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# Sentinel lymph nodes in vulvar cancer: Management dilemmas in patients with positive nodes and larger tumors☆

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## HIGHLIGHTS

- The risk of groin recurrence is low in vulvar SCC and SLN micrometastasis when groin dissection is replaced with radiation
- The risk of contralateral groin recurrence is low with a unilateral +SLN and vulvar tumors <4 cm without a groin dissection
- Groin recurrence rate may be higher in patients with large (>4 cm) tumors and negative SLN

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## ABSTRACT

*Background.* Although sentinel lymph node (SLN) biopsy has been routinely used in the treatment of invasive squamous cell carcinoma (SCC), questions still remain regarding the management of patients with positive nodes, as well as its use in patients with larger tumors.

*Methods.* Retrospective study of all patients at a single institution with primary vulvar cancer who had SLN biopsy (2008–2015). Patient and tumor characteristics were collected from hospital records. For patients with positive SLN and for those with tumors ≥40 mm, recurrence rates and location were specifically recorded.

*Results.* SLN biopsy was successful in 159 patients (245 groins). Median follow-up was 31 months.
120 patients (187 groins) had a negative SLN without an inguinofemoral lymph node dissection (IFL); there were 6 ipsilateral groin recurrences (5%).
7 patients had micrometastasis (≤2 mm) in the SLN and were treated by radiotherapy. There were no recurrences in the irradiated groins.
19 patients with a positive unilateral SLN had bilateral IFL. One (5.3%) had a positive node in the contralateral groin. 9 patients with positive unilateral SLN had subsequent ipsilateral IFL; there were no groin recurrences in the contralateral groin.
20 patients had tumor size ≥40 mm. 11 patients had a negative SLN biopsy, and thus no IFL; of these patients, 1 had an isolated groin recurrence (9%).

*Conclusion.* These data suggest it is reasonable to omit a full groin dissection for micrometastatic disease in the SLN, and to perform a unilateral groin dissection in patients with unilateral SLN metastasis. SLN alone in larger tumors may have a higher groin recurrence rate.



## 1. Introduction

Vulvar cancer accounts for 4% of all gynecologic cancers, and for an estimated 1150 deaths in 2017 in the United States alone. The rate of new vulvar cancer has been increasing over the past 10 years by 0.6% per year on average [1]. Squamous cell carcinoma (SCC) is the most common histological subtype, comprising 90% of cases. The presence of lymph node metastasis is the most important prognostic factor in

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invasive SCC of the vulva. A full inguinofemoral lymphadenectomy (IFL) carries up to an 85% risk of wound infection, wound breakdown and long-term associated morbidity, and a 30% risk of chronic lymphedema [2].

Following landmark studies published in 2008 [3] and 2012 [4], sentinel lymph node (SLN) biopsy to assess the inguinal nodes has been routinely used by many institutions in the treatment of invasive SCC of the vulva. GROINSS-V-I [3] was a multicenter prospective observational study which included 403 patients, 259 of whom had a negative sentinel node and no further treatment for unifocal early invasive vulvar SCC. They concluded that in this patient population, a negative SLN biopsy is associated with a 3% risk of groin recurrence, and an excellent survival rate. The study also found that compared to patients who underwent SLN biopsy and full IFL, patients who had SLN biopsy only had lower rates of wound 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]. In GOG-173 [4], 453 women with clinically early invasive vulvar SCC underwent SLN biopsy, followed by IFL in order to determine the safety and accuracy of the SLN procedure. In patients with primary vulvar tumors <4 cm, SLN biopsy alone had a low false negative predictive value of 2%.

Despite the adoption of the SLN procedure, questions still remain regarding the management of cases when the SLN is positive. Although it is generally accepted that a patient with a positive SLN with macrometastasis should undergo a full groin node dissection, it is unclear whether patients with micrometastatic SLN (<2 mm) should also undergo a full groin node dissection. This question is currently being evaluated in GROINSS-V-II, a prospective observational study where patients with SLN positive micrometastatic disease undergo adjuvant postoperative groin radiation rather than a full groin dissection [5]. Similarly, if a patient has a positive sentinel node unilaterally, it is unclear from the literature whether both groins should undergo a full groin dissection or whether a SLN biopsy can be done on the contralateral groin. Finally, there is little existing data whether SLN biopsy is an accurate intervention for patients with primary vulvar tumors >4 cm.

