

ORIGINAL RESEARCH ARTICLE

Can late lymphoscintigraphy be omitted in the sentinel node procedure in early-stage vulvar cancer?

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Abstract

Introduction: In the Netherlands, the sentinel lymph node procedure protocol consists of preoperative lymphoscintigraphy combined with intraoperative blue dye for identifying sentinel lymph nodes in early vulvar squamous cell carcinoma. This study aimed at investigating the role of early and late lymphoscintigraphy.

Material and methods: From January 2015 to January 2019, early and late lymphoscintigraphies of 52 women were retrospectively analyzed. Lymphoscintigraphy was performed 30 minutes (early) and 2.5–4 hours (late) after vulvar injection of ^{99m}Tc-labeled nanocolloid. We calculated the concordance correlation coefficient (CCC) between number of sentinel lymph nodes detected on both images using the Lins concordance coefficient and correlated with clinicopathological data.

Results: Thirty-four women had a midline tumor and 18 had a lateral tumor. Detection rates with early and late scintigraphy were 88.5% and 98.1%, respectively. Median number of detected nodes was 1.0 (0–7) and 2.0 (0–7). Good statistical correlation between number of sentinel lymph nodes detected on early and late imaging was found (CCC = 0.76) in most patients. In 18 women (35%) a mismatch occurred: a higher number of nodes was detected on late imaging. In 11 of 18 women re-injection was performed because no sentinel lymph nodes were visualized on early images. Late imaging and intraoperative detection showed a good statistical correlation (CCC = 0.61). One woman showed an isolated groin recurrence despite negative sentinel lymph nodes.

Conclusions: This study showed good statistical correlations between early and late scintigraphy in most patients. However, in 35% of women late scintigraphy detected more nodes. In case of poor visualization after the first scintigraphy, re-injection should be considered. Late scintigraphy is probably helpful in confirming successful re-injection and in showing deviating lymph flow in women with failed mapping after the first injection and successful re-injection. Because missing metastatic sentinel lymph nodes often leads to a poor prognosis, we prefer optimal correlations between imaging and intraoperative identification. Hence, late scintigraphy cannot be safely omitted.

Abbreviations: CCC, concordance correlation coefficient; IFL, inguinofemoral lymphadenectomy; SLN, sentinel lymph node; VSCC, vulvar squamous cell carcinoma.

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KEYWORDS

lymphoscintigraphy, re-injection, sentinel lymph node dissection, timing, vulvar cancer

1 | INTRODUCTION

Vulvar cancer is a relatively rare disease, accounting for 4%–5% of all gynecological malignancies.^{1,2} Lymph node metastases in the groin occur in 25%–35% of patients with early vulvar squamous cell carcinoma (VSCC).^{3–7} The presence of lymph node metastases is the most important prognostic factor, because groin recurrences are associated with high mortality rates.^{8,9} For years, inguinofemoral lymphadenectomy (IFL) was the standard treatment of vulvar cancer. However, because of the high morbidity associated with IFL, there was a need for less invasive techniques.

Levenback et al were the first to show that intraoperative lymphatic mapping with isosulfan blue was feasible in vulvar cancer.^{10,11} Introduction of the combined technique of ^{99m}Tc-nanocolloid and blue dye showed even higher identification rates.¹² Since 2008, after publication of the GROINSS-V-I study,⁸ the sentinel lymph node (SLN) procedure has been integrated as standard care for patients with early VSCC.

In the Netherlands, all nine gynecological oncology centers carry out early (30 minutes) and late (2–4 hours) imaging on the day of preoperative injection of ^{99m}Tc-nanocolloid. Some centers perform additional imaging (a third photograph) the next day (2-day protocol) in a selection of women for logistical reasons. There is a lack of evidence on the right timing and interval of imaging. In the early phase, dynamic series often show the direct flow to SLNs. On the one hand, late lymphoscintigraphy might be expected to increase the visualization rate of additional SLNs. On the other hand, late lymphoscintigraphy is time consuming and there is also concern that a delay in imaging could lead to uptake in more second echelon nodes that are not true SLNs.

