Time to extend the indication for sentinel node biopsy in vulvar cancer? Results from a prospective nationwide Swedish study

Diana Zach ,[1,2] Katja Stenström Bohlin,[3] Paivi Kannisto,[4] Louise Moberg,[5] Preben Kjölhede[6]

For numbered affiliations see end of article.

Correspondence to
Dr Diana Zach, Division for Obstetrics and Gynecology, Karolinska University Hospital, Stockholm 171 76, Sweden; diana.zach@ki.se

Received 4 July 2023
Accepted 11 October 2023
Published Online First 2 November 2023

To cite: Zach D, Stenström Bohlin K, Kannisto P, *et al. Int J Gynecol Cancer* 2023;**33**:1845–1852.

ABSTRACT

Objective To assess detection rates and negative predictive values of sentinel node biopsy in vulvar squamous cell carcinoma with tumors ≥4 cm, multifocal tumors, and in locally recurrent disease.

Methods Between December 2019 and December 2022, patients with vulvar squamous cell carcinoma with tumors ≥4 cm (group 1), multifocal tumors (group 2), or a first local recurrence without or with previous groin treatment (groups 3 and 4, respectively) were included in a prospective, nationwide multicenter interventional pilot study. The participants underwent a sentinel node biopsy followed by inguinofemoral lymph node dissection. Detection rates, negative predictive values, the proportion of micrometastases, and isolated tumor cells were determined separately for each group.

Results In all, 64 women were included, 36 women in group 1 (56%), and 17 women in group 2 (27%). Due to the small number and heterogeneity of the 11 women in groups 3 and 4, they were excluded from further analyses. In groups 1 and 2, 25 women (47%) were diagnosed with node-positive disease, and in 16 women (64%) only in the sentinel nodes. The detection rates varied between 94.1–100% per patient and 84.1–85.3% per groin. No false-negative sentinel nodes were identified, giving a negative predictive value of 100% for group 1 (95% CI 91.2% to 100%) and for group 2 (95% CI 83.9% to 100%). Of the node-positive patients, 32% had micrometastasis or isolated tumor cells only. One third of the metastases were detected by ultrastaging. In 27% of the non-mapping groins, metastases were found in the lymphadenectomy specimen, and in 75% the metastases showed extranodal growth.

Conclusion In this small cohort of patients, we provide further data that may widen the indication of the sentinel node technique to women with tumors ≥4 cm and multifocal tumors.

Trial registration number NCT04147780.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Based on two large prospective trials, sentinel node biopsy is the recommended treatment in unifocal, primary vulvar squamous cell carcinoma <4 cm. Previous subgroup analyses of tumors ≥4 cm and multifocal tumors revealed unacceptably high rates of false negative sentinel nodes and isolated groin recurrences.

WHAT THIS STUDY ADDS

⇒ This prospective, nationwide single arm interventional pilot study provides detection rates and negative predictive values for primary vulvar squamous cell carcinoma with tumors ≥4 cm or multifocal tumors comparable to those of unifocal tumors <4 cm. However, the results need to be confirmed by a larger prospective study, ideally a randomized controlled trial.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study results indicate that the extension of the indication of sentinel node biopsy to tumors ≥4 cm and to multifocal tumors may be feasible and oncologically safe. Prior to a change of clinical practice, confirmation by a prospective, multinational trial is warranted.

INTRODUCTION

Sentinel lymph node (SLN) biopsy has evolved to become a widespread technique, used for assessing the lymph node status in numerous cancer types, such as malignant melanoma, breast cancer, and endometrial cancer.[1–3] Compared with traditional lymphadenectomy, the method has the advantages of less surgical morbidity and a more precise identification of metastatic dissemination.[4–8]

In vulvar squamous cell carcinoma, two prospective studies have confirmed the oncological safety of the technique.[5 9] In 2008, the GROINSS-V-I study reported an inguinal recurrence rate of 2.3% after a negative SLN in 457 women with vulvar squamous cell carcinoma and tumors <4 cm in diameter.[5] Women with multifocal tumors were excluded after the occurrence of two inguinal recurrences within the 19 included node-negative women.[5]

In 2012, the GOG-173 study reported a negative predictive value of 3.7% in 452 women with squamous cell vulvar carcinoma undergoing both an SLN biopsy and an inguinofemoral lymphadenectomy.[9] However, in women with tumors 4–6 cm in diameter the authors found a detection rate of 92.0% and seven false-negative SLNs, resulting in a false-negative predictive value of 7.4%.

