Sentinel lymph node procedure in early-stage vulvar cancer: correlation of lymphoscintigraphy with surgical outcome and groin recurrence

Warmerdam, D.H.M.; Geloven, N. van; Beltman, J.J.; Kroon, C.D.D.; Rietbergen, D.D.D.; Poelgeest, M.I.E. van; Gaarenstroom, K.N.

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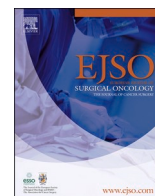Daniëlle H.M. Warmerdam [a], Nan van Geloven [b], Jogchum J. Beltman [a], Cor D. De Kroon [a], Daphne D.D. Rietbergen [c], Mariette I.E. van Poelgeest [a], Katja N. Gaarenstroom [a,*]

[a] Department of Gynecology, Leiden University Medical Center, P.O. Box 9600, 2300 RC, Leiden, the Netherlands
[b] Department of Biomedical Data Sciences (section Medical Statistics), Leiden University Medical Center, P.O. Box 9600, 2300 RC, Leiden, the Netherlands
[c] Daphne D.D. Rietbergen: Department of Radiology, Section Nuclear Medicine, Leiden University Medical Center, P.O. Box 9600, 2300 RC, Leiden, the Netherlands

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ABSTRACT

Introduction: In early-stage vulvar squamous cell carcinoma (VSCC) a sentinel lymph node (SLN) procedure is regarded successful if at least one SLN is removed with minimal residual radioactivity. An inguinofemoral lymphadenectomy is considered if not all SLNs visualized on lymphoscintigraphy can be found, with subsequent increased morbidity. We correlated lymphoscintigraphy findings with surgical outcome and groin recurrence with focus on number of SLNs found.
Methods: This study concerns a retrospective cohort of 171 women treated for early-stage VSCC who underwent a SLN procedure between 2000 and 2020. The risk of groin recurrence was compared after either a successful or complete SLN procedure, i.e. removal of all SLNs that were visualized on lymphoscintigraphy.
Results: In 13 (7.6%) groins of 171 patients SLN visualization on lymphoscintigraphy failed. In 230 of the 246 (93.5%) groins in which a SLN was visualized, at least one SLN was found during surgery. In 224 of the 246 (91.1%) groins the SLN procedure was regarded either successful (n = 14) or complete (n = 210). An isolated groin recurrence was documented in 5 out of 192 (2.6%, 95%-CI; 0.34 to 4.9) SLN-negative groins after a median follow-up of 47.0 months. All recurrences were noted in the complete SLN group (5/180 groins). The difference with the successful SLN group (0/12 groins) was not significant.
Conclusion: Risk of groin recurrence was 2.6% after SLN negative biopsy in early-stage VSCC. The risk appeared not increased if at least one SLN was found with minimal residual radioactivity, in case more SLNs were visualized on lymphoscintigraphy.

1. Introduction

Standard treatment of early-stage unifocal vulvar squamous cell carcinoma (VSCC) measuring less than 4 cm and without suspicious or enlarged inguinofemoral lymph nodes, consists of a radical local excision of the tumor and a sentinel lymph node (SLN) procedure [1–5]. The results of the observational GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V)-I showed that in case of a tumor negative SLN biopsy it is safe to omit an inguinofemoral lymphadenectomy (IFL) in early-stage VSCC [5]. In the study of Van der Zee et al. [5], a groin recurrence rate of 2.3% was noted after a median follow-up of 35

months in 259 groins with negative SLN biopsy with a 3-year survival rate of 97%. At 5 years follow-up an isolated groin recurrence rate of 2.5% was documented [6]. The safety of the SLN procedure in early-stage VSCC was further confirmed by the Gynecologic Oncology Group (GOG)-173 trial [7]. In this study, 452 patients with VSCC and tumor size between 2 and 6 cm and >1 mm infiltration depth underwent SLN biopsy, followed by an IFL [7]. The false-negative predictive value of the SLN biopsy regarding lymph node metastases was 2% for tumors measuring between 20 and 39 mm [7].