Most previous studies focusing on the role of second imaging and the optimal time schedule of the protocol concern breast cancer.^{13–19} No difference in SLN detection between same-day and next-day imaging is demonstrated.^{13–15} Three studies evaluated a 1-day protocol with early and late imaging on the same day.^{17–19} Two showed higher detection rates with late imaging^{17,18} and one showed no difference between early and late imaging.¹⁹

In vulvar cancer the price of missing a lymph node metastasis is extremely high because the prognosis of a groin recurrence is very poor.²⁰ The aim of this study was to investigate the role of early and late lymphoscintigraphy in the visualization and identification of SLNs in patients with early VSCC.

2 | MATERIAL AND METHODS

Care for patients with vulvar cancer is centralized in the Netherlands, meaning that treatment is performed in nine specialized gynecological oncology centers. This historical cohort study was performed in the Radboud University Medical Center Nijmegen, one of those nine

Key message

A well-known fact in vulvar squamous cell carcinoma is the correlation between missing metastatic sentinel lymph nodes and worse prognostic outcomes. In 35% of women, late scintigraphy detected more lymph nodes. Leaving out late scintigraphy could result in missing sentinel lymph nodes with metastases.

centers. Medical records and lymphoscintigrams of patients who underwent an SLN procedure in addition to vulvectomy for early VSCC were evaluated. The SLN procedure is shown in [Figure 1](#).

Women with primary unifocal tumors less than 4 cm and a preoperative diagnosis of VSCC, without suspicious lymph nodes (clinically and on ultrasound), were eligible for SLN dissection in addition to vulvectomy. Women with lateral tumors (i.e. >1 cm from midline) were planned for unilateral SLN dissection and those with midline tumors were planned for bilateral SLN dissection. In the case of a midline tumor with unilateral drainage on lymphoscintigraphy, IFL was indicated. IFL was also indicated when no SLNs or fewer SLNs than seen on scintigraphy were found during surgery. From January 2015 to January 2019, in 52 women who underwent SLN dissection for a histologically confirmed diagnosis of VSCC, results of early and late lymphoscintigraphy were available.

Before lymphoscintigraphy, ^{99m}Tc-nanocolloid was injected at four quadrants around the tumor. A dose of 4×10 MBq radiotracer was used in the 1-day protocol, and 4×20 MBq was used in the 2-day protocol. Before the injection, lidocaine prolocain crème 5% (EMLA®) was applied on and around the tumor for local pain relief. Planar scans of the vulvar and inguinal areas in anterior projections were obtained. Immediately after injection, dynamic shots were performed during 30 minutes with frames of 60 seconds. Static images were obtained 30 minutes (early) and 2.5–4 hours (late) after radiotracer injection in the 1-day protocol. Imaging after 30 minutes, 2.5 hours, and 18 hours was obtained in the 2-day protocol. Re-injection was performed when no lymph nodes were visualized on the images at 30 minutes. Identified SLNs were marked on the skin. Early imaging was performed to confirm mapping and in case of poor visualization, an indication for re-injection could be made. The purpose of late imaging was to visualize the effect of re-injection or, when no re-injection was performed, to see what the effect of time was on detection of lymph nodes. In practice, women who were allocated to the 2-day protocol only underwent the third imaging the next day when no SLNs were visualized on the day of injection. In this study we focused on differences between the same day images. Of the 52 women in this cohort, 37 underwent a 1-day and 15 a 2-day protocol. All women underwent early (30 min) and late (2.5–4 h) imaging. The third photograph in women allocated to the 2-day protocol was omitted from this study, as it applied to only three patients.