Our institution is one of the early adopters of the SLN procedure, where a confirmatory IFL was omitted for patients with negative SLNs starting in 2007. The primary objective of this study is to evaluate the rates and patterns of recurrence in invasive vulvar SCC in patients with negative SLN, positive SLN when the size of the SLN metastatic deposit is <2 mm or when there is a unilateral positive SLN, and in patients with tumors >4 cm.

## 2. Materials and methods

### 2.1. Patient selection

This was a retrospective observational cohort study approved by the Institutional Review Board. Between January 2008 and December 2015, patients with vulvar SCC who had a successful SLN procedure were included in this study, defined as the identification of at least 1 SLN. At our institution, all consecutive patients with invasive SCC of the vulva with clinically normal nodes were considered candidates for SLN during the study period, if no previous SLN biopsy had been done. Patients with any primary tumor size, including multifocal disease, were included in this study. Data inclusion starts after a 4 year learning curve during which a confirmatory IFL followed the SLN detection to ensure accuracy. Sentinel node biopsies were performed by five Gynecologic Oncologists at our center.

During the pre-operative and intra-operative assessments, it was determined if the vulvar tumor was midline or lateralized similar to GROINSS-V-I protocol [3]. A vertical imaginary line was drawn from the clitoris to the anus and the distance from this imaginary line to the medial margin of the lesion was estimated. If this distance was found to be >1 cm, the lesion was deemed lateralized and unilateral SLN biopsy was performed. Patients with midline lesions underwent bilateral SLN biopsy.

The vulvar tumors were treated by radical wide local excision, or by primary chemoradiation if deemed surgically unresectable. Patients with unresectable tumors were those whom at the time of their first exam by a Gynecologist Oncologist and a Radiation Oncologist at our center were deemed to have a high likelihood of losing anal sphincter function or require primary exenteration in order to achieve removal of the primary tumor with adequate margins. Wide local excision was performed with 1 cm gross margins around the tumor or around the scar in cases where the primary tumor had already been excised.

Patients with positive lymph nodes were referred to a Radiation Oncologist specializing in gynecologic malignancies for consideration of adjuvant radiotherapy plus or minus concurrent chemotherapy.

Patient demographics, as well as clinical, surgical and pathologic data were collected and recorded in an electronic database.

### 2.2. The SLN Procedure

The morning of the procedure, 0.1–0.2 mci of filtered sulfur colloid technetium was injected intradermally in 2–4 injection sites around the vulvar lesion or if the vulvar lesion was previously resected then into the scar. If no lymph nodes were identified with technetium, 4 ml of lymphazurin blue dye was injected intradermally at the leading edge of the lesion at the start of the surgery. SLNs were confirmed by radioscintigram prior to the operation. SLNs were detected intraoperatively using a handheld gamma probe (Navigator GPS System; Dilon, Newport News, VA). Lymph node basins, bordered by the inguinal ligament superiorly, the sartorius muscle laterally and the adductor longus muscle medially, were scanned with the gamma probe in a systematic fashion. Lymph nodes that were considered 'hot' were removed, labelled as SLNs, and sent for intraoperative pathological review; to be 'hot', a lymph node had to have a radioactive count that was at least 5 times the background count. Scanning was complete when the lymph node basin was scanned and no further hot spots were found.

If the SLN was positive on frozen section, a full ipsilateral IFL was completed, and the patient was referred for consideration of adjuvant radiotherapy to the groins and pelvis. When one SLN was positive the decision for contralateral IFL was surgeon and patient dependent. Patients with resection margins <8 mm also received adjuvant radiotherapy to the vulva. If the SLN was negative, no further surgery was performed on the groin.

### 2.3. Histopathology

The SLNs were sectioned in 2–3 mm segments perpendicular to their long axis. When the SLN was too small, it was sent intact or sectioned in half for frozen section. The specimens were then cut at 5 μm segments; the section that was evaluated at the time of the frozen section was stained by hematoxylin and eosin (H&E), then fixed in 10% formalin for permanent section. Other 5 μm segments were obtained from paraffin-embedded frozen tissue; the first 2 segments were H&E stained, and the others were used for immunohistochemical evaluation. When a SCC diagnosis was made, the specimen was stained by pan cytokeratin cocktail AE1/AE3 (Dako-Canada, Ontario) immunoperoxidase stain. The last section was used as a negative immunoperoxidase control.