Based on these two studies, SLN biopsy in vulvar cancer became restricted to women with primary,

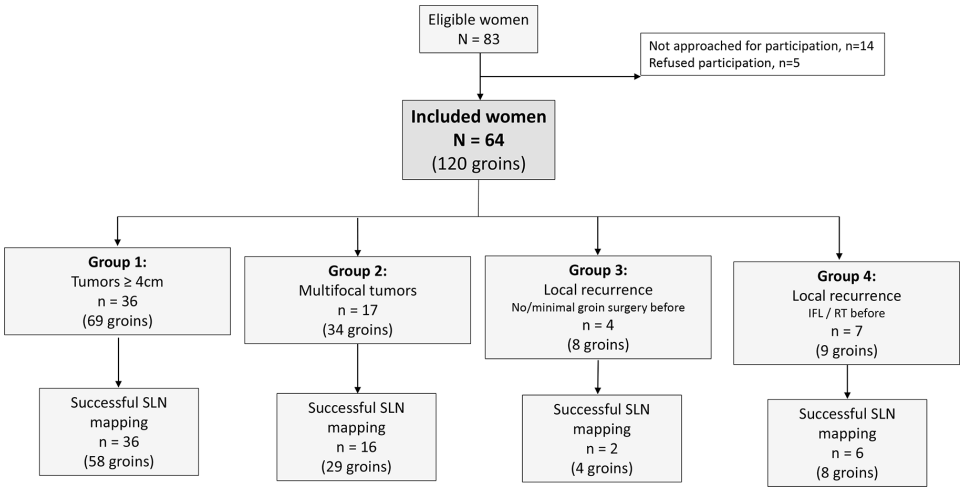

Figure 1 Flowchart study cohort. IFL, inguinofemoral lymph node dissection; RT, radiotherapy; SLN, sentinel lymph node.

unifocal vulvar squamous cell carcinoma <4 cm. An inguinofemoral lymphadenectomy is still recommended as the standard treatment in a large proportion of women with newly diagnosed and recurrent vulvar cancer. High complication rates and the risk of postoperative lymphedema might result either in a negative impact on the women's quality of life or in the reluctance of surgeons to offer surgical groin staging, especially to elderly and frail patients.[10–14] However, no further attempts have been made to extend the SLN technique to women with larger or multifocal tumors.

A small retrospective study investigated the SLN technique in 27 women with locally recurrent vulvar cancer[15] and concluded that the technique seemed to be feasible and safe, even in local recurrent disease, but data from larger prospective studies are needed to ensure the safety and feasibility in clinical practice. Reducing the treatment-related morbidity of women with vulvar cancer by extending the indication for SLN biopsy is desirable. The aim of this study was to investigate the feasibility of SLN biopsy in tumors currently not eligible for the technique such as tumors ≥4 cm, multifocal tumors, and in first local recurrences.

METHODS

Study Design, Setting, Participants

This is a prospective, non-randomized nationwide multicenter interventional pilot study, conducted between December 2019 and December 2022. The study protocol has previously been published.[16]

Since 2017, vulvar cancer treatment has been centralized to four tertiary care hospitals in Sweden, and eligible women were identified at the weekly national digital multidisciplinary conference where all women with newly diagnosed or recurrent vulvar cancer were discussed. Patients were included if they had squamous cell vulvar carcinoma with a primary tumor ≥4 cm (group 1), multifocal disease (group 2), a first local recurrence without previous groin treatment or only SLN biopsy (group 3), or a first local recurrence with previous inguinofemoral lymphadenectomy and/or radiotherapy of the groins (group 4). Exclusion criteria were clinical or radiological signs of inguinal lymph node metastases, ongoing pregnancy, age <18 years, or an Eastern Cooperative Oncology Group performance status ≥3. Tumor size and multifocality were assessed clinically pre-operatively. Multifocality was defined as two macroscopically separate invasive tumor components, both confirmed by biopsy.

Intervention

Women in groups 1, 2, and 3 underwent SLN biopsy and inguinofemoral lymphadenectomy. Women in group 4 underwent SLN biopsy if the pre-operative scintigraphy revealed an inguinofemoral SLN. In cases without mapping, no groin surgery was performed in group 4. The SLN procedure was standardized according to the GROINSS-V-I protocol, with the mandatory use of a radiotracer and optional use of blue dye.[5] The pathological workup included routine hematoxylin and eosin (H&E) staining and so-called ultrastaging in cases without metastases on H&E staining. Briefly, the SLNs were further cut into three sections per millimeter and examined either with H&E or with cytokeratin immunostaining. According to the Cancer Staging Manual of the American Joint Committee on Cancer, micrometastases were defined as lymph node metastases >0.2 mm and ≤2 mm in diameter, and isolated tumor cells as tumor cell clusters ≤0.2 mm in diameter.[17]

Pre-operative imaging work-up comprised ultrasonography of the groins, MRI, or CT. Surgical treatment of the vulvar tumor and adjuvant treatment were performed according to the Swedish National Guidelines.[18]