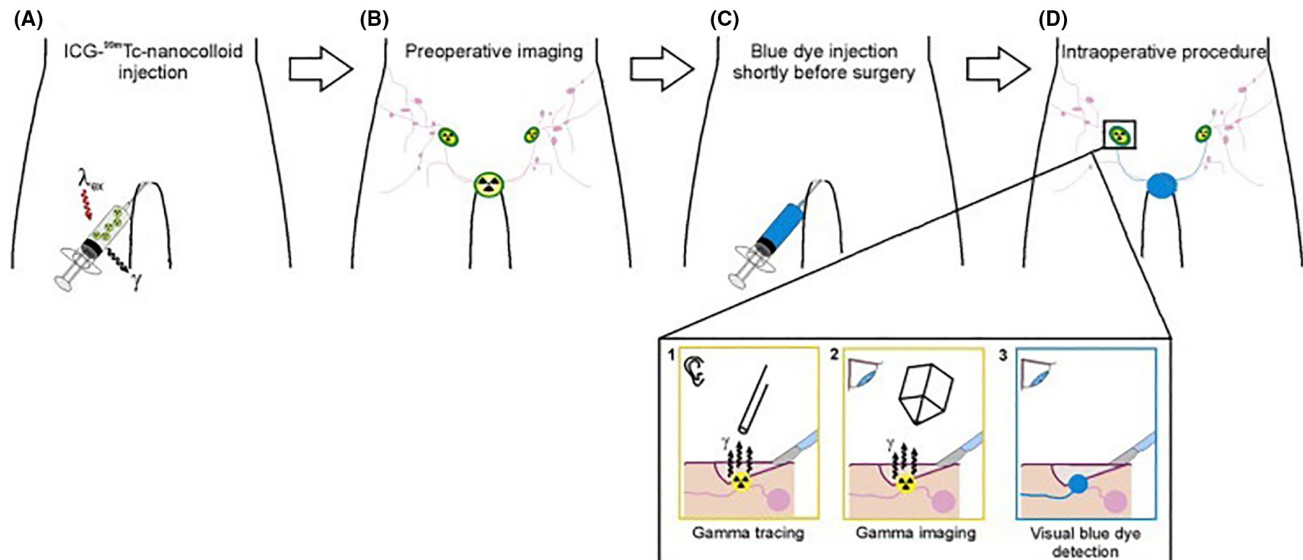


FIGURE 1 Preoperative sentinel node procedure. Adapted from [Figure 1](#) in *Gynecol Oncol.* 2013;131:720–725. Mathéron HM, van den Berg NS, Brouwer OR, et al. *Multimodal surgical guidance towards the sentinel node in vulvar cancer.* Doi: [10.1016/j.ygyno.2013.09.007](https://doi.org/10.1016/j.ygyno.2013.09.007),³⁰ with permission from Elsevier.

Methylene blue dye was injected around the tumor at the four quadrants. During surgery the gamma detecting probe (Europrobe) was used to locate the SLNs. After inguinal incision, SLNs were identified. Each lymph node containing radioactivity and/or blue dye was considered as an SLN and removed separately. After removal of the SLNs, the groin was re-examined with the probe to detect residual radioactivity to ascertain that all SLNs had been identified and removed. If the SLN could not be identified, IFL was indicated. In the same surgical session, a vulvectomy or wide local excision of the tumor was performed.

All SLN specimens were formalin-fixed and sent separately for histopathological examination. Adequate pathological examination of SLNs involves ultrastaging, which mandates serial sectioning of each node at multiple levels, and immunohistochemical staining with pancytokeratin antibodies if the tumor is not identified on examination of routinely stained sections. Women with lymph node metastases, independent of size, will be recommended to undergo additional IFL.

Patient background characteristics, tumor characteristics, and follow-up data were collected and stored in a database. The following data were retrieved from the medical records: age, location, position and diameter of the tumor, histopathological characteristics obtained from biopsy preoperatively, protocol (1- or 2-day), number of SLNs and higher echelon nodes per groin visualized on lymphoscintigraphy (higher echelon nodes were defined as nodes receiving lymphatic drainage directly from the SLNs), number of SLNs (blue and/or hot) removed, results of final pathology (lymphovascular space invasion, differentiation grade, tumor type, diameter, invasion depth, minimal free margin, number of removed SLNs, and presence of metastases), results of final pathology after IFL, additional radiotherapy, recurrences, and mortality. Because lymphoscintigraphy reports were not available in all women, all

lymphoscintigraphy images were re-evaluated again for this study by the same nuclear physician (MJ) without knowing the surgical and pathological results.

2.1 | Statistical analyses

Statistical analyses were performed using SPSS version 25.0. Descriptive statistics for all variables were calculated, using medians because we could not assume normal distribution in this relatively small study population. To calculate the correlation between number of SLNs detected on early imaging and late imaging and between preoperative imaging and intraoperative detection and removal, we used the Lin's concordance correlation coefficient (CCC). We opted for the Lin's CCC because the outcome measure was a continuous variable. This method compares two measurements of the same variable.²¹ In line with other literature,²² CCCs were statistically interpreted as follows: CCC < 0.40 poor correlation, 0.40–0.59 moderate correlation, 0.60–0.79 good correlation, ≥ 0.80 excellent.

