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Long term outcomes in patients with sentinel lymph nodes (SLNs) identified by injecting remaining scar after previously excised vulvar cancer

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HIGHLIGHTS

- SLN biopsy can be performed by injecting the remaining scar in patients with previous macroscopic excision of vulvar SCC.
- A SLN detected by peri-scar injection accurately reflects the nodal status.
- Long term oncologic outcomes are not impacted in patients with negative SLN detected by peri-scar injection.
- Despite the absence of a macroscopic lesion in the vulva, invasive disease is still present in a fifth of these patients.
- Wide re-excision of the scar is recommended at the time of SLN biopsy if margins are positive or close at initial resection.

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ABSTRACT

Background. Lymph node metastasis is the most important prognostic factor in patients with vulvar squamous cell carcinoma (SCC). Previous excision of the vulvar tumor may disrupt lymphatic channels and alter the accuracy of the sentinel lymph node (SLN) biopsy. The purpose of this study was to measure outcomes after SLN biopsy in patients with and without previous excision of the vulvar tumor.

Methods. Retrospective study of patients at a single institution with primary vulvar cancer, clinically negative nodes, and vulvar tumors < 4 cm treated with surgical excision who had SLN biopsy (2008–2015).

Results. There were 106 cases of concomitant wide local excision (WLE) and SLN biopsy and 24 additional cases of patients who had previous vulvar surgery and no visible tumor; these patients underwent scar re-excision and SLN biopsy. Median follow-up was 31 months. Patients who had previous tumor excision were more likely to be of younger age ($p = 0.0001$), have a smaller tumor ($p = 0.002$), and less depth of invasion ($p = 0.02$). In the wide local excision of the scar specimen, 11 patients (46%) had no residual disease left, 8 patients (33%) had only vulvar intraepithelial neoplasia (VINIII), 4 patients (17%) had carcinoma in situ with focal invasion and 1 patient (4%) had invasive carcinoma within the second specimen, resected with clear margins. There were no groin recurrences in patients who underwent scar re-excision and who had a negative SLN biopsy.

Conclusion. SLN biopsy is feasible and safe in patients who have had previous excision of the vulvar tumor and present with a scar. When a SLN is detected by injecting the remaining scar, this accurately reflects the nodal status and does not negatively impact oncologic outcomes.

1. Introduction

The technique of sentinel node biopsy was first described in the management of cutaneous malignant melanoma [1], and later by Decesare and colleagues in the assessment of clinically negative inguinal nodes in patients with invasive squamous cell carcinoma (SCC) of the vulva [2]. Numerous studies have shown that the presence of lymph node metastasis is the most important prognostic factor in vulvar cancer. In the last decade, many institutions have adopted the SLN procedure in the treatment of clinically early vulvar SCC; patients with sentinel node metastasis are offered therapeutic inguinal femoral lymphadenectomy (IFL), while patients with histologically negative SLNs are not. Patients who undergo SLN biopsy without an IFL have been shown to have lower morbidity, with lower rates of wound

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breakdown (11.7% vs 43%), lower rates of cellulitis (4.5% vs 21.3%), and lower rates of lymphedema (1.9% vs 25.2%) [3], while the low risk of a groin recurrence is not increased (3–5%) [3,4].

GOG-173 [5] was a prospective multicenter observational study in which 453 women with clinically early invasive SCC of the vulva had SLN biopsy followed by inguinal femoral lymphadenectomy. They showed that in patients with primary vulvar tumors < 4 cm, SLN biopsy alone had a low false negative predictive value of 2%. This study included 48 women who had a prior wide local excision and had blue dye with or without radiocolloid injected around the scar. SLN detection was possible in 42 out of the 48 women (87.5%), a rate similar to the detection rate in the rest of the women who had clinically visible tumor (93.1%, $p = 0.15$).