Variables and Data Source

Clinical, pathological, and demographic characteristics of the participants comprised age, performance status, body mass index, smoking, comorbidity, International Federation of Gynecology and Obstetrics (FIGO) tumor stage,[19] tumor characteristics, type of vulvar surgery, and data on adjuvant treatment. Furthermore, postoperative complications within 60 days were registered and classified according to Clavien-Dindo.[20]

Endpoints and Sample Size

The primary endpoint of the study was the detection rate and the negative predictive value for the SLN procedure, calculated separately for each subgroup. For group 4, only the detection rate could be calculated, as no additional inguinofemoral lymphadenectomy was performed. Secondary endpoints were the number of retrieved

Table 1 Demographic and clinical characteristics of women with vulvar cancer

	Group 1 Tumors ≥4 cm (n=36)	Group 2 Multifocal tumors (n=17)	Groups 3 and 4* First local recurrence (n=11)
Number of operated groins, n (%)	69 (95.8)	34 (100)	17 (77.3)
Age (years), median (IQR)	73 (68–80)	74 (60–78)	67 (57–76)
BMI (kg/m^2), median (IQR)	26 (21–30)	30 (27–33)	30 (26–33)
Smoking, n (%)			
No	32 (88.9)	15 (88.2)	9 (81.8)
Yes	4 (11.1)	2 (11.8)	2 (18.2)
Comorbidities†, n (%)			
None	7 (19.4)	3 (17.7)	4 (36.4)
1	13 (36.1)	6 (35.3)	5 81.8)
≥2	16 (44.4)	8 (47.1)	2 (18.2)
ECOG performance status, n (%)			
0–1	33 (91.7)	14 (82.4)	11 (100)
2	3 (8.3)	3 (17.6)	0
FIGO stage‡, n (%)			
IB	21 (58.3)	9 (52.9)	NA
II	1 (2.8)	0	
IIIA	7 (19.4)	3 (17.7)	
IIIB	1 (2.8)	2 (11.8)	
IIIC	6 (16.7)	3 (17.7)	
Histology, n (%)			
Squamous cell carcinoma	36 (100)	17 (100)	10 (90.9)
Invasive vulvar Paget's disease	0		1 (9.1)
Pathological tumor size (mm)§, median (IQR)	50 (41–57)	25 (13–35)	26 (4–36)
Focality, n (%)			
Unifocal tumor	36 (100)	1¶ (5.9)	6 (54.6)
Multifocal tumor		16 (94.1)	5 (45.4)
Surrounding pre-cancerous lesion**, n (%)			
dVIN	15 (41.7)	11 (64.7)	4 (36.4)
HSIL	9 (25.0)	2 (11.8)	3 (27.3)
Both dVIN and HSIL	1 (2.8)	1 (5.9)	0
Neither dVIN nor HSIL	7 (19.4)	3 (17.6)	3 (27.3)
Missing	4 (11.1)	0	1 (9.1)
p16-immunostaining, n (%)			
Positive	13 (36.1)	2 (11.8)	2 (18.2)
Negative	21 (58.3)	13 (76.5)	4 (36.4)
Missing	2 (5.6)	2 (11.8)	5 (45.5)
p53-immunostaining, n (%)			
Positive	13 (36.1)	9 (52.9)	1 (9.1)
Negative	13 (36.1)	5 (29.4)	3 (27.3)
Missing	10 (27.8)	3 (17.7)	7 (63.6)
Extent of vulvar surgery, n (%)			
Wide excision	26 (72.2)	16 (94.1)	5 (45.5)
Complete vulvectomy	8 (22.2)	1 (5.9)	4 (36.4)

Continued

Table 1 Continued

	Group 1 Tumors ≥4 cm (n=36)	Group 2 Multifocal tumors (n=17)	Groups 3 and 4* First local recurrence (n=11)
Pelvic exenteration	2 (5.6)	0	2 (18.2)
Reconstruction with flap, n (%)			
Yes	10 (27.8)	3 (17.7)	1 (9.1)
No	26 (72.2)	14 (82.4)	10 (90.9)
Extend of groin surgery, per groin, n (%)	72 (100)	34 (100)	22 (100)
No groin surgery	3†† (4.2)	0	5‡‡ (22.7)
SLN only	0	0	6§§ (27.3)
IFL only due to failed mapping	11 (15.9)	5 (14.7)	5 (22.7)
IFL and SLN	58 (80.1)	29 (85.3)	6 (27.3)
Surgical excision margin (mm), median (IQR)	4 (2–7)	6 (3–9)	6 (4–7)
Adjuvant treatment, n (%)			
No adjuvant treatment	22 (61.1)	11 (64.7)	9 (81.8)
Adjuvant radiotherapy	5 (13.9)	3 (17.6)	0
Adjuvant radiochemotherapy	9 (25.0)	3 (17.6)	2 (18.2)
Radiotherapy targets, n (%)			
Groins and pelvis	7 (50.0)	4 (66.7)	2 (100)
Vulva	2 (14.3)	1 (16.7)	0
Vulva, groins, and pelvis	5 (35.7)	1 (16.7)	0