2.2 | Ethics statement

The institutional ethics committee of the Radboud University Medical Center Nijmegen reviewed this study project and provided ethical approval (file no 2019-5795) on October 10, 2019.

3 | RESULTS

In the study period, 52 women underwent an SLN procedure. An overview of women included in this study is depicted in [Figure 2](#). Treatment

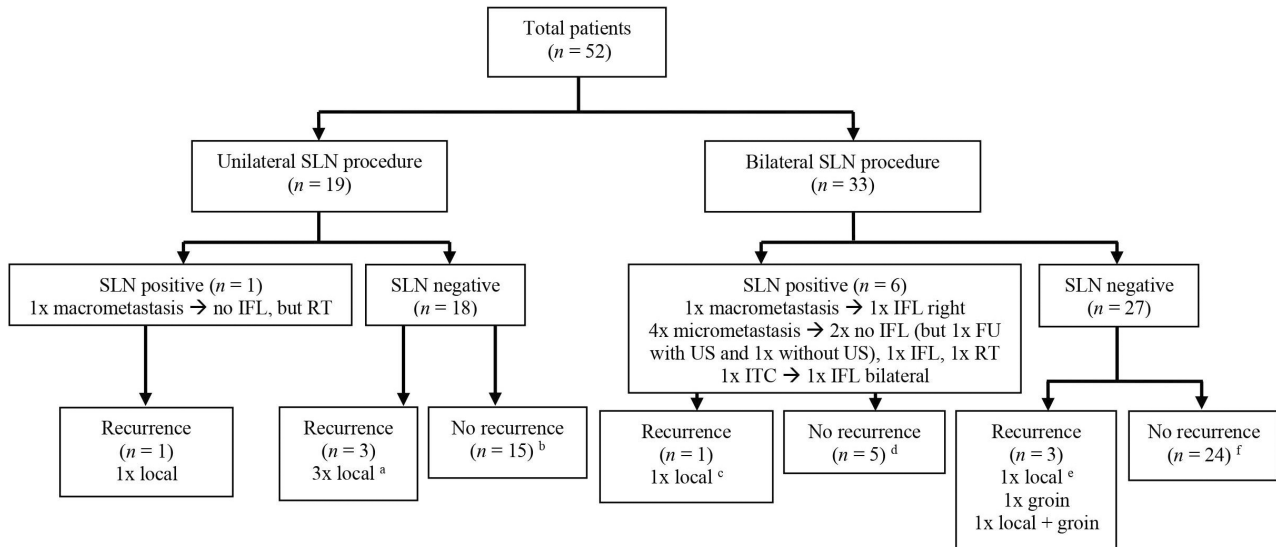


FIGURE 2 Overview of women included in this study. FU, follow up; IFL, inguinofemoral lymphadenectomy; ITC, isolated tumor cells; RT, radiotherapy; SLN, sentinel lymph node. Local means vulvar recurrence. Seventeen women underwent re-injection (a t/m f): ^an = 1, ^bn = 3, ^cn = 1 (micrometastasis and RT), ^dn = 2 (1x micrometastasis and no IFL + 1x macrometastasis and IFL right), ^en = 1, ^fn = 9.

characteristics, tumor characteristics, and follow up are shown in [Table 1](#). Unilateral SLN procedure was performed in 19 (36.5%) women and a bilateral procedure was performed in 33 (63.5%). Median age was 69.0 years (41–89 years), and 34 had a midline tumor and 18 a lateral tumor. Of the 34 women with a midline tumor, 30 underwent a bilateral procedure. In 4 of the 34 a unilateral procedure was performed, because the SLN was only visualized on one side. After counseling, patients preferred follow up instead of additional IFL ([Table 2](#)). Of the 18 women with a lateral tumor, 15 underwent a unilateral procedure and three a bilateral procedure (because SLNs were visualized on both sides). Intraoperative detection rate based on radioactive gamma tracing in combination with blue dye visualization was 98.1%.

3.1 | Patients with an indication for additional IFL

In 16 of 52 women IFL was indicated. In four of them this was actually carried out: two women had a metastatic SLN, one woman had isolated tumor cells (ITC) in the SLN and in one woman final pathology showed a multifocal tumor. In the other 12 women IFL was not performed and a different treatment policy was followed. Indications for IFL and actual treatment in these women are shown in [Table 2](#).