It is important that the SLN procedure is adequately performed, to ensure that no groin node metastases are missed and the risk of groin

recurrence is minimized, which is associated with a very poor prognosis [5,6,8–10]. Zach et al. [10] documented a 2-year survival rate of 17.2% and 4-year survival rate of 10.3% after groin recurrence. If no SLNs are visualized on lymphoscintigraphy or the SLN is not found during surgery, an IFL is recommended, which is still required in about 3–8% of the cases [4].

In general, the SLN procedure is considered successful if at least one SLN is found during surgery and remaining tissue shows less than 10% radioactivity compared to the most radioactive SLN [1,8,11]. However, sometimes more than one SLN is visualized on lymphoscintigraphy. It can be hypothesized that the risk of groin recurrence is increased if not all SLNs are found during surgery because tumor positive SLNs may be missed. Therefore, an IFL is considered if not all SLNs visualized on lymphoscintigraphy, can be found during surgery.

However, complications after IFL are very common; such as wound infection, lymphocele, wound dehiscence, lymphedema, and recurrent cellulitis/erysipelas [12]. One of these complications occur in approximately 66%–85% of the patients [12,13]. Patients undergoing a SLN procedure will experience significantly fewer treatment-related morbidity [3,5,6,9,14].

In an earlier study, comparing near-infrared fluorescence imaging with the hybrid tracer ICG (indocyanine green)-^{99m}Tc-nanocolloid to standard SLN detection with ^{99m}Tc-nanocolloid and blue dye, we distinguished either a successful or complete SLN procedure [11]. A complete SLN procedure was defined as the removal of all SLNs that were visualized on lymphoscintigraphy [11]. The focus of the present study was to correlate lymphoscintigraphy findings with surgical outcome of the SLN procedure in early-stage VSCC, including number of SLNs and risk of groin recurrence.

2. Methods

This study concerns a retrospective cohort study which was centrally approved by the Medical Ethics Committee Leiden Den Haag Delft (protocol G20.194). We will provide our data for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

Data were collected from a consecutive series of patients with clinical early-stage VSCC who underwent surgery between January 2000 and December 2020 at the Leiden University Medical Center in the Netherlands. Patients who underwent a standard SLN procedure with unifocal early-stage VSCC, tumor size <4 cm in diameter and >1 mm invasion depth, and without suspicious or enlarged (>1.5 cm) inguinofemoral lymph nodes on preoperative radiologic imaging, were included in the present study. Clinical data were retrieved from the medical files.

2.1. Preoperative imaging

The SLN procedure was performed as described previously and according to the GROINSS-V protocol [5,8]. On the day before, or day of surgery, 3–4 peritumoral injections of a total dose of approximately 0.5 ml 40–100 MBq ^{99m}Tc-nanocolloid, were administered. In some patients this was combined with the hybrid tracer ICG-^{99m}Tc-nanocolloid because of study participation [11,15–17]. Following administration of the radioactive tracer, an early and late dynamic lymphoscintigraphy was performed [18]. The number and site of SLNs visualized on lymphoscintigraphy per groin were noted.

2.2. Surgical procedure

A handheld gamma probe (Europrobe) was used for intraoperative radioguidance, combined with blue dye and/or ICG or ICG-^{99m}Tc-nanocolloid for visual guidance. A SLN was defined as a (first) lymph node that showed adequate concentration of tracer, i.e. radioactive signal and/or a blue and/or fluorescent node [18,19]. In patients with a tumor involving the midline, a bilateral SLN should be expected. If only an unilateral SLN was identified on lymphoscintigraphy, an IFL including superficial and deep lymph node dissection, was advised on the side in which no SLN was identified. In case the tumor did not involve the midline, unilateral visualization of a SLN on lymphoscintigraphy and removal during surgery was appropriate according to the GROINSS-V protocol [5].