Figures indicate number (%) or median (IQR).
*Group 3: first local recurrence, no previous groin surgery/SLN only (n=4). Group 4: first local recurrence, previous IFL/radiotherapy (n=7).
†Comorbidities comprising cardiac (including hypertonia), pulmonary, diabetes mellitus, renal failure, previous stroke, psychiatric disease, and others.
‡FIGO stage according to the 2009 classification, only for women with primary diagnosis.
§Tumor size of the largest tumor focus in multifocal disease.
¶Clinically assessed as multifocal, in pathological analysis unifocal.
**Surrounding the invasive tumor in the surgical specimen (pathological assessment).
††Only unilateral groin surgery due to lateral tumor.
‡‡No groin surgery due to failed mapping in women with previous IFL.
§§SNB only in women with previous IFL (group 4)
BMI, body mass index; dVIN, differentiated vulvar intraepithelial neoplasia; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HSIL, high-grade squamous intraepithelial lesion; IFL, inguinofemoral lymphadenectomy; NA, not applicable; SLN, sentinel lymph node.

SLNs, the proportion of metastases diagnosed by ultrastaging, and the proportion of lymph nodes with micrometastases or isolated tumor cells.

Based on previous data on the prevalence of lymph node metastasis in vulvar cancer, a sample size of at least 100–150 negative groins would have been necessary to show a negative predictive value of at least 95% (lower boundary of 95% CI), with a risk for a type I error of 5% and for a type II error of 20%. In Sweden, about 160 patients are diagnosed with primary vulvar cancer each year, and we expected an inclusion of 10–20 women into each group per year. Thus, the necessary sample size did not seem to be achievable within a realistic timeframe by recruiting patients in Sweden only. This resulted in the design of this nationwide Swedish pilot study to evaluate whether a multinational approach would be worth pursuing. We aimed at including at least 20–30 patients into each subgroup.

The study was registered at ClinicalTrials.gov (ID: NCT04147780).

RESULTS

A total of 64 patients were enrolled, resulting in 120 operated groins and 99 successful SLN biopsies (Figure 1). Table 1 displays the demographic, clinical, and treatment characteristics of the cohort, and Table 2 provides details of the SLN procedure for groups 1 and 2. Most women were included in group 1 (36 patients, 56%) and group 2 (17 patients, 27%). Groups 3 and 4 comprised only four and seven patients and, due to the small numbers and heterogeneity, were consequently excluded from further analyses.

The detection rates of groups 1 and 2 reached 100% and 94.1% per patient, respectively (Table 3A). Twenty-five patients (47%) were diagnosed with node-positive disease. However, in eight of the patients (32%) the metastases comprised only isolated tumor cells or micrometastases, and in nine patients (36%), the metastases were detected only by ultrastaging. Sixteen of the 25 patients

Table 2 Details of the sentinel node procedure and groin surgery in groups 1 and 2

Use of tracer for SLN detection	
Technetium-99m+blue dye	41 (77.4%)
Technetium-99m only	11 (20.7%)
Blue dye only	1 (1.9%)
Protocol for radiotracer injection (technetium-99m)	
1 day protocol*	42 (80.8%)
2 days protocol†	10 (19.2%)
Amount of radiotracer (MBq), median (IQR)	
1 day protocol	44 (34–120)
2 days protocol	119 (60–120)
Retrieved nodes per groin	
SLN, mean (SD)	1.6 (1.0)
IFL, mean (SD)	6.0 (2.8)

Figures denote number (%), median (IQR), or mean (SD).
*Injection of radiotracer on the morning of surgery, scintigraphy 30 min after injection.
†Injection of radiotracer on the afternoon the day before surgery, scintigraphy 30 min after injection.
IFL, inguinofemoral lymphadenectomy; IQR, Interquartile range; MBq, megabecquerel; SLN, sentinel lymph node.

(64%) had no further non-SLN metastases in the lymphadenectomy specimen.

In total, metastases were found in 13% (22/173) of the SLNs and in 2.1% (13/615) of the non-SLNs. Four metastatic SLNs showed extranodal growth. The metastatic lesions in these SLNs were between 2 and 18 mm in diameter. A detailed distribution of metastases is depicted in Figure 2. No false-negative SLNs were found, resulting in a negative predictive value of 100% (Table 3B). However, in four of the 15 groins without successful SLN mapping (27%), metastatic lymph nodes were detected in the lymphadenectomy specimen. These four patients were 55–80 years of age and had p53-mutated tumors 5–50 mm in size. One tumor was multifocal, and in three of the cases (75%) the lymph node metastases showed extranodal growth.