3.2 | Comparison of early and late lymphoscintigraphy

The SLN detection rate with early scintigraphy was 88.5% and with late scintigraphy was 98.1%. The median number of nodes detected with early and late scintigraphy were 1.0 (range 0–7) and 2.0 (range 0–7), respectively. In 18 of 52 women there was a mismatch between number of SLNs detected on early vs late imaging.

In all mismatching lymphoscintigraphies there were more SLNs detected on the second, late imaging. In 17 women, re-injection with ^{99m}Tc-nanocolloid was performed 0.5–2 hours after the first injection. In 11 of 17 women more SLNs were detected on late imaging. These 11 women were part of the 18 women with a mismatching lymphoscintigraphy ([Table 3](#)). Comparing results of early and late scintigraphy resulted in a CCC of 0.76 (95% confidence interval [CI] 0.63–0.85).

3.3 | Comparison of preoperative imaging and intra-operative detection

Poor correlation of 0.35 (95% CI 0.15–0.51) was found between number of SLNs detected on preoperative early imaging and intraoperative detection and removal. The comparison between late imaging and intraoperative detection showed a good correlation of 0.61 (95% CI 0.43–0.74). In only one woman (1.9%) fewer nodes were removed during surgery than seen on late imaging ([Table 4](#)). In 46% the opposite was the case: more nodes were removed than detected on preoperative late imaging.

3.4 | Follow up: recurrences

Women were followed for a median of 13.0 months (range 0–47 months). As the number of recurrences was very low in this cohort, no statistical analysis could be performed on the relation between SLN detection during preoperative imaging and recurrence rate. In this cohort, one woman developed a vulvar and groin recurrence on the right side 6 weeks after primary surgery. Another woman developed an isolated groin recurrence on the ipsilateral side

TABLE 1 Patient and tumor characteristics, sentinel node procedure, and postoperative findings of all patients (*n* = 52)

Age (years), median (range)	69.0 (41–89)	
Location of the tumor, <i>n</i> (%)		
Labium minus	26	50.0
Labium majus	4	7.7
Clitoris	14	26.9
Posterior commissure/perineum	8	15.4
Position of the tumor		
Midline ^a	34	65.4
Lateral	18	34.6
Number of SLN detected, median (range)		
Early lymphoscintigraphy		
Total	1.0 (0–7)	
Left groin	1.0 (0–4)	
Right groin	1.0 (0–3)	
Late lymphoscintigraphy		
Total	2.0 (0–7)	
Left groin	1.0 (0–4)	
Right groin	1.0 (0–3)	
Peroperative		
Total	3.0 (1–5)	
Left groin	2.0 (1–3)	
Right groin	2.0 (0–4)	
Sentinel node dissection, <i>n</i> (%)		
Unilateral	19	36.5
Bilateral	33	63.5
Squamous cell carcinoma, <i>n</i> (%)	49	94.2
Microinvasive squamous cell carcinoma, <i>n</i> (%)	1	1.9
dVIN with microinvasive growth, <i>n</i> (%)	1	1.9
Basal cell carcinoma ^b , <i>n</i> (%)	1	1.9
Differentiation, <i>n</i> (%)		
Well	21	40.4
Moderately	20	38.5
Poorly	6	11.5
Missing	5	9.6
Pathological tumor maximum diameter (mm), median (range)	15.0 (1–50)	
Missing	4	
Tumor invasion depth (mm), median (range)	3.5 (0.2–14)	
Missing	1	
Tumor minimum free margin (mm), median (range)	5.0 (0–12)	
Missing	2	
Lymphovascular space involvement, <i>n</i> (%)		
Yes	3	5.8
No	40	76.9
Missing	9	17.3

(Continues)

TABLE 1 (Continued)

Sentinel lymph node metastasis, <i>n</i> (%)	7	13.5
Unilateral ^c	7	
Bilateral	0	
Inguinofemoral lymph node dissection (second surgery), <i>n</i> (%) ^d	4	7.7
Unilateral, <i>n</i> (%)	2	
Bilateral, <i>n</i> (%)	2	
Recurrence, <i>n</i> (%)	8	15.4
Locoregional	6	
Groin	1	
Locoregional + groin	1	
Mortality, <i>n</i> (%) ^e	4	7.7
Follow up (months), median (range)	13.0 (0–47)	

Abbreviations: dVIN, differentiated vulvar intraepithelial neoplasia; SLN, sentinel lymph node.