Wide local excision (WLE) of the vulvar tumor and SLN biopsy is conventionally performed at the same time. Occasionally, patients are referred after vulvar tumor resection, for completion of surgical staging and further treatment. This can occur if the initial biopsy showed <1 mm stromal invasion, where nodal assessment is not recommended or in cases where the initial lesion was not suspicious for cancer. Previous tumor resection carries the theoretical risk of disruption of the lymphatic channels and inaccuracy of the SLN procedure. However, in patients with malignant melanoma and previous WLE, studies have shown that the SLN procedure is safe and accurate [6–8].

Studies involving SLN procedures in previously excised vulvar cancer cases have focused on the feasibility of identifying the SLN after injection of the remaining scar, by performing a full lymphadenectomy after the SLN is identified, and determining the accuracy rate [5,13,19]. Our institution was an early adopter of the SLN procedure, where a confirmatory IFL was omitted in patients with negative SLNs starting in 2007; this case series is thus one of the largest to include patients with previous vulvar excisions and injection of the remaining scar to identify the SLN. This study was not designed to assess the accuracy rate of SLN detection by injecting the scar, given that all patients with a negative SLN did not have a full groin dissection. The purpose of this study is to report long term outcomes in patients who had a SLN procedure by injecting the remaining scar after previous resection of the primary vulvar tumor, and to compare them with the rest of the patient cohort who had the standard vulvar resection of tumor and SLN biopsy by peri-tumoral injection.

2. Methods

2.1. Patient selection

Approval was obtained from the institutional ethics review board for this retrospective observational cohort study. Since 2007, a SLN biopsy without confirmatory IFL was offered to all patients with invasive SCC of the vulva and clinically negative nodes. All patients who had a specimen labelled “inguinal sentinel node” submitted to pathology between January 2008 and December 2015 were identified. Patients with vulvar tumors >4 cm were excluded from this cohort, as were patients who had primary chemoradiation.

2.2. Surgical procedure and adjuvant treatment

Patients with lateralized tumors, defined as having the medial lesion border > 1 cm from the midline, had unilateral SLN biopsy. Bilateral SLN biopsy was performed for patients with midline lesions.

One to two hours before the surgery, a total volume of 0.1–0.2 ml filtered sulfur colloid technetium was intradermally infiltrated at 2–4 sites around the vulvar lesion (clinically visible tumor or scar of previous excision). If this method did not identify any lymph nodes on preoperative scintigram, 4 ml of lymphazurin blue dye was intradermally infiltrated at the leading edge of the vulvar lesion before the start of the procedure. A handheld gamma probe (Navigator GPS; Dilon, Newport News, VA) was used to scan the lymph node basin bordered by the inguinal ligament superiorly, the sartorius muscle laterally and the adductor longus muscle medially. Nodes with a radioactive count of at least 5 times the background count were labelled as SLNs and sent for intraoperative pathological review. When no more ‘hot’ nodes were detected, scanning was terminated. If no SLN was identified in a groin, either by technetium or blue dye, the patient underwent a full unilateral inguinofemoral lymphadenectomy.

Patients who were found to have nodal metastasis were considered for adjuvant radiation therapy with or without concurrent chemotherapy on a case by case basis. In general, patients were offered adjuvant treatment if they had a complete IFL with 2 or more positive nodes > 5 mm.

2.3. Histopathology

Intraoperatively, each SLN was sectioned in 2–3 mm thick segments longitudinally in the frozen section pathology lab. For small SLNs, these were examined intact or cut in half. They were all subsequently sectioned in 5 micrometer thick segments. One section was stained by hematoxylin and eosin (H&E) and assessed at the time of frozen section, then fixed in 10% formalin for permanent section. Further 5 micrometer thick sections were obtained from paraffin-embedded frozen specimens. Two sections were H&E stained, one section was used as a negative immunoperoxidase stain, while the rest were used for immunohistochemical staining. All SCC specimens were stained with pan cytokeratin cocktail AE1/AE3 (Dako-Canada, Ontario) immunoperoxidase stain.