Within 60 days post-operatively, 45% of patients developed one or more complications related to the groin surgery, and 28% developed complications related to the vulvar surgery (Table 4).

DISCUSSION

Summary of Main Results

In this prospective pilot study, we found detection rates and negative predictive values of SLN biopsy for women with primary squamous cell vulvar cancer ≥4 cm and multifocal tumors comparable to the results for smaller, unifocal tumors. Moreover, we found no false-negative SLN in the whole cohort. In every third patient, the metastasis comprised only micrometastases or isolated tumor cells and could only be detected by ultrastaging. Due to the heterogeneity and small numbers in groups 3 and 4, no conclusions can be drawn concerning recurrent disease.

Results in the Context of Published Literature

Three prospective cohorts investigating SLN biopsy in vulvar cancer reported detection rates of 88–97% per patient.[5 9 21] In a meta-analysis from 2020, di Donna et al calculated a pooled detection rate of 93% per groin.[22] Although somewhat lower per groin, we achieved comparable detection rates in groups 1 and 2. We could only identify two prospective studies investigating tumors ≥4 cm.[9 21] The GOG-173 study reported for this subgroup an unacceptable high false-negative predictive value of 7.4% with a wide confidence interval. However, the circumstances in which that study was conducted were radically different from ours today. The 10-year accrual period with 47 participating institutions resulted in an average of one patient per year and center, at a time when SLN biopsy in vulvar cancer was not regarded as a routine treatment and no proof of surgical proficiency was required. Furthermore, no pre-operative imaging was required, and during the first 2 years of the study a radiotracer was not mandatory for detection.[9] In 2017,

Table 3 Sentinel lymph node detection rates (A) and negative predictive values (B) for groups 1 and 2

A			B					
	Detection rate					False negative SLN	Sensitivity	Negative predictive value
Number of women and groins	Per women	Per groin	Result of SLN biopsy	SLN metastasis: No	SLN metastasis: Yes	N	% (95% CI)	% (95% CI)
Group 1	100%	84.1%	Negative	40	0	0	100	100
36 women			Positive	0	18		(81.5 to 100)	(91.2 to 100)
69 groins			Successful mapping: 58 groins					
Group 2	94.1%	85.3%	Negative	21	0	0	100	100
17 women			Positive	0	8		(63.1 to 100)	(83.9 to 100)
34 groins			Successful mapping: 29 groins					

Group 1, tumors ≥4 cm; group 2, multifocal tumors. Group 3 (local recurrence without previous inguinofemoral lymphadenectomy) and group 4 (local recurrence with previous inguinofemoral lymphadenectomy) were excluded from the analysis (sensitivity and negative predictive value cannot be calculated as only SLN biopsy without inguinofemoral lymphadenectomy was performed).
SLN, sentinel lymph node.

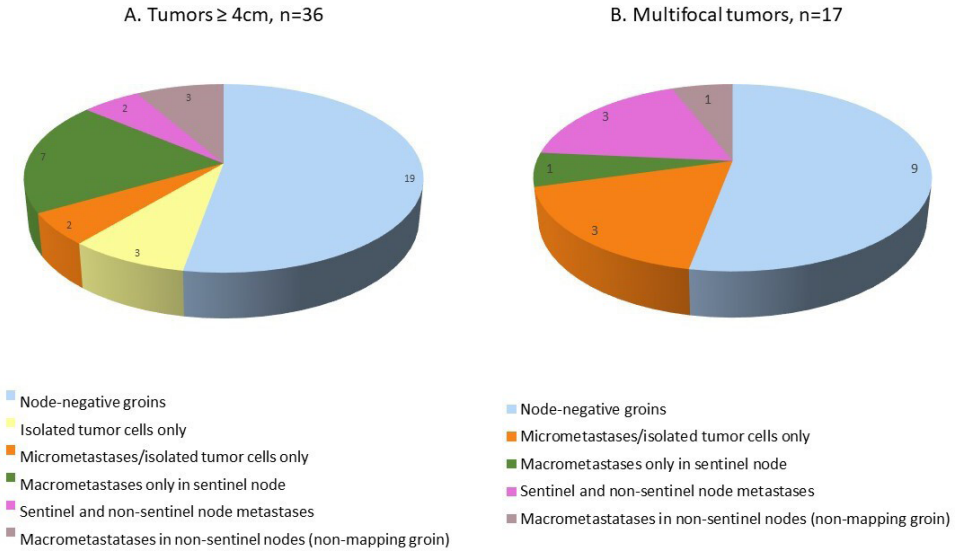

Figure 2 Distribution of lymph node metastases in the subgroups. (A) Tumors ≥4 cm, n=36 (58/69 groins with successful sentinel mapping). (B) Multifocal tumors, n=17 (29/34 groins with successful sentinel mapping).