All non-SLNs were fixed in 10% formalin, and sectioned in 2–3 mm segments perpendicular to their long axis. One 5 μm thick segment was obtained from the paraffin fixed tissue and stained by H&E.

### 2.4. Data collection

After the cohort was established, patient clinical charts, operative reports and pathology reports were reviewed. Data parameters included patient and tumor baseline characteristics, surgical and pathological

data, as well as all adjuvant treatments and recurrences. Specifically, the following parameters were collected: patient age and comorbidities, tumor size, depth of invasion, tumor grade, presence of lymphovascular space invasion (LVSI), method of SLN detection, presence and size of SLN metastasis, further groin surgery and number of lymph nodes removed, presence and size of metastasis, and whether any adjuvant treatment was administered. Location, treatment and date of all recurrences was also collected, as well as last date of follow-up. Local recurrence was defined as a subsequent vulvar cancer, which was in the same "general" location as the primary tumor resection. Distant recurrence was defined as any recurrence diagnosed pathologically or radiologically which was distant to the vulva, groin or pelvis. Progression-free survival was defined as the time from SLN biopsy to the recurrence date or to the date of last follow-up.

### 2.5. Statistical analysis

Non parametric testing was used. Groups were compared by Wilcoxon rank-sum test for continuous variables, and Chi-Squared test or Fisher exact test for categorical variables. Survival analysis was performed; Kaplan-Meier curves were compared by log-rank tests. Two-tailed $p$-values $< 0.05$ were considered statistically significant. Statistical analysis was completed using SAS 9.4.

## 3. Results

### 3.1. Patient characteristics

Between January 2008 and December 2015, of the 163 patients who underwent attempted SLN biopsy, 159 were successful. Despite the use of technetium-99 m and lymphazurin, no SLN was identified in 4 patients; these patients had full IFL and were removed from the cohort.

Patient characteristics are detailed in Table 1. Median age was 65 years (range 31–94), median tumor diameter was 13 mm (range 0.1–65) and median depth of invasion was 4 mm (range 0.3–30). The majority of patients (89%) had their primary vulvar tumor treated surgically, while 11% received primary radiotherapy to the vulva after the SLN procedure due to having an unresectable vulvar tumor.

Of the 159 patients (245 groins), the SLN biopsy was negative in 120 (75%) patients (187 groins) and positive in 39 (25%). Patients with positive SLNs were found to be older ($p = 0.04$), have larger vulvar tumors ($p = 0.004$), and have tumors with greater depth of invasion ($p = 0.004$), and higher grade ($p = 0.001$). (Table 1).

In 5 instances, the frozen section was reported as negative, and the final pathology was positive for metastasis: 1 macrometastasis (>2 mm), 1 micrometastasis (≤2 mm), and 3 isolated tumor cells (ITCs). The patient with macrometastasis was taken back to the OR for completion IFL. All patients were referred to an expert Radiation Oncologist in treatment of vulvar cancer, and the decision for adjuvant groin radiation therapy was individualised based on patient's age, comorbidities, tumor depth of invasion, and LVSI. Two patients with ITCs had adjuvant groin radiation.