Non-SLNs from patients who underwent full IFL were fixed in 10% formalin and sectioned in 2–3 mm thick segments longitudinally. One 5 micrometer thick section was H&E stained.

2.4. Data collection

Patient demographics, clinical, surgical and pathologic data were recorded in our database. We recorded patients' age and comorbidities, whether any adjuvant treatment was administered, location, date of recurrences and last date of follow-up from clinical charts. We also collected information regarding tumor size, depth of invasion, grade, whether lymphovascular space invasion (LVSI) was observed, number of lymph nodes collected, and presence and size of metastatic deposits from pathological reports. From operative reports, we collected information regarding the method of SLN detection and details about further groin surgery. The presence of a clinically obvious vulvar lesion versus a scar from previous excision was systematically documented for all patients from the report of the first clinical encounter.

The clinical outcomes of interest are recurrence, and residual disease in the re-excisions specimen. We defined a local recurrence as a vulvar cancer at the same location as the patient's index cancer. A subsequent vulvar cancer in a different location was recorded as a new primary cancer. A recurrence which was distant to the vulva, groin or pelvis was documented as a distant recurrence. Progression-free survival (PFS) was calculated as the time in months from SLN biopsy to a recurrence or to the date of last documented follow-up.

2.5. Statistical analysis

Non-parametric testing was performed. The primary surgery and secondary scar excision groups were compared by Wilcoxon rank-sum test for continuous variables or Fisher exact test for categorical variables. Kaplan-Meier survival curves were compared by log-rank tests. Two-sided p values <0.05 were considered statistically significant. Statistical analysis was completed using SAS 9.4.

3. Results

3.1. Patient characteristics

A total of 163 patients who had a specimen labelled "inguinal sentinel node" submitted to pathology were identified between January 2008 and December 2015. Despite the use of technetium-99m and lymphazurin, no SLN was identified in the sample submitted from 4 patients; these patients had full IFL and were removed from the cohort. All of these 4 patients in whom a SLN was not identified in the tissue submitted at the time of surgery had a visible vulvar tumor. 31 more patients were excluded from the cohort because the primary vulvar tumors were >4 cm in size, were unresectable and treated with primary chemoradiation, or both. 128 patients were left and included in this analysis. Among this group, 24 patients had a previously resected vulvar tumor and had the remaining vulvar scar injected to identify the SLN (Fig. 1).

Two of the patients had a lateralized tumor treated with wide local excision and had negative unilateral SLN biopsy; they were subsequently found to have a new primary tumor lateralized to the contralateral vulva, and were again treated with a wide local excision and had negative unilateral SLN biopsy. The second cancer was thus considered a new case, for a total of 130 cases.

At least 1 SLN was identified in all 24 patients who had scar injection in this cohort. They were identified using technetium-99m alone in 18 cases (75%) and technetium-99m plus lymphazurin dye in 6 cases (25%). By comparison, technetium-99m alone was used in 80% of the cases of peritumoral injection and technetium-99m plus lymphazurin was used in 20%.

Patient and tumor characteristics are detailed in Table 1. Median age was 64 years (range 31–94), median tumor diameter was 12 mm (range 0.1–38) and median depth of invasion was 4 mm (range 0.3–30).

Of the 130 cases (194 groins), the SLN biopsy was negative in 91 (70%) (155 groins) and positive in 39 (30%) patients (43 groins). There were 106 cases where the patients underwent primary vulvar surgery and SLN biopsy at the same time. Of the 106, the SLN biopsy was negative in 69 (65%) cases and positive in 37 (35%). All of the 24 patients who had re-excision of the scar at the time of SLN biopsy were referred after primary excision of their vulvar lesion. The SLN biopsy was negative in 22 (92%) patients and positive in 2 (8%).