The SLN procedure was defined as successful when at least one SLN was detected during surgery per involved groin, and remaining tissue showed less than 10% radioactivity compared to the most radioactive SLN [1,8,11]. The SLN procedure was defined as complete as the intraoperative detection and removal of all SLNs that were visualized on lymphoscintigraphy in the respective groin and minimal residual radioactivity [11].

2.3. Follow-up

The occurrence of an isolated groin recurrence, i.e. without previous local or simultaneous vulvar recurrence, after negative SLN biopsy was compared between the group with either a successful or complete SLN procedure. Time to first groin recurrence was calculated from the date of initial groin surgery until histologically proven groin recurrence. Period of follow-up was calculated from date of initial groin surgery until date of last visit or death.

2.4. Pathological examination

The removed SLNs were fixed in formalin and embedded in paraffin for haematoxylin, eosin, and immunopathological staining for AE1/AE3 at multiple levels (ultra-staging) with an interval of 250 μm [5,6].

2.5. Statistical analysis

Data analysis was performed using SPSS, P-values below 0.05 were considered significant. The analyses were performed at patient and groin level, depending on the research question. In the analyses considering groin level we ignored correlation between groins of the same patient. The comparison between groups with either a complete or successful SLN procedure was done by means of an independent *t*-test for numerical variables and a Chi-square test or Fisher's exact test for binary variables.

3. Results

3.1. Patient and tumor characteristics

Between 2000 and 2020, 455 patients underwent surgery for primary early-stage VSCC, of whom 171 patients were scheduled for standard SLN procedure (Fig. 1). Patient characteristics are shown in Table 1. Median age was 69.0 years and median follow-up was 43.0 months. At least one histologically proven groin metastasis was found in 36 (21.1%) of the 171 patients.