**Table 1**
Patient characteristics.

| | Sentinel lymph node pathology | | | p-value* |
|---|---|---|---|---|
| | All patients ($N = 159$) | Negative ($n = 120$) | Positive ($n = 39$) | |
| Age (years) | | | | **0.04** |
| Median | 65.0 | 63.5 | 69.0 | |
| (range) | (31.0–94.0) | (31.0–93.0) | (48.0–94.0) | |
| Primary vulvar tumor location | | | | 0.44 |
| Midline | 100 (63.7%) | 78 (65.5%) | 22 (57.9%) | |
| Lateralized | 57 (36.3%) | 41 (34.5%) | 16 (42.1%) | |
| Diameter (mm) | | | | |
| Median | 13.0 | 12.0 | 22.0 | **0.004** |
| (range) | (0.1–65.0) | (0.1–65.0) | (2.4–60.0) | |
| Diameter categories | | | | **0.014** |
| <20 mm | 95 (64.2%) | 79 (70.5%) | 16 (44.4%) | |
| ≥20 but <40 mm | 36 (24.3%) | 23 (20.5%) | 13 (36.1%) | |
| ≥40 mm | 17 (11.5%) | 10 (10%) | 7 (19.5%) | |
| Depth (mm) | | | | **0.004** |
| Median | 4.0 | 3.5 | 5.5 | |
| (range) | (0.3–30.0) | (0.30–30.0) | (0.5–20.0) | |
| Grade | | | | **0.001** |
| 1 | 54 (37.5%) | 48 (43.6%) | 6 (17.6%) | |
| 2 | 74 (51.4%) | 55 (50.0%) | 19 (55.9%) | |
| 3 | 16 (11.1%) | 7 (6.4%) | 9 (26.5%) | |
| Lymphovascular space invasion (LVSI) | | | | 0.05 |
| Negative | 124 (85.5%) | 98 (89.1%) | 26 (74.3%) | |
| Positive | 21 (14.5%) | 12 (10.9%) | 9 (25.7%) | |

Significant p-values are emboldened. Missing data: tumor location ($n = 2$), diameter ($n = 11$), depth ($n = 15$), grade ($n = 15$), LVSI ($n = 14$).

### 3.2. Recurrences

Median follow-up was 31 months. 15 patients (9%) were followed at their local hospital, closer to home and were lost to follow-up immediately after the first post-operative encounter. An attempt was not made to contact these patients or their providers at the time of data collection.

Overall, 23% of patients developed a recurrence with a median time to recurrence of 7 months (range: 2–44 months). The local vulvar recurrence rate was 12%, primary isolated groin recurrence 5% and distant and/or pelvis recurrence rate was 3.8%.

In sentinel node negative patients, there were 6 isolated groin recurrences (5%). Two of the patients with isolated groin recurrence were treated by surgical debulking of the involved nodes followed by adjuvant radiotherapy with concurrent 5-FU chemotherapy and both were still alive after 5 years. The other 4 patients with isolated groin recurrence died shortly after being diagnosed from their recurrence although all received palliative groin radiotherapy, and one received concurrent 5-FU chemotherapy.

Among the sentinel node positive patients, there were 2 isolated groin recurrences (5%). One of the patients with isolated groin recurrence underwent surgical debulking of the groin nodes followed by adjuvant chemoradiation and was alive at 3 years. The other patient received palliative radiotherapy and died from the recurrence. Neither of these patients had received adjuvant radiation therapy following their initial surgery, because the SLN was the only positive node (4 mm and 5 mm respectively).

Median PFS was 31.7 months in SLN-negative patients and 13.6 months for SLN-positive patients. SLN-negative patients had 1-year and 5-year progression-free survival rates (PFS) of 90% and 80% respectively. PFS was significantly worse ($p < 0.0001$) for SLN-positive patients; 81% and 50% at 1 and 5 years, respectively (Fig. 1 (a)).

### 3.3. Patients with micrometastases in the SLN

Ten patients had micrometastasis (≤2 mm deposit) in the SLN. Three of these had a full IFL (2 bilateral and 1 unilateral). One of these 3 patients had a local vulvar recurrence, treated with extensive abdominoperineal resection, which was unfortunately followed by a distant pelvic sidewall recurrence, unresponsive to radiation therapy. The other 7 patients with micrometastasis in the SLN were treated with adjuvant radiotherapy only, without full groin dissection. Three of these 7 patients had isolated tumor cells (ITC). There were no significant differences in age, tumor location, depth of invasion or LVSI between SLN patients with micrometastasis ($N = 10$) and macrometastasis ($N = 29$) (data not shown). Four of the 7 patients had midline tumors, and SLN biopsy was performed bilaterally. Metastases were found unilaterally in all 4 patients (2 micrometastasis and 2 ITC), and they all received adjuvant radiotherapy to the ipsilateral