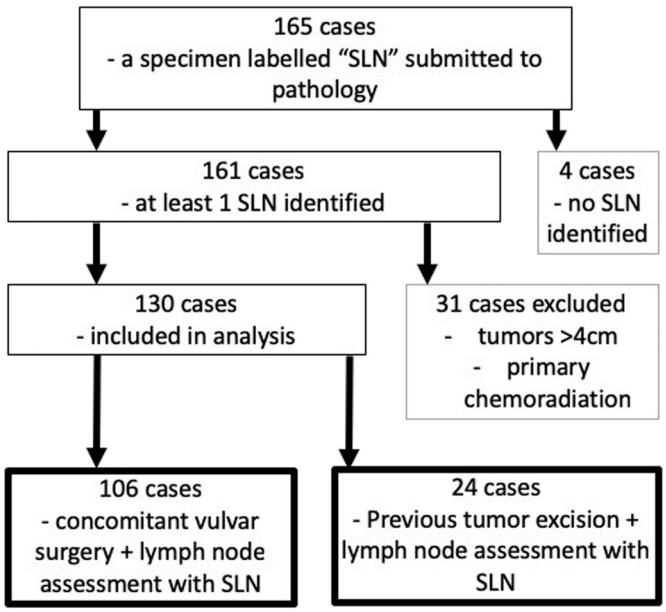

Fig. 1. Patient cohort.

Table 1
Patient characteristics.

	Vulvar surgery			p-Value*
	All patients (N = 128)	Primary vulvar surgery (n = 104)	Scar re-excision (n = 24)	
Age (years)				**0.0001**
Median	66	68	53	
(Range)	(31–94)	(38–94)	(31–78)	
Duration of follow-up (months)				0.2
Median	32	31	22	
(Range)	(0.03–103)	(0.3–103)	(0.03–96)	
	Vulvar surgery			**p-Value***
	All tumors (N = 130)	Primary vulvar surgery (n = 106)	Scar re-excision (n = 24)	
Diameter (mm)				
Median	12.0	13.0	8.0	
(Range)	(6.5–21.0)	(7.8–22.0)	(4.0–12.0)	
Depth (mm)				**0.02**
Median	4.0	4.3	2.7	
(Range)	(2.0–6.0)	(2.2–6.5)	(1.5–4.0)	
Primary vulvar tumor location (%)				0.07
Midline	77 (59%)	67 (63%)	10 (42%)	
Lateralized	53 (41%)	39 (37%)	14 (58%)	
Grade (%)				0.2
1	49 (39%)	38 (37%)	11 (50%)	
2	64 (51%)	53 (51%)	11 (50%)	
3	13 (10%)	13 (12%)	0 (0%)	
Lymphovascular space invasion (LVSI) (%)				0.7
Negative	113 (88%)	91 (87%)	22 (92%)	
Positive	16 (12%)	14 (13%)	2 (8%)	

* Significant p-values are emboldened. 3 missing: n = 3 for diameter, n = 3 for depth, n = 4 for grade, n = 1 for LVSI.

Patients who had SLN detected by scar injection were more likely to be younger (p = 0.0001), more likely to have a smaller tumor to start (p = 0.002), and to have less depth of invasion (p = 0.02). There were no statistically significant differences in terms of tumor grade or lymphovascular space invasion (LVSI) between these 2 groups.

Twelve patients (11%) from the primary surgery group required adjuvant radiotherapy to the vulva after surgery, compared with none of the patients in the scar injection group. However, this did not reach statistical significance (p = 0.1).

3.2. Secondary scar excision

After the first vulvar excision, none of the 24 patients had clinically visible disease. In 11 patients (46%), the margins were positive for invasive carcinoma in the initial resection specimen and in another 46% (11 patients) the margins were clear, but <8 mm. Detailed histopathological data from the first excision was not available for 2 patients.

After repeat wide local excision of the vulva, the histopathological results of the specimens were as follows: 11 patients (46%) had no residual disease, 8 patients (33%) had VINIII, 4 patients (17%) had carcinoma in situ with focal invasion and 1 patient (4%) had invasive carcinoma within the second specimen, with clear margins by 4 mm (Fig. 2). When compared to the initial excision, 10/11 patients with negative but close margins had no residual disease after scar re-excision, while 1 had focal invasion.