3.2. Lymphoscintigraphy

In 128/171 patients with a tumor not involving the midline, unilateral drainage on lymphoscintigraphy was found in 83 (64.8%) and bilateral drainage in 45 (35.2%) patients (Fig. 1). In one of these patients with a tumor not involving the midline, the lymphoscintigraphy showed a SLN only in the contralateral groin and non-visualization in the ipsilateral groin. In 43/171 patients with a midline tumor, bilateral drainage was found in 31 (72.1%), and only unilateral drainage in 12 (27.9%) patients. Thus, visualization of a SLN on lymphoscintigraphy as should be expected, failed in 13 groins of 171 (7.6%) patients.
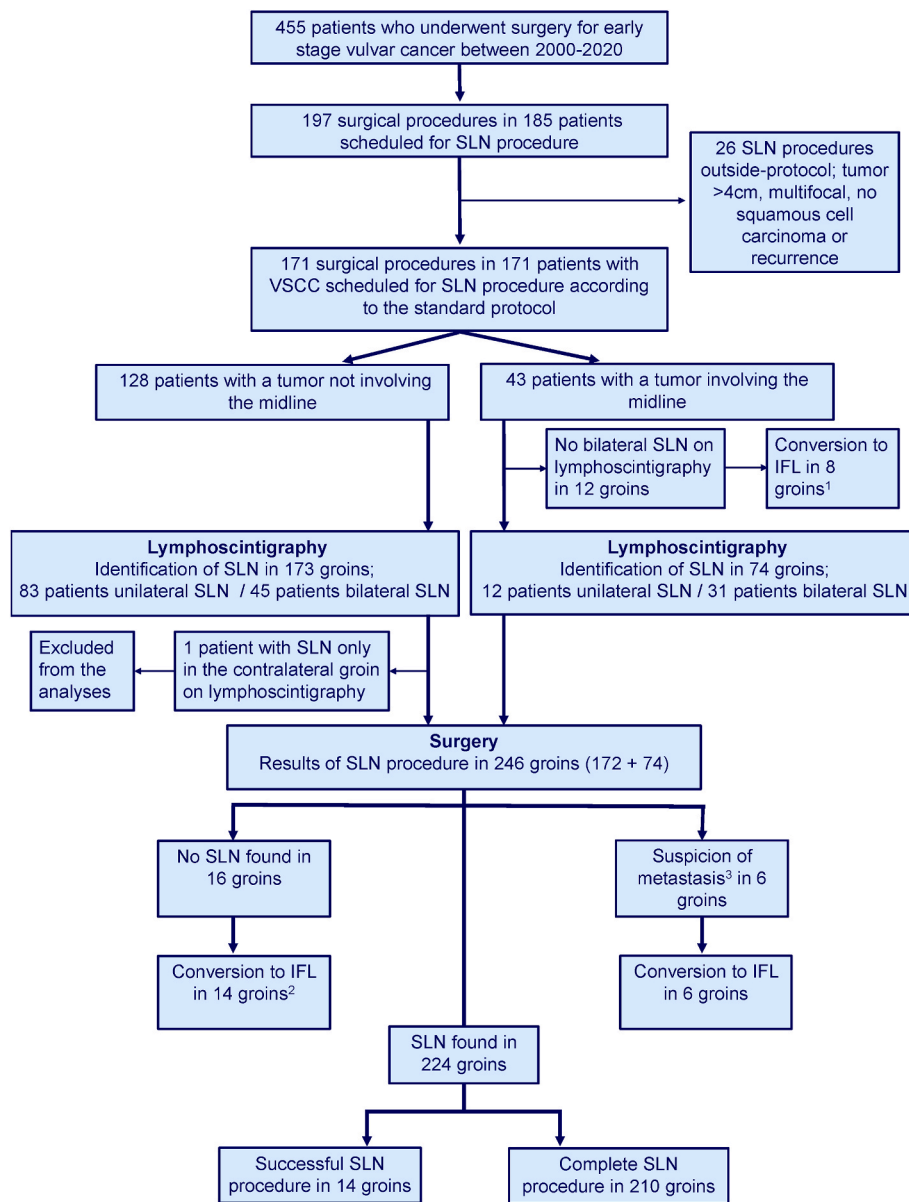
Fig. 1. Flow diagram of the study.

Abbreviations: SLN; sentinel lymph node, VSCC; vulvar squamous cell carcinoma, IFL; inguinofemoral lymphadenectomy including superficial and deep lymph node dissection.

[1] In four of the 12 groins in which no SLN was visualized on lymphoscintigraphy, an IFL was omitted because of age, co-morbidity or wish of the patient.

[2] In two patients with a tumor not involving the midline, but with bilateral drainage, the SLN was not found in the contralateral groin. In one of these patients an IFL was omitted because of severe comorbidity, in the other patient the reason is unknown.

[3] Confirmed by frozen section.

3.3. Intraoperative SLN detection

In 230 (93.5%) of the 246 groins, in which at least one SLN was visualized on lymphoscintigraphy as should be expected, at least one SLN was found during surgery (Fig. 1). Intraoperative SLN detection failed in 16 (6.5%) groins. In 6 of the 246 (2.4%) groins the SLN procedure was converted into an IFL, because of lymph node metastasis on frozen section. Finally, the SLN procedure was completed in 224 of the 246 (91.1%) groins. The SLN procedure was considered successful in 14/224 (6.2%) groins and complete in 210/224 (93.8%) of these groins (Fig. 1).

3.4. Clinical outcome after SLN procedure

Fig. 2 gives an overview of additional treatment after tumor positive SLN biopsy and groin recurrences after either a successful or complete SLN procedure. No significant difference was found between the number of tumor positive SLNs in either group (p = 1.00 Chi-square test).

In Table 2, clinical and tumor characteristics of 192 groins with negative SLN biopsy after either successful or complete SLN procedure

are presented. In the successful group significant more often two or three SLNs were visualized on lymphoscintigraphy (p-value <0.001; Chi-square test). No significant differences were found regarding; age, tumor characteristics, radiocolloid dose, timing of the injection the day before or day of surgery, number of SLNs found during surgery and period of follow-up.