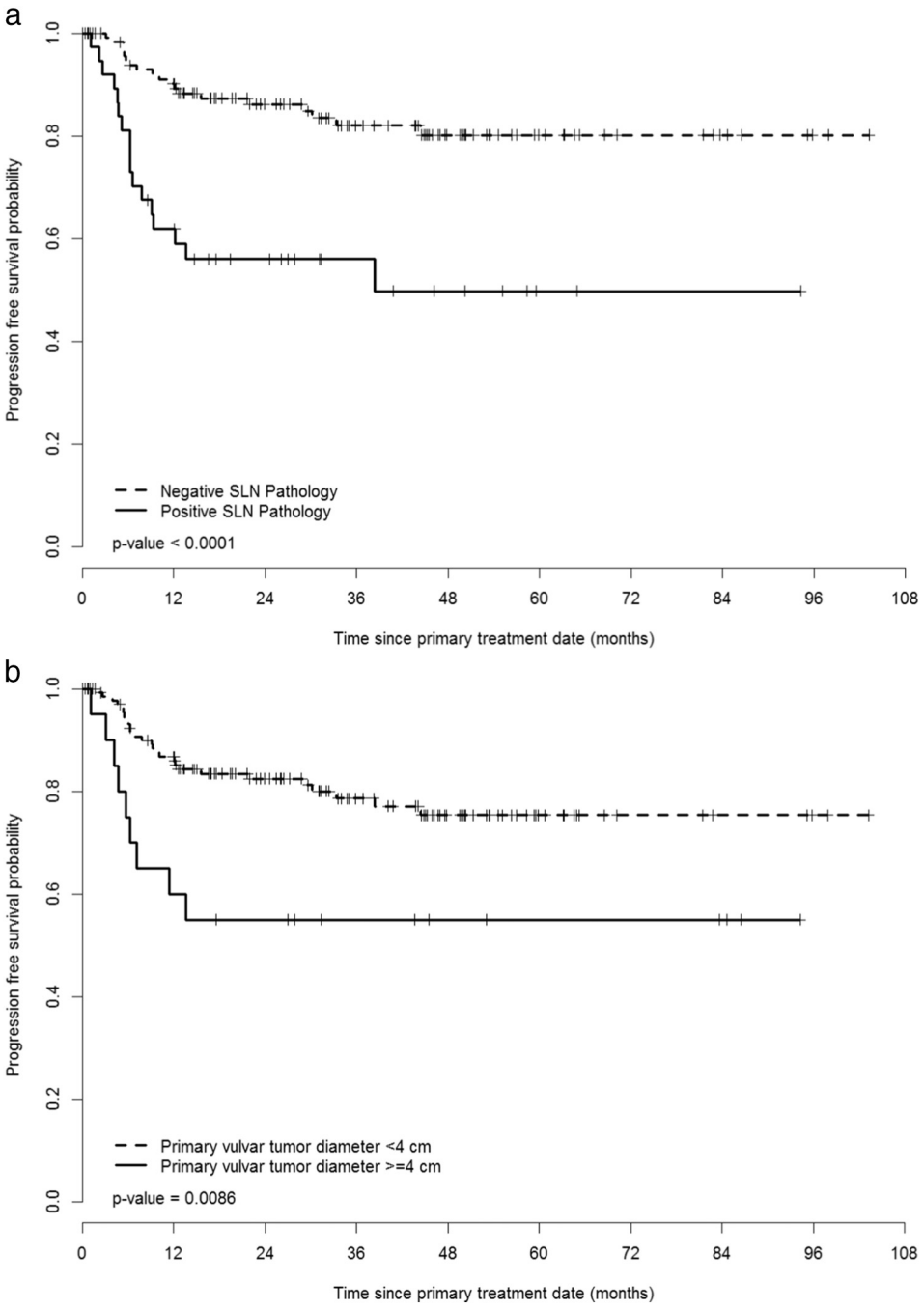


**Fig. 1.** (a): Progression-free survival (PFS) for SLN-negative and SLN-positive patients. (b): Progression-free survival (PFS) for patients with tumors < 4 cm and ≥4 cm.

groin and pelvis. The other 3 patients had lateralized tumors and SLN biopsy was performed on that side only; one of these had ITCs and 2 were found to have micrometastatic deposits in the SLN. The patient with ITCs and one patient with micrometastasis received adjuvant radiotherapy to both groins and pelvis, while the third received radiotherapy to the ipsilateral groin and pelvis. There were no groin recurrences in any of the 7 patients with micrometastasis after adjuvant groin irradiation.