At least 1 SLN was identified in all 24 cases. 15 patients underwent unilateral SLN biopsy and 9 patients had bilateral SLN biopsy. Only 2 patients were found to have a positive SLN (2 mm and 5 mm in size respectively). One of the 2 patients underwent full IFL for a 5 mm

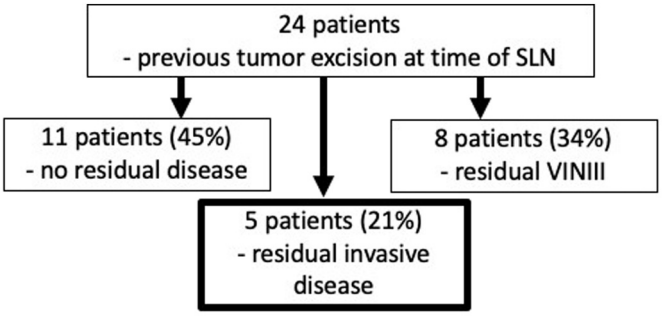

Fig. 2. Results after secondary wide local excision of the scar.

metastatic deposit in the SLN, and the SLN was the only positive node. This patient received no adjuvant treatment. The other patient had a 2 mm metastatic deposit in the SLN and received adjuvant groin radiotherapy, but no complete groin dissection.

3.3. Recurrences

Median follow-up was 31 months. Nine patients (7%) were lost to follow-up immediately after the surgery with the plan to be followed at a hospital closer to their home. We did not attempt to contact the patients or their providers.

Overall, 24 patients (18%) developed a recurrence with a median time to recurrence of 9 months. Most recurrences (96%) occurred in the primary vulvar surgery group. In this primary surgery group, 22% of cases recurred. The local recurrence rate in the vulva was 13%, and the isolated groin recurrence rate was 5%. 3 cases (3%) presented with a distant or pelvic recurrence and 1 case (1%) with a synchronous recurrence in the vulva and groin.

In the scar injection group, we observed one recurrence (4%) in the groin. This patient had a midline tumor and a positive unilateral SLN biopsy with a 5 mm intra-capsular metastatic deposit. She had bilateral IFL and there were no other positive lymph nodes found. The patient then presented 2 months post scar re-excision with a non-healing lesion in the vulva which was re-biopsied and found to be persistent SCC. A repeat wide local excision (WLE) was performed at this time. The patient did not receive any adjuvant treatment. She was seen several times for lichen sclerosus and persistent VINIII which was treated with laser vaporization. Nine months after the repeat WLE she presented with a groin recurrence. This was treated with repeat groin dissection and palliative radiotherapy.

There were no significant differences between primary surgery and scar injection groups in the proportion of recurrences by location or the time to recurrence (Table 2). There was a higher recurrence rate in the primary surgery group ($p = 0.046$). Median progression free survival (PFS) was 26 months in the primary vulvar surgery group and 38 months in the scar injection group. Patients in the scar injection group had 1-year and 5-year PFS of 96%. PFS in the primary vulvar surgery group with 86% and 71% at 1-year and 5-years respectively ($p = 0.05$).

Table 2
Pattern of recurrence.

Recurrence	All tumors (N = 130)	Primary vulvar surgery (n = 106)	Scar re-excision (n = 24)	p-Value
None	106 (82%)	83 (78%)	23 (96%)	0.046
Vulva/local	15 (11%)	14 (13%)	0 (0%)	
Isolated groin	5 (4%)	5 (5%)	1 (4%)	
Pelvis/distant	3 (2%)	3 (3%)	0 (0%)	
Synchronous vulva/local and groin	1 (1%)	1 (1%)	0 (0%)	