^aDefined as <1 cm from midline (medial margin).

^bPreoperative biopsy showed moderately differentiated squamous cell carcinoma. However, final pathology showed a 4.5 cm basal cell carcinoma.

^c1× Isolated tumor cells (ITC).

^dIn one woman bilateral inguinofemoral lymphadenectomy was performed because of diagnosis of multifocal tumor after surgery.

^eTwo patients died of metastatic vulvar disease. Other causes of death: primary lung carcinoma and urosepsis.

14 months after the vulvectomy and SLN procedure. In both women, early and late lymphoscintigraphy showed the same number of SLNs and the removed SLNs showed no metastases.

3.5 | Outcomes of patients with a mismatch between scintigraphy and postoperative pathology

Comparison between late imaging and final pathology showed a CCC of 0.61 (95% CI 0.42–0.75). In four women (7.7%) final pathology showed fewer lymph nodes than seen on preoperative lymphoscintigraphy (Table 4). In the first woman, final pathology showed a microinvasive tumor, therefore IFL was not indicated. In the second, an 86-year-old woman, it was decided preoperatively to withhold from additional IFL if necessary. The third woman presented with a lateral tumor. Preoperative imaging also detected one SLN on the contralateral side, which was removed preoperatively. However, on final pathology the contralateral specimen composed only fat and connective tissue. After counseling the patient about IFL, it was decided not to perform additional surgery. The fourth woman was diagnosed with a midline tumor and she was planned for vulvectomy and bilateral SLN procedure. Lymphoscintigraphy showed two SLNs on both groin sides. Preoperatively two SLNs were detected on both sides, which were removed. However, final pathology showed only one lymph node on each side, both without metastases. After counseling about additional IFL, she was planned for follow up with ultrasound of the groin every 3 months. After 14 months, she developed

TABLE 2 Patients with an indication for IFL, but a different treatment policy was followed

Patient	Indication IFL	Reason why IFL was not performed	Treatment
1	Metastatic SLN and final pathology showed less nodes than seen on scintigraphy	Refusal by the patient	Radiotherapy
2	Metastatic SLN	Refusal by the patient	Radiotherapy
3	Metastatic SLN	Refusal by the patient	FU with ultrasound of the groins
4	Metastatic SLN	Comorbidities	FU without ultrasound of the groins
5	SLN only found on one side in a midline tumor	Location of tumor ^a /refusal by the patient	FU without ultrasound of the groins ^b
6	SLN only found on one side in a midline tumor	Location of tumor ^a /refusal by the patient	FU with ultrasound of the groins
7	SLN only found on one side in a midline tumor	Location of tumor ^a /refusal by the patient	FU with ultrasound of the groins
8	SLN only found on one side in a midline tumor	Location of tumor ^a /refusal by the patient	FU with ultrasound of the groins
9	Tumor size >4 cm on final pathology	Comorbidities	FU with ultrasound of the groins
10	Tumor size >4 cm on final pathology	Refusal by the patient	FU with ultrasound of the groins
11	Final pathology showed less nodes than seen on preoperative scintigraphy	Not mentioned	FU without ultrasound of the groins
12 ^c	Final pathology showed less nodes than seen on preoperative scintigraphy	Not mentioned	FU with ultrasound of the groins

Abbreviations: IFL, inguinofemoral lymphadenectomy; SLN, sentinel lymph node.

^aSmall tumor, located 0–1 cm from the midline, without crossing the midline (impresses like a lateral tumor).

^bFinal pathology showed a microinvasive tumor, so IFL was no longer indicated.

^cAfter 14 months groin recurrence.

an isolated groin recurrence on the left side. She refused IFL and opted for palliative radiotherapy.