### *3.4. Patients with unilateral positive sentinel node*

Twenty-eight patients with metastatic disease in the SLN subsequently had a complete groin dissection (40 groins) (Fig. 2). The SLN was the only positive node in 31 (78%) groins.

Nineteen patients underwent full bilateral groin dissection after finding a unilateral positive SLN (17 with macrometastatic disease and 2 with micrometastasis); Thirteen of these patients had midline tumors, and 6 were lateralized. One patient with a 6-cm vulvar tumor had a positive non-SLN in the contralateral groin (5.3%).

Nine patients with unilateral positive SLN (8 with macrometastasis and 1 with micrometastasis) underwent ipsilateral full groin dissection only. Three of these had midline tumors and negative contralateral SLN and 6 had lateralized tumors. Six patients received adjuvant radiotherapy to both groins and pelvis. There were no groin recurrences in the contralateral, undissected groins.

There were 2 isolated groin recurrences in patients who underwent bilateral groin dissection after a unilateral positive SLN; one recurrence was in the SLN-positive groin, and the other was in the contralateral groin although all nodes were negative at the time of the IFL.

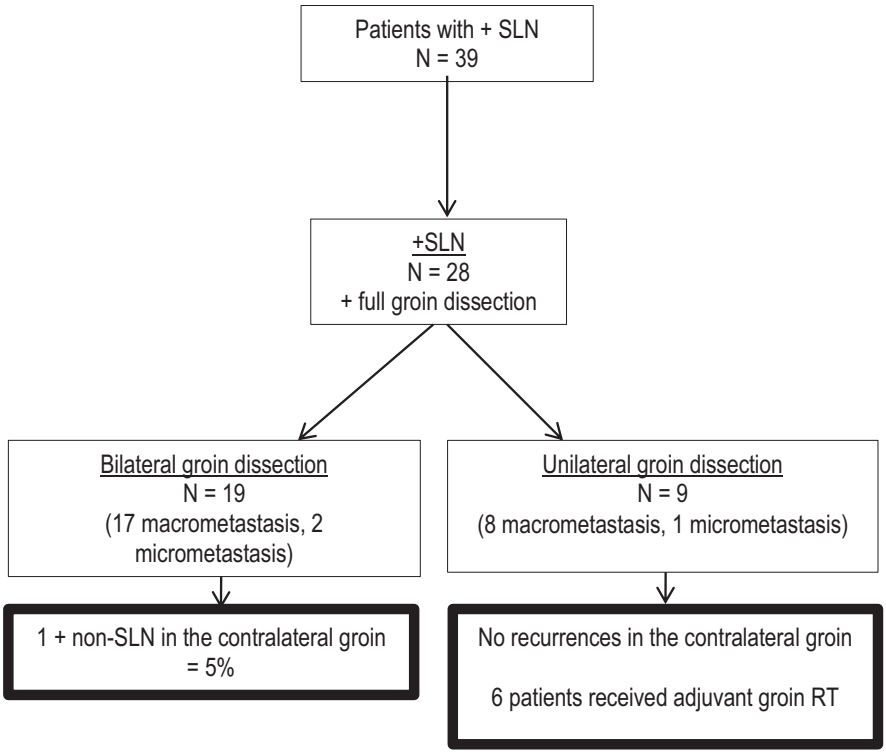


**Fig. 2.** Outcomes of patients with positive SLN who had a complete groin dissection.

### *3.5. Patients with tumors larger than 4 cm*

There were 20 patients (38 groins) whose primary vulvar tumor size was ≥40 mm who underwent SLN biopsy. The clinical and pathologic characteristics of these patients are detailed in Table 2. Median tumor size in this group of patients with larger lesions was 48 mm (range: 40–65 mm), and median depth of invasion was 10 mm (range: 0.75–20 mm). Compared to patients with tumors <40 mm, patients with larger tumors were more likely to have a midline lesion ($p = 0.01$), have greater depth of invasion ($p = 0.009$), have a positive SLN ($p = 0.048$), and to have a recurrence ($p = 0.01$). There were no statistically significant differences between the 2 groups in median age, tumor grade or LVSI status.