The median follow-up of all patients with a tumor negative SLN biopsy was 47.0 months, with a mean of 54.3 months (range 1–180). In total, 14 (7.3%) groin recurrences were documented after negative SLN biopsy in 192 groins (Fig. 2). Of these, an isolated groin recurrence without previous or simultaneous local recurrence, was documented in five (2.6%, 95%CI; 0.34 to 4.9) out of these 192 groins (Fig. 2). This considered 5/180 (2.8%) isolated groin recurrences in the complete SLN group versus 0/12 (0%) in the successful SLN group (p = 1.00; Fisher's Exact test). The median time to isolated groin recurrence was 16.0 months (range 6–26).

The characteristics of the five patients with an isolated groin recurrence after negative SLN biopsy are shown in Table 3. Two out of these five patients developed a contralateral groin recurrence. This considered patients with a near-midline tumor 1–10 mm from the midline, with

Table 1

Patient and tumor characteristics of 171 patients with early-stage vulvar squamous cell carcinoma, scheduled for standard sentinel lymph node procedure.

Characteristics	Numbers (n)
Number of patients	171
Age (years)	
Median (range)	69.0 (24–89)
Location of primary tumor	
Not involving midline	128 (74.9%)
Involving midline	43 (25.1%)
Tumor diameter (mm)[a]	
Mean (range)	16.5 (2.0–36.0)
Tumor invasion depth (mm)[a]	
Mean (range)	4.3 (1.1–32.0)
Number of patients with at least	
1 groin metastasis (either in SLN or IFL)[b]	36 (21.1%)
Follow-up (months)	
Mean	51.6
Median (range)	43.0 (1–188)

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

[a] Tumor size and invasion depth in mm at pathology.

[b] Histologically proven.

bilateral drainage and bilateral SLN detection during surgery. The other nine out of the 14 groin recurrences in the entire study cohort occurred after previous or simultaneous local recurrence. Characteristics of the latter nine patients are shown in Table 4.

4. Discussion

4.1. Summary of main results

In the present study, we evaluated the outcome of the SLN procedure in early-stage VSCC and the correlation between the number of SLNs

visualized on lymphoscintigraphy, found during surgery and groin recurrence. In 7.6% groins SLN visualization on lymphoscintigraphy failed. Bilateral drainage was documented in 35.2% of tumors not involving the midline and in 72.1% of midline tumors. Furthermore, in 93.5% of the groins in which a SLN was visualized as expected, at least one SLN was found during surgery. An isolated groin recurrence was documented in 2.6% of 192 groins after tumor negative SLN biopsy, of which no recurrences were noted in the successful SLN group. This was however, not significantly different from the complete SLN group, in whom all SLNs were found.

4.2. Results in the context of published literature

A failure rate of 27.9% of bilateral SLN visualization on lymphoscintigraphy in midline tumors corresponds to the literature [1,4,7]. In up to 30% of the cases failure of bilateral drainage has been described in midline tumors [4]. Our finding of at least one SLN during surgery in 93.5% of the groins is consistent with the literature [1,3,20]. The mean SLN detection rate per groin with the combined technique using ^{99m}Tc-nanocolloid and blue dye was estimated between 86.9% and 97.7% in two large meta-analysis [1,3]. Furthermore, the safety of the SLN procedure was confirmed in our study by the low percentage of isolated groin recurrences (2.6%) after negative SLN biopsy [1,5,6]. Median time to isolated groin recurrence was 16.0 months (range 6–26) which is consistent with the literature ranging from six to 16 months in the GROINSS-V-I study [5,6].