4 | DISCUSSION

Based on our study, we recommend to maintain late lymphoscintigraphy, although we showed a statistically good correlation between early and late lymphoscintigraphy for the detection of SLNs in the majority of patients. Based on this statistical result, one could argue to consider omitting late lymphoscintigraphy. However, the number of SLNs was higher on the second scintigraphy compared with the first in 18 of 52 women (35%). The number of nodes of the second scintigraphy seemed to correlate better with the number of nodes removed peroperatively. Because of the poor prognosis of a groin recurrence, the removal of possibly too many nodes (including higher echelon nodes) has been generally accepted. In our cohort we observed a low recurrence rate (i.e. one isolated groin recurrence). However, this occurred in a patient in whom fewer SLNs were removed than preoperatively visualized. This is an important pitfall that was described earlier.²³ We therefore recommend maintaining the late lymphoscintigraphy to reduce the chance of missing any SLN.

There could be several reasons for non-detection of lymph nodes on early scintigraphy: (a) incorrect injection (consider re-injection instead of waiting), (b) very slow lymphatic flow (consider waiting until

detection), (c) SLNs with large metastases are potentially unable to drain lymphatic fluid, and (d) disrupted lymph ducts due to previous surgery.

In this study in 11 of the 18 women with a mismatching lymphoscintigraphy a re-injection after early scintigraphy was performed. The question arises whether the higher number of visualized nodes on late imaging was due to waiting or re-injection. Re-injection could be considered a new intervention, that makes the late photograph actually a new, early photograph. The effect of re-injection is probably much higher than waiting a few hours for a second scintigraphy. From clinical experience, after re-injection, visualization of SLNs appears to be better related to the exact location of the injection rather than to the time since injection. This also indicates the importance of a correct first injection. Re-injection adds extra complexity to the comparison of early vs late scintigraphy; however, this very much reflects how it works in daily practice.

In this study we did not only observe a mismatch in the number of nodes between early and late imaging, but also in the number of nodes between preoperative imaging and peroperative detection. In one woman, fewer nodes were removed peroperatively than detected on scintigraphy. Also, final pathology showed fewer nodes. In another three women, the surgeon was thought to have removed the same number of nodes as seen on scintigraphy, but final pathology showed fewer nodes, which sets an indication for additional IFL. Both situations are potentially dangerous and represent pitfalls in the SLN procedure in vulvar cancer. If there is any doubt about the

TABLE 3 Characteristics of women with a mismatching lymphoscintigraphy (n = 18)

	Procedure	Lymphoscintigraphy						Number of SLNs removed peroperatively	Number of SLNs on final pathology			Metastases	Number of metastatic SLNs		
		Number of SLNs at 30 min (early)			Number of SLNs at 2.5 h (late)				L	R	T				
Re-injection															
		L	R	T	L	R	T	L	R	T	L	R	T		
1	Unilateral	0	0	0	0	2	2	-	4	4	-	5	5	No	0
2	Unilateral	0	0	0	1	0	1	2	-	2	2	-	2	No	0
3	Bilateral	0	0	0	1	1	2	1	2	3	2	1	3	No	0
4	Bilateral	1	0	1	1	1	2	1	1	2	1	0	1	Yes	1 (L)
5	Bilateral	1	0	1	1	1	2	1	1	2	1	1	2	No	0
6	Bilateral	0	1	1	1	1	2	1	2	3	1	2	3	Yes	1 (R)
7	Bilateral	1	0	1	1	1	2	1	1	2	4	1	5	Yes	1 (R)
8	Bilateral	0	2	2	2	2	4	2	2	4	2	2	4	No	0
9	Bilateral	1	0	1	1	1	2	1	2	3	1	3	4	No	0
10	Bilateral	0	0	0	1	2	3	1	2	3	1	2	3	No	0
11	Bilateral	0	1	1	2	1	3	2	1	3	2	1	3	No	0
No re-injection															
12	Unilateral	0	2	2	0	3	3	-	3	3	-	3	3	No	0
13	Unilateral	0	0	0	0	2	2	-	3	3	-	3	3	No	0
14	Bilateral	1	0	1	1	1	2	1	1	2	1	1	2	No	0
15	Bilateral	0	1	1	1	1	2	2	2	4	2	2	4	No	0
16	Bilateral	1	1	2	1	2	3	2	2	4	2	2	4	No	0
17	Bilateral	2	0	2	2	2	4	2	2	4	2	2	4	Yes	1 (L)
18	Bilateral	1	0	1	1	1	2	2	1	3	2	1	3	Yes	1 (L)

Abbreviations: L, left groin; R, right groin; SLN, sentinel lymph node; T, total.

