used to measure ex vivo the radioactivity of SLNs (ex vivo counting) and the background radioactivity in order to confirm the correct removal of all SLNs (i.e. LNs with at least 10% of the ex vivo counting of the hottest SLN) [78]. Recently, a portable gamma camera has been used for increasing the intraoperative detection rate [29]. When ICG is injected fluorescence probe should be used for the intraoperative localisation. Finally, all excised SLNs are sent for pathological examination. The SLNs are subjected to routine haematoxylin and eosin

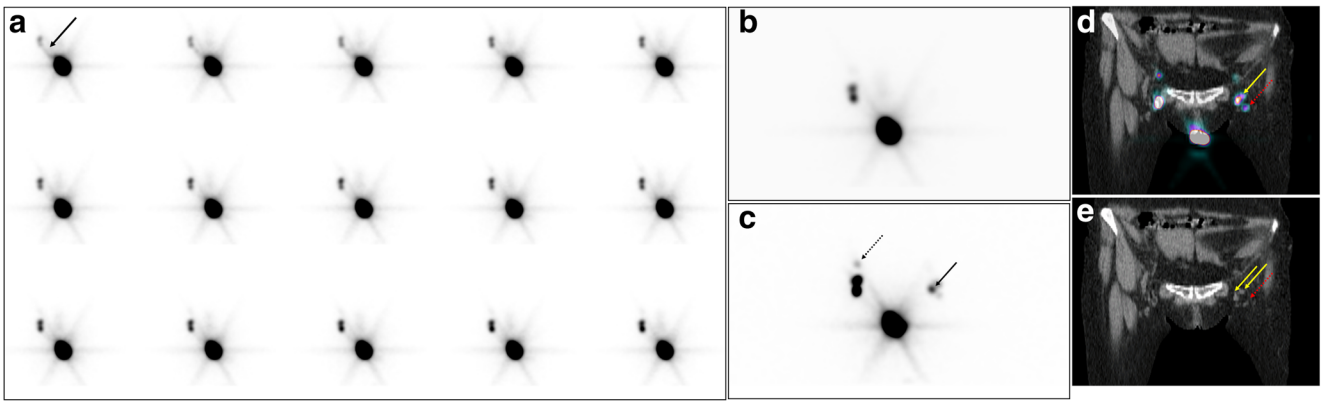

Fig. 3 A 59-year-old woman who had midline vulvar tumour. Anterior dynamic images (**a**) show unilateral lymphatic drainage with visualisation of a right lymphatic duct (arrow) directly draining from the injection site to two lymph nodes (SLNs). Anterior early image (**b**) shows the two SLNs in the right groin. Anterior late image (**c**) shows bilateral drainage with two SLNs in the right groin, one higher-echelon node (dashed arrow) in the right pelvic region, and one SLN in the left groin corresponding with one allocated uptake (yellow arrow) on coronal-fused SPECT/CT image (**d**) and two nearby lymph nodes (yellow arrows) located in the medial inferior inguinal zone on coronal low-dose CT (**e**). The remaining node (red dashed arrow) is a higher-echelon node located in the medial inferior inguinal zone

(H&E) staining, and when no metastases are detected ultrastaging with cytokeratin 1% AE1:AE3 antikeratin solution will be performed for revealing more and smaller metastases. Since no cut-off size for SLN metastases has been found below which the risk of non-SLN metastases is negligible [88], every patient with metastatic SLNs is until now scheduled for IFL.

Learning curve

Given the rarity of VC, SLNB should be performed in referral oncology centres by experienced gynaecologic oncologists with at least 10 successful cases per year and no false negative results [9]. Therefore, the importance of centralising care flows towards reference structures.

Pregnancy

SLNB using radiotracer can be performed during pregnancy after a careful evaluation by multidisciplinary board [89] whilst the use of blue dye is avoided for the possibility of anaphylactic allergic reactions.

Outcome

Negative SLNs correspond with low incidence of groin relapse (Table 1). Particularly, te Grootenhuis et al. reported a groin recurrence rate of 2.5% after a SLN-negative procedure at a median follow-up of 105 months. Moreover, they reported three-, five- and ten-year disease-specific survival rates of 97% [9], 93.5% and 90.8% respectively [12], in early-stage disease with a unifocal primary tumour and a negative SLNB.

Cost-effectiveness and cost-utility

The SLNB is the most cost-effective treatment strategy compared with IFL in women with early-stage VC. In particular, Sutton et al. showed that SLNB using ^{99m}Tc and blue dye with ultrastaging is the most cost-effective approach for two-year morbidity-free survival [90]. Erickson et al. reported that SLNB was less costly because of both lower treatment costs and fewer morbidities, and three-year inguinal-femoral recurrence-free survival was similar between IFL and SLNB groups [91]. Similarly, McCann et al. found that SLNB was less costly ($13,449 versus $14,261) and more effective (4.16 quality-adjusted life years (QALYs) versus 4.00 QALYs) than IFL. The key factor responsible for the differences between women with negative LNs treated with SLNB only compared with IFL was the lower incidence of lymphedema in women with SLNB [13].

Conclusions

In conclusion, SLNB is the standard procedure in well-selected women with clinically negative LNs, and is associated with low groin relapse and good 5-year disease-specific survival rates in negative SLN patients. Currently, SLNB is the most cost-effective treatment strategy than IFL in women with early-stage VC. However, further multicentric trials are needed to investigate if it is safe to extend the indication of SLNB in VC in a further attempt to decrease the surgical morbidity.

Although the combination of radiotracer and optical agent is widely used in the clinical routine, there is an increasing interest in the use of new tracers like ICG-^{99m}Tc-nanocolloid.

Finally, we strongly believe that it is pivotal to standardise the acquisition protocol including the SPECT/CT images in clinical work-up and centralise this procedure in experienced centres towards an individualised approach.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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