**Table 2**
Characteristics of patients with large vulvar tumors.

| | Primary vulvar tumor size | | p-value* |
|---|---|---|---|
| | **< 4 cm (*n* = 139)** | **≥ 4 cm (*n* = 20)** | |
| Age (years) | | | 0.33 |
| Median | 65 | 67 | |
| (range) | (31.0–94.0) | (48.0–93.0) | |
| Primary vulvar tumor location | | | **0.01** |
| Midline | 83 (60.1%) | 17 (89.5%) | |
| Lateralized | 55 (39.9%) | 2 (10.5%) | |
| Depth (mm) | | | **0.009** |
| Median | 3.9 | 10.0 | |
| (range) | (0.3–30.0) | (0.8–20.0) | |
| Grade | | | 0.72 |
| 1 | 50 (38.4%) | 4 (28.6%) | |
| 2 | 66 (50.8%) | 8 (57.1%) | |
| 3 | 14 (10.8%) | 2 (14.3%) | |
| Lymphovascular space invasion (LVSI) | | | 0.097 |
| Negative | 115 (87.1%) | 9 (69.2%) | |
| Positive | 17 (12.9%) | 4 (30.8%) | |
| SLN pathology | | | **0.048** |
| Negative | 109 (78.4%) | 11 (55.0%) | |
| Positive | 30 (21.6%) | 9 (45.0%) | |
| Recurrence | | | |
| None | 112 (80.6%) | 11 (55.0%) | **0.01** |
| Vulva/Local | 15 (10.8%) | 4 (20.0%) | |
| Isolated groin | 7 (5.0%) | 1 (5.0%) | |
| Pelvis/Distant | 4 (2.9%) | 2 (10.0%) | |
| Synchronous vulva and groin | 1 (0.7%) | 2 (10.0%) | |

Significant p-values are emboldened. Missing data: tumor location (n = 2), depth (n = 15), grade (n = 15), LVSI (n = 14).

In this group, 50% of the patients were treated by a radical vulvectomy while the rest were treated with primary vulvar chemoradiation after the SLN procedure.

Nine out of 20 patients had a positive SLN biopsy (45%). Of these 20 patients, 11 (22 groins) had a negative SLN without full groin dissection. In this group, there were 2 isolated groin recurrences in the same patient (bilateral groins) for an isolated groin recurrence rate of 9%. This patient was treated with bilateral groin dissection but died of her recurrence. Also in this group, 3 patients (23.1%) had a local vulva recurrences. One patient (9%) had a pelvic recurrence, treated with radiotherapy followed by a groin recurrence that was treated by surgical excision.

Median PFS in patients with tumors <4 cm was 27 months and 22 months in patients with tumors ≥4 cm. Patients with smaller tumors had 1-year and 5-year PFS of 87% and 76% respectively. PFS was significantly worse ($p = 0.009$) for patients with larger tumors with 60% and 55% at 1 and 5 years, respectively (Fig. 1 (b)).

## 4. Discussion

SLN biopsy in the treatment of invasive SCC of the vulva has been previously shown to be safe and accurate [4,6]. Despite the limited number of patients in this cohort, this data set suggests that the use of SLN biopsy without groin dissection may be extended to certain subgroups of patients with positive SLN. In this study, omitting groin dissection in patients with SLN micrometastasis who then received adjuvant radiation therapy, and omitting contralateral groin dissection when unilateral metastasis is found in the SLN had low rates of groin recurrence.

The rate of isolated groin recurrence in patients with stage IB vulvar cancer who had SLN biopsy alone, and in whom the SLN was negative is reported to be low (2.5–6.7%) [7–10]. More importantly, this rate is similar to the historic rate of groin recurrence in women who underwent full IFL (4–7%) [11,12]. We found an isolated groin recurrence rate of 5%, which is similar to previous reports [7–10]. The low rate of groin recurrence is reassuring, because prognosis is poor in these cases, with high disease specific mortality rates (67–100%) [7,8].