To our knowledge, no previous studies focused on the relationship between the number of SLNs visualized on lymphoscintigraphy and number of SLNs removed during surgery with respect to risk of groin recurrence. Currently, we aim to perform a complete SLN procedure. and if not all SLNs can be found, an IFL is considered with subsequent increased morbidity. However, in 6.2% of the groins an IFL was omitted if the SLN procedure was regarded successful, because of comorbidity or
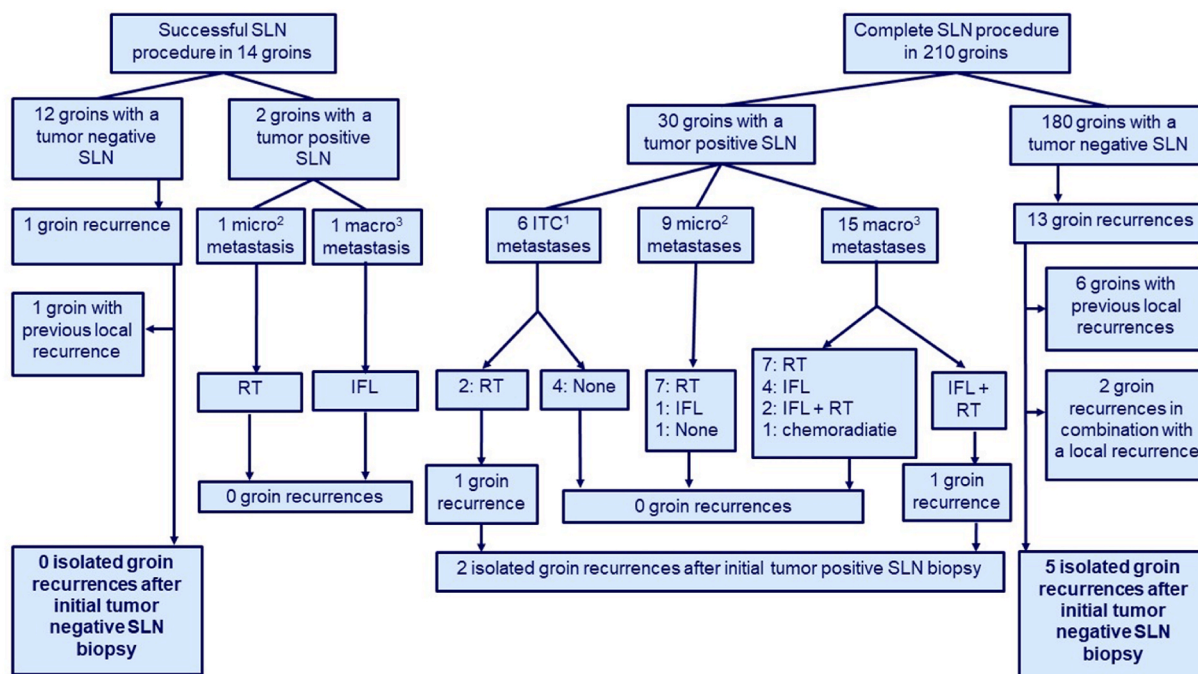
Fig. 2. Groin recurrence after either a successful or complete SLN procedure.

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

[1] ITC; isolated tumor cells. Four of the six patients with ITC received no adjuvant treatment because of; old age (86 and 85 years); in one case the assumption that one ITC would not impair prognosis; and one patient who died two weeks after surgery because of severe co-morbidity.

[2] Micrometastasis ≤2 mm. One out of nine patients with micrometastasis received no adjuvant treatment because of old age (86 years).

[3] Macrometastasis >2 mm.

Table 2

Clinical and tumor characteristics of 192 groins with negative SLN biopsy after either successful or complete SLN procedure.