Garganese et al reported on 12 patients with tumors >4 cm undergoing an SLN biopsy followed by inguinofemoral lymphadenectomy. No patients in this cohort had a false-negative SLN.[21]

As the outcome negative predictive value is a function of the sensitivity of the test and prevalence of the condition, a higher prevalence of lymph node metastases in larger tumors may be reflected by somewhat lower negative predictive values compared with smaller tumors with a lower probability of lymph node metastases.

Table 4 Post-operative complications within 60 days in groups 1 and 2

	Number of women (%)*
Complications in groins††	
No	29 (54.7)
Infection	17 (32.1)
Lymphocyst	13 (24.5)
Wound breakdown	5 (9.4)
Hematoma	2 (3.8)
Complications in vulva††	
No	38 (71.7)
Wound breakdown	10 (18.9)
Infection	9 (17.0)
Hematoma	1 (1.9)
CD classification of complications	
No complications	20 (37.7)
CD 1	3 (5.7)
CD 2	22 (41.5)
CD 3	7 (13.2)
CD 4	1 (1.9)

*Denominator=all women of Group 1 and 2 (n=53)
†More than one complication possible per patient.
CD, Clavien-Dindo.

However, by optimizing the technique, excluding patients with radiological signs of metastases, and with solid surgical proficiency and optimal tracer use, our study showed that even for larger tumors the results seemed to achieve satisfactory oncological safety.

The accrual of 17 multifocal tumors in the present study was lower than anticipated and reflects the rarity of the condition. Because of unsatisfactory oncological safety, the GROINSS-V-I study stopped the inclusion of multifocal tumors after two early inguinal recurrences between the hitherto 19 included patients.[5] Garganese et al included nine women with multifocal tumors in their study, with no false-negative SLN.[21] The early exclusion of this subgroup from the GROINSS-V-I study might have been premature, and in our opinion, further evaluation seems justified, albeit the relatively small number of eligible patients and a probable higher risk for lymph node metastases than in unifocal tumors.

All patients in the Garganese et al study went through a preoperative positron emission tomography-CT scan to detect even smaller metastases; consequently, a lower percentage of women than in our cohort showed metastatic growth.[21] Excluding patients with grossly metastatic disease from the procedure is paramount to avoid false-negative lymph nodes due to tumor cells obstructing lymph channels.[23–25] On the other hand, small metastases may not pose a risk of establishing false negativity. According to the results of the recently published GROINSS-V-II study, patients with metastatic SLN can be treated by radiotherapy instead of an inguinofemoral lymphadenectomy. Oonk et al reported low inguinal recurrence rates for women with micrometastases or isolated tumor cells in the SLNs, treated by radiotherapy instead of inguinofemoral lymphadenectomy, with significantly reduced treatment-related morbidity.[26] However, the GROINSS-V-II study was restricted to unifocal tumors <4 cm. If similar results could be assumed for micrometastasis or isolated tumor cells in larger or multifocal tumors, even node-positive women with low-volume metastases could benefit from the lower morbidity of an SLN biopsy combined with post-operative radiotherapy. Taken together with the 28 node-negative patients in groups 1 and 2, more than two-thirds of the women could have been successfully treated without the morbidity

of a full inguinofemoral lymphadenectomy. This is further supported by the fact that 64% of the patients in this cohort had no further non-SLN metastases in their lymphadenectomy specimen. Moreover, the detection of about a third of all metastases by ultrastaging underlines the increased precision and accuracy of surgical staging by the SLN technique. Only 2% of all non-SLN bore metastases.

The number of patients recruited in groups 3 and 4 was far below what had been anticipated. Common reasons for non-eligibility were pre-operative suspicious lymph nodes, inoperable vulvar disease, severe comorbidities, or late treatment side-effects impeding further groin surgery. Patients with local recurrent disease and no previous groin surgery commonly underwent SLN biopsy only. Hence, no conclusions regarding oncological safety can be drawn. Furthermore, given the low inclusion rate, we would be reluctant to propose a larger study for this subgroup. A prospective, national multicenter study was recently launched in the Netherlands, aiming to investigate the feasibility and safety of sentinel node biopsy in the first local recurrences of vulvar carcinoma.[27] The study aims at a sample size of at least 150 node-negative patients to demonstrate oncological safety. First results from that study might shed more light on the feasibility of a further attempt to start a larger, international study.

Every fourth groin with failed mapping in our study showed metastatic disease, in most cases with extranodal extension. In these cases, tumor cells might have obstructed the lymphatic vessel to the metastatic SLN.[23–25] Thus, particularly in non-mapping groins, an inguinofemoral lymphadenectomy seemed to be mandatory to exclude undetected metastasis.