There are, at present, no generally established guidelines for the management of SLN micrometastasis (≤2 mm deposit) or ITCs (≤0.2 mm). In the GROINSS-V study the rate of positive non-SLNs was found to be low in patients with ITCs (4.2%) and in patients with micrometastasis (11.1%) [17]; however, the authors concluded that no cut-off size was found below which the chance of non-SLN metastasis was close to zero, emphasizing the role of adjuvant treatment. The GROINS-V-II study was designed to determine whether complete IFL could be replaced by adjuvant radiotherapy in patients with early invasive vulvar SCC who had SLN micrometastatic disease. Patients with breast cancer and SLN micrometastasis have a significantly lower likelihood of positive non-SLN than patients with macrometastatic disease. Moreover, patients with breast cancer and SLN submicrometastasis (≤0.2 mm) [13,14] and patients with melanoma and SLN submicrometastasis (≤0.1 mm) have the same prognosis as SLN negative patients [15,16], albeit, adjuvant therapy in patients with breast cancer and melanoma relies more heavily on characteristics of the primary tumor. In our study, 7 patients were found to have unilateral micrometastasis or ITCs after SLN biopsy and were treated with adjuvant radiotherapy. There were no groin recurrences in any of these patients. Therefore, it may be reasonable to omit a full groin dissection for micrometastatic disease, as the risk of groin recurrence is low with adjuvant radiotherapy. At a time when results from a large multi-center study (GROINS-V-II) are pending, outcomes from our smaller retrospective study are encouraging and timely. A study comparing morbidity from groin radiotherapy to that from complete IFL would also be useful in the future to justify a change in practice.

In patients with lateralized vulvar tumors (>1 cm from midline), the risk of contralateral groin metastases is low [18,19], especially if the ipsilateral nodes are negative. Gonzalez Bosquet et al. [19] retrospectively looked at a group of 320 patients, most (>95%) of whom underwent bilateral IFL. That study found that none of the patients with lateralized vulvar tumors had contralateral groin metastases if their tumor was <2 cm diameter or had <5 mm depth of invasion. The rate of bilateral groin metastases was 4.9% of all patients with lateralized tumors. Data is not available from GROINS-V-I concerning the risk of positive contralateral non-SLN in patients with unilaterally positive SLN. Best management of the contralateral groin when the patient is found to have unilateral positive SLN is still controversial. In this current study there were 19 patients who underwent bilateral full groin dissection after finding a unilateral positive SLN. One positive non-SLN node was found in the full contralateral groin dissection (5.3%) in a patient with a large (6 cm) primary vulvar tumor. We also had 9 patients with unilateral positive SLN who underwent ipsilateral groin dissection only. There were no groin recurrences in the contralateral, undissected groins. Six out of 9 patients received postoperative radiotherapy to the groins, which may have sterilized microscopic disease. Patient numbers are low; however, based on these findings, we would hypothesize that in patients with a unilateral positive SLN and vulvar tumors <4 cm, the risks of positive contralateral nodes and contralateral groin recurrence are low. A retrospective study of 33 patients with unilateral positive SLN [20] who had bilateral complete IFL also showed 0% rate of positive contralateral non-SLN. Similar to our findings, one patient was found to have a groin recurrence in the SLN negative groin, despite having undergone a full negative groin dissection [20]. Based on this retrospective data, this generates further questions of whether a contralateral groin dissection can be omitted, or whether adjuvant radiation to the bilateral groins and pelvis should be considered.

GOG-173 found the false negative predictive value of the SLN procedure to be 2% in patients with tumors <4 cm. The false negative predictive value was higher, at 7.4% in patients when the tumor was larger than 4 cm. A recent review by Covens et al. [21] concluded that there was not enough evidence to make a recommendation regarding SLN procedures in these patients with larger tumors. Our patient cohort included 20 patients with tumors larger than 4 cm who underwent SLN biopsy alone; we conclude that these patients are at increased risk of having more advanced disease with metastatic spread, at increased risk of recurrence and have a significantly worse PFS. Among patients with tumors >4 cm and negative SLN, the isolated groin recurrence rate may be higher than in patients with smaller tumors and negative SLN (9% vs 5%). Nonetheless, since the study only identified one groin recurrence in this group, numbers are small and we cannot determine whether the SLN procedure is safe; one would have to proceed with caution when offering SLN to such patients. Patients with a