Characteristics	Successful SLN procedure	Complete SLN procedure	P-value
Number of groins	12	180	
Age			
Mean (SD)	71.2 (14.0)	66.3 (13.0)	p = 0.211[c]
Radiocolloid dose in Mbq			
Mean (SD)	86.7 (16.0)	77.5 (21.2)	p = 0.145[c]
Timing of injection radiocolloid[a]			
• Day of surgery	6 (50.0%)	76 (42.2%)	
• Day before surgery	6 (50.0%)	104 (57.8%)	p = 0.598[d]
Number of SLNs per groin visualized on lymphoscintigraphy			
1 *SLN*	0 (0.0%)	157 (87.2%)	p < 0.001[d]
2 *SLNs*	10 (83.3%)	22 (12.2%)	
3 *SLNs*	2 (16.7%)	1 (0.6%)	
Number of SLNs per groin detected during surgery			
1 *SLN*	10 (83.3%)	132 (73.3%)	p = 0.365[d]
2 *SLNs*	2 (16.7%)	39 (21.7%)	
3 *SLNs*	0 (0.0%)	9 (5.0%)	
Tumor diameter (mm)[b]			
Mean (SD)	16.8 (6.1)	14.9 (8.6)	p = 0.457[c]
Tumor invasion depth (mm)[b]			
Mean (SD)	2.8 (1.2)	3.8 (2.4)	p = 0.193[c]
Follow-up (months)			
Median (range)	73.5 (13–163)	45.0 (1–188)	p = 0.067[e]

Abbreviation: SLN; sentinel lymph node.

[a] Range of 1-day protocol was 3.2 h till 6.5 h. Range of 2-day protocol was 17.9 h till 25.7 h.

[b] Tumor size (largest diameter) and invasion depth in mm according to the pathology report.

[c] Independent *t*-test (2-tailed).

[d] Chi-square test for trend.

[e] Mann-Whitney *U* test.

wish of the patient. Nevertheless, no isolated groin recurrences were documented in these patients. It is noted that in the successful SLN group more often, two or three SLNs were visualized on lymphoscintigraphy, whereas in most cases only one SLN was detected during surgery in both study groups. However, this is inherent to the definition of a successful SLN procedure.

It is emphasized that it is important to adhere to the protocol and only regard the SLN procedure as successful when at least one SLN is found and residual radioactivity <10% compared to the most radioactive SLN [1,8,11]. In the GROINSS-V-I study it was reported that in two out of eight patients with a groin recurrence after negative SLN biopsy, the lymphoscintigraphy showed two SLNs in retrospect, whereas only one SLN was removed [5]. No additional information on residual radioactivity in the groin was given. Woelber et al. [21] investigated the correlation of isotope count with SLN positivity in early-stage vulvar cancer and found that in 21.7% of 46 groins, the SLN with the highest radioactive count, was not the metastatic SLN. The authors concluded that the highest radioactive count does not always reliable detect the positive SLN and recommended to continue to remove all SLNs accumulating relevant radioactive tracer over background activity.

The search for all SLNs which are visualized on lymphoscintigraphy and hereby minimizing the risk of missing lymph node metastases, can be facilitated by intraoperative visual imaging using free ICG or the hybrid tracer ICG-^{99m}Tc- nanocolloid [11,15–17,22–25]. In a previous randomized study, we achieved a complete SLN procedure in 97.1% of 35 groins by fluorescence imaging using the hybrid tracer ICG-^{99m}Tc-nanocolloid [11].

Sometimes the use of a radiocolloid tracer has been abandoned when fluorescence imaging was used. However, bilateral lymph drainage to both groins has been documented in up to 25% of the cases with a lateral vulvar tumor, which is generally defined as a tumor >1 cm from the midline [4,5]. In the present study we noted bilateral drainage in 35.2% of the groins in tumors not involving the midline, including patients with a near-midline tumor between 1 and 10 mm distance from the midline. Therefore, we still recommend the use of a radiocolloid tracer and lymphoscintigraphy to identify bilateral drainage or unexpected drainage patterns [18].

Table 3

Characteristics of patients with early-stage vulvar squamous cell carcinoma, with an isolated groin recurrence[a] after tumor negative sentinel lymph node biopsy.