TABLE 4 Characteristics of the women with fewer nodes removed during surgery and fewer nodes on final pathology than seen on scintigraphy (n = 1)

	Lymphoscintigraphy						Number of SLNs removed peroperatively	Number of SLNs on final pathology			Metastases	Recurrence		
	SLN at 30 min (early)			SLN at 2.5 h (late)				L	R	T				
	L	R	T	L	R	T	L	R	T	L	R	T		
1	4	3	7	4	3	7	2	1	3	2	3	5	No	No ^a
Additional women (n = 3) with fewer nodes on final pathology than seen on scintigraphy														
1	2	2	4	2	2	4	2	2	4	1	1	2	No	Groin ^b
2	2	0	2	2	0	2	2	-	2	1	-	1	No	No
3	1	0	1	1	1	2	1	1	2	1	0	1	Yes	Local

Abbreviations: L, left groin; R, right groin; SLN, sentinel lymph node; T, total.

^aFinal pathology showed a microinvasive vulvar squamous cell carcinoma, so inguinofemoral lymphadenectomy was no longer indicated.

^bUnilateral.

number of nodes removed peroperatively, frozen section should be considered. These examples stress that it is pivotal to perform the sentinel node procedure accurately and meticulously.²³

This is the first study that evaluates the role of early and late lymphoscintigraphy in vulvar cancer. In breast cancer this has been evaluated before, although studies are difficult to compare because of the use of different protocols.^{13-18,24} Several studies showed

comparable detection rates with early imaging performed on the day of injection and late imaging performed the next day.¹³⁻¹⁵ Two other studies compared early and late imaging on the same day and showed higher detection rates with late imaging.^{17,18} For SLN mapping in cutaneous melanoma both 1-day and 2-day protocols seem safe and accurate.^{25,26} However, there is an important difference between sentinel node procedures in vulvar cancer and breast cancer

or melanoma, prohibiting extrapolation of these findings to vulvar cancer.

In melanomas and breast cancer the lymphatic pathway is often linear from the tumor to cranial, whereas in vulvar cancer lymphatic flow patterns from the vulva to the groin appear to be much more complex.²⁷⁻²⁹ Theoretically, the first lymph node that is immediately visualized on early imaging is defined as the SLN. Lymph nodes that are subsequently visualized are considered higher echelon nodes. However, in practice, in vulvar cancer the lymph nodes that are visualized later can be located as far from the tumor as the first visualized lymph node. Hence, it is possible that a secondary visualized lymph node is a second SLN with its own draining tract from the tumor to the groin. In this way, the number of imagings (one, two or sometimes even three) could influence the surgery.

Some limitations and strengths of our study need to be discussed. It is a strength that the time between early and late imaging was fairly constant in this study. Previous studies showed varied and sometimes large intervals between consecutive scintigrams and therefore results are difficult to interpret. This study provides a realistic representation of clinical practice with the associated pitfalls and treatment dilemmas.

Limitations are the small sample size and the retrospective character of this unicentric study. Due to the observational and retrospective study design, true causal relations cannot be determined. In 18 women, the early and late images did not match. As a result of this small number of women and the low recurrence rate, it was not possible to associate oncological outcomes, such as survival and recurrence with scintigraphy mismatching.

5 | CONCLUSION

We showed good statistical correlation between early and late scintigraphy in the majority of patients. However, in 18 of 52 women (35%) late scintigraphy detected more nodes. Because also a higher number of "hot" nodes were found during surgery, we suggest that omitting late scintigraphy could potentially result in missing SLNs with metastases. If there are any doubts regarding visualization after the first scintigraphy, re-injection should be considered. Maintaining late scintigraphy could help in confirming successful re-injection and in showing deviating lymph flow in women with failed mapping after the first injection and successful re-injection. Outweighing benefits and disadvantages, we feel that it is still valid to perform both early and late scintigraphy.

AUTHOR CONTRIBUTIONS

DT and JA were involved in study design, data analysis, data charting, interpretation of results, and write up of the manuscript. DT and MJ were involved in data collection, chart review and data analysis. MJ also contributed to interpretation of results and writing the manuscript. JH was involved in study design, interpretation of results and was a major contributor to write up of the manuscript. All authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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