Strengths and Weaknesses

A strength of this study is the prospective, nationwide design and the well-established cooperation between all four participating centers, resulting in the inclusion of 77% of all eligible patients. Pre-operative workup, imaging, and treatment are synchronized and clearly defined in national guidelines. Thus, high internal validity, and in similarly centralized healthcare systems high external validity, can be assumed.

The study has limitations. One limitation might be the rarity of the disease and consequently the low number of eligible patients, even in a nationwide context. The study was designed without a control group and without quality control for imaging or surgery. Furthermore, the protocol did not provide standards for pre-operative imaging. The use of indocyanine green in combination with a radiotracer might have enhanced the detection rates of SLNs. The results should only be applied to vulvar squamous cell carcinoma, and may not be generalized to other healthcare systems.

Implications for Practice and Future Research

Based on the results, further efforts to launch a multinational trial confirming our results seem to be justified and highly warranted. The extension of the SLN technique could spare a large proportion of patients with tumors ≥4 cm and multifocal tumors the morbidity from undergoing an inguinofemoral lymph node dissection. The introduction of indocyanine green as a new, non-radioactive tracer for SLN biopsy in vulvar cancer may lead to further refinements of the technique. In locally recurrent disease, sufficient evidence on the oncological safety of sentinel node biopsy is still lacking and might be difficult to obtain.

CONCLUSION

In a centralized healthcare system with high proficiency, SLN biopsy might be a safe treatment option for women with primary vulvar squamous cell carcinoma with tumors ≥4 cm and multifocal tumors. Detection rates and negative predictive values seem to be comparable to those of smaller, unifocal tumors. For patients with a first local recurrence, no conclusions can be drawn about the safety of the procedure.

Author affiliations
[1]Division for Obstetrics and Gynecology, Karolinska University Hospital, Stockholm, Sweden
[2]Department for Women's and Children's Health, Karolinska Institute, Stockholm, Sweden
[3]Department of Obstetrics and Gynecology, University of Gothenburg Sahlgrenska Academy, Goteborg, Sweden
[4]Obstetrics and Gynecology, Lund University Hospital, Lund, Skåne, Sweden
[5]Obstetrics and Gynecology, Skånes Universitetssjukhus Lund, Lund, Skåne, Sweden
[6]Obstetrics and Gynecology, Linkopings Universitet Institutionen for Klinisk och Experimentell Medicin, Linkoping, Sweden

Acknowledgements The authors wish to thank Mats Fredrikson, Linköping University, for statistical support.

Contributors DZ: conceptualization and design, data acquisition and management, data analysis and interpretation, manuscript writing, editing, final approval, guarantor for the overall content. KSB: conceptualization and design, data acquisition, data interpretation, manuscript editing, final approval. PK: conceptualization, data acquisition, data interpretation, manuscript editing, final approval. LM: conceptualization and design, data interpretation, manuscript editing, final approval. PK: conceptualization and design, data acquisition and management, data analysis and interpretation, manuscript writing, editing, final approval.

Funding This study was partially funded by a grant from the Swedish Society for Gynecologic Oncology, SSGO, 2018.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Swedish Ethical Review Authority (diary number 2019-04647). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. In accordance with the journal's guidelines, 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.

ORCID iD
Diana Zach http://orcid.org/0000-0002-2871-5951

REFERENCES

1 Morton DL, Thompson JF, Cochran AJ, *et al*. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med* 2014;370:599–609.
2 Brackstone M, Baldassarre FG, Perera FE, *et al*. Management of the axilla in early-stage breast cancer: Ontario Health (Cancer Care Ontario) and ASCO guideline. *J Clin Oncol* 2021;39:3056–82.
3 Concin N, Matias-Guiu X, Vergote I, *et al*. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. *Int J Gynecol Cancer* 2021;31:12–39.