Patient	Age	Distance to midline and tumor side	Tumor size (mm)	Invasion depth (mm)	SLNs lympho-scintigraphy	SLNs during surgery	Groin recur-rence	Time to groin recurrence (months)
1	84	>10 mm L	36	4.5	1 L	1 L	L	16
2	83	>10 mm L	8	1.3	1 L	1 L	L	16
3	59	1–10 mm L	15	2.0	1 L	1 L	L	6
4	68	1–10 mm L	10	1.5	1 L + R	1 L + R	R	26
5	80	1–10 mm L	23	6.0	1 L + R	1 L + R	R	11

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

[a] An isolated groin recurrence without previous or simultaneous local recurrence.

Table 4

Characteristics of patients with a first groin recurrence after tumor negative sentinel lymph node biopsy, but with previous or simultaneous local recurrence.

Patient	Age	Distance to midline and tumor side	Tumor size (mm)	Invasion depth (mm)	SLNs lympho-scinti-graphy	SLNs during surgery	Groin recur-rence	Number of recur-rences[a]	Time to first groin recurrence (months)
1	69	>10 mm L	17	35.0	1 L	1 L	L	Seventh	182
2	58	>10 mm L	13	8.0	1 L	1 L	R	Third	168
3	71	>10 mm R	25	2.0	1 R	1 R	L^2	First[b]	15
4	81	>10 mm L	28	3.0	1 L	1 L	L	Second	13
5	71	>10 mm L	6	1.7	1 L	2 L	L	First[b]	23
6	71	1–10 mm L	12	2.5	1 L	1 L	R	Second	49
7	66	1–10 mm L	21	2.0	2 L	1 L	R	Second	44
8	70	1–10 mm R	9	3.0	1 R	2 R	L	Second	27
9	89	>10 mm L	18	3.0	1 L	1 L	R	Second	47

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

[a] Number of recurrence(s) includes the current groin recurrence with simultaneous or previous local recurrences.

[b] Simultaneous first local and groin recurrence.

4.3. Strengths and weaknesses

Strength of our study was the relatively large sample size of 192 groins with a tumor negative SLN biopsy and long-term median follow-up of 47.0 months. However, the sample size of the successful SLN group was limited and no firm conclusions can be drawn.

Drawbacks of the current study include its retrospective nature and to distinguish the SLN procedure in retrospect in either a successful or complete SLN group. The number of SLNs may be underestimated on the lymphoscintigraphy as clustering of lymph nodes is possible [11]. This might influence the assumed number of SLNs and division into either a complete or successful SLN group. Furthermore, the residual radioactivity in the groin was not always properly documented in the past. In these cases, we regarded the SLN procedure as either successful or complete according to the final decision of the surgeon and number of SLNs found.

4.4. Implications for practice and future research

We questioned whether an IFL can be safely omitted in an attempt to reduce morbidity, if at least one SLN is found with minimal residual radioactivity, but more SLNs were visualized on lymphoscintigraphy in the respective groin. However, a larger study is needed to investigate this dilemma.

5. Conclusion

Our results confirmed the safety of the standard SLN procedure in primary early-stage VSCC. An isolated groin recurrence after negative SLN biopsy was documented in 2.6% of the groins. Although no recurrences were noted in the successful SLN group, it remains unclear whether an IFL can be safely omitted if not all SLNs can be found during surgery, because of the limited number of successful SLN procedures.

Declaration of interest

None.

CRediT authorship contribution statement

Daniëlle H.M. Warmerdam: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Project administration, Visualization, Writing – original draft. **Nan van Geloven:** Supervision, Formal analysis, Methodology, Writing – review & editing. **Jogchum J. Beltman:** Writing – review & editing. **Cor D. de Kroon:** Writing – review & editing. **Daphne D.D. Rietbergen:** Writing – review & editing. **Mariette I.E. van Poelgeest:** Conceptualization, Investigation, Writing – review & editing. **Katja N. Gaarenstroom:** Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Visualization, Writing – review & editing, Supervision.

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