4. Discussion

The concept of SLN biopsy is largely based on a preserved, predictable lymphatic drainage pattern which aids in the detection of one, or several "sentinel nodes". If these are negative for metastasis, the risk of other femoral or pelvic lymph nodes harboring disease is remote [11]. The theoretical risk exists that previous excision of the primary vulvar cancer may disrupt the lymphatic channels, affect lymphatic mapping and alter SLN accuracy. Larger studies in malignant melanoma have shown that SLN biopsy is safe and accurate even after the primary lesion has been removed with wide margins and the remaining scar is injected instead [6–8]. A 51 month follow-up found 0% nodal recurrence in this population, independent of tumor location [8]. As described earlier, prior studies [5,13,19] demonstrated that SLN detection rate in patients with vulvar cancer who had prior wide local excision was similar to the detection rate in patients with a visible vulvar tumor. In these studies patients had a SLN biopsy followed by a complete inguinofemoral groin dissection, and no long-term follow-up. Results from the current study suggest that when a lymph node is identified intraoperatively, by injecting technetium-99m or technetium-99m and blue dye around the scar in patients who have had prior excision of the vulvar lesion, this node can reliably be considered to be the sentinel node; in our patient cohort there were no recurrences in SLN-negative patients.

To our knowledge, there has only been one other study [14] analyzing outcomes of patients with SLN procedures after previous vulvar cancer excision. This study included a total of 106 patients, 32 of which had previous partial or complete excision of the primary tumor. Similar to that study, we found a groin recurrence rate of 5% (vs 5.4% by Woelber et al. [14]). This is comparable to other studies which did not include patients with previous excision of the vulvar tumor (2.5–6.7%) [4,12,15,16], and similar to the historic rate of groin recurrence in women who had a full IFL (4–7%) [17,18].

In our study, we noted a trend towards decreased recurrence rates and improved survival in the scar injection group. This is likely reflective of confounding, with patients in this group having smaller tumors and more superficial tumors with better prognosis, and thus having had their primary tumor removed at the first excisional biopsy. This finding is similar to that observed by Woelber et al. [14]. In our cohort, these patients had primary excision of the vulvar lesion with a general gynecologist and were referred for definitive treatment. Despite the absence of any macroscopic lesion in the vulva, invasive disease was still present in 21%, emphasizing the importance of wide re-excision of the scar to obtain clear margins.

While our results show that outcomes after SLN biopsy are similar when the vulvar lesion has been previously excised, none of the tumors had been excised with margins >8 mm. Consequently, a comment cannot be made on the oncologic safety of the SLN procedure in cases where the excision margins are very wide or where extensive reconstruction has taken place.

The limitations of this study include the small number of patients in the scar injection subgroup, measurement bias secondary to missing information due to the retrospective nature of the data collection, and attrition bias. At our center, patients often receive follow-up care at institutions closer to home after the first post-operative visit, and this resulted in the shorter median follow-up of 31 months, despite the data being collected over 8 years. The low incidence of vulvar cancer and even lower incidence of cases when the vulvar tumor has been previously excised make a large observational study to address this issue not feasible. Although the number of patients included in this analysis is relatively low, practice in this area will be guided by smaller observational studies like ours.

Based on these results, we would recommend that general gynecologists continue to perform appropriate biopsies on suspicious lesions without excising the tumor in its entirety. If an excision of the lesion is performed without knowledge of the presence of invasive disease and

the final histopathology shows >1 mm invasion, SLN biopsy can still be performed and patient outcomes do not seem to be negatively impacted. However, due to the scarcity of data on this topic, concurrent wide local excision and SLN biopsy at first surgery is preferred.

Author contributions

The contribution of the individual authors is as follows: Dr. Nica performed data collection, analysis and wrote the manuscript. Drs. Covens, Vicus, and Kupets were involved in the surgical treatment of patients and manuscript editing. Dr. Gien is the Senior Author, involved in the surgical treatment of patients, and also responsible for the study idea, and for supervising data collection, analysis, and manuscript editing.

Declaration of competing interest

Drs Nica, Covens, Vicus, Kupets, and Gien have no conflict of interest to declare.

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