4 Oonk MH, van Hemel BM, Hollema H, *et al*. Size of sentinel-node metastasis and chances of non-sentinel-node involvement and survival in early stage vulvar cancer: results from GROINSS-V, a multicentre observational study. *Lancet Oncol* 2010;11:646–52.
5 Van der Zee AGJ, Oonk MH, De Hullu JA, *et al*. Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. *JCO* 2008;26:884–9.
6 Persson J, Salehi S, Bollino M, *et al*. Pelvic sentinel lymph node detection in high-risk endometrial cancer (SHREC-Trial) - the final step towards a paradigm shift in surgical staging. *Eur J Cancer* 2019;116:77–85.
7 Del Bianco P, Zavagno G, Burelli P, *et al*. Morbidity comparison of sentinel lymph node biopsy versus conventional axillary lymph node dissection for breast cancer patients: results of the Sentinella-GIVOM Italian randomised clinical trial. *Eur J Surg Oncol* 2008;34:508–13.
8 Robison K, Steinhoff MM, Granai CO, *et al*. Inguinal sentinel node dissection versus standard inguinal node dissection in patients with vulvar cancer: a comparison of the size of metastasis detected in inguinal lymph nodes. *Gynecol Oncol* 2006;101:24–7.
9 Levenback CF, Ali S, Coleman RL, *et al*. Lymphatic mapping and sentinel lymph node biopsy in women with squamous cell carcinoma of the vulva: a Gynecologic Oncology Group study. *JCO* 2012;30:3786–91.
10 Pouwer A-FW, Arts HJ, van der Velden J, *et al*. Limiting the morbidity of inguinofemoral lymphadenectomy in vulvar cancer patients; a review. *Expert Rev Anticancer Ther* 2017;17:615–24.
11 Novackova M, Halaska MJ, Robova H, *et al*. A prospective study in detection of lower-limb lymphedema and evaluation of quality of life after vulvar cancer surgery. *Int J Gynecol Cancer* 2012;22:1081–8.
12 Rahm C, Adok C, Dahm-Kähler P, *et al*. Complications and risk factors in vulvar cancer surgery - a population-based study. *Eur J Surg Oncol* 2022;48:1400–6.
13 Zach D, Åvall-Lundqvist E, Falconer H, *et al*. Patterns of recurrence and survival in vulvar cancer: a nationwide population-based study. *Gynecol Oncol* 2021;161:748–54.
14 Gien LT, Sutradhar R, Thomas G, *et al*. Patient, tumor, and health system factors affecting groin node dissection rates in vulvar carcinoma: a population-based cohort study. *Gynecol Oncol* 2015;139:465–70.
15 van Doorn HC, van Beekhuizen HJ, Gaarenstroom KN, *et al*. Repeat sentinel lymph node procedure in patients with recurrent vulvar squamous cell carcinoma is feasible. *Gynecol Oncol* 2016;140:415–9.
16 Zach D, Kannisto P, Stenström Bohlin K, *et al*. Can we extend the indication for sentinel node biopsy in vulvar cancer? A nationwide feasibility study from Sweden. *Int J Gynecol Cancer* 2020;30:402–5.
17 Greene FL, Page DL, American Joint Committee on Cancer. *AJCC cancer staging manual*. New York, NY, 2002.
18 Regional cancer centers (RCC). National guidelines for the treatment of vulvar cancer in Sweden. 2023. Available: https://kunskapsbanken.cancercentrum.se/diagnoser/vulvacancer/vardprogram/
19 Olawaiye AB, Cotler J, Cuello MA, *et al*. FIGO staging for carcinoma of the vulva: 2021 revision. *Int J Gynaecol Obstet* 2021;155:43–7.
20 Dindo D, Demartines N, Clavien PA. Classification of surgical complications. *Ann Surg* 2004;240:205–13.
21 Garganese G, Collarino A, Fragomeni SM, *et al*. Groin sentinel node biopsy and ^{18}F-FDG PET/CT-supported preoperative lymph node assessment in cN0 patients with vulvar cancer currently unfit for minimally invasive inguinal surgery: the Grosnapet study. *Eur J Surg Oncol* 2017;43:1776–83.
22 Di Donna MC, Quartuccio N, Giallombardo V, *et al*. Detection of sentinel lymph node in vulvar cancer using 99mTc-labeled colloid lymphoscintigraphy, blue dye, and indocyanine-green fluorescence: a meta-analysis of studies published in 2010-2020. *Arch Gynecol Obstet* 2023;307:1677–86.
23 Borgstein PJ, Pijpers R, Comans EF, *et al*. Sentinel lymph node biopsy in breast cancer: guidelines and pitfalls of lymphoscintigraphy and gamma probe detection. *J Am Coll Surg* 1998;186:275–83.
24 Iversen T, Aas M. Lymph drainage from the vulva. *Gynecol Oncol* 1983;16:179–89.
25 Nieweg OE, Estourgie SH. What is a sentinel node and what is a false-negative sentinel node? *Ann Surg Oncol* 2004;11:169S–73S.
26 Oonk MHM, Slomovitz B, Baldwin PJW, *et al*. Radiotherapy versus inguinofemoral lymphadenectomy as treatment for vulvar cancer patients with micrometastases in the sentinel node: results of GROINSS-V II. *J Clin Oncol* 2021;39:3623–32.
27 van Doorn HC, Oonk MHM, Fons G, *et al*. Sentinel lymph node procedure in patients with recurrent vulvar squamous cell carcinoma: a proposed protocol for a multicentre observational study. *BMC Cancer* 2022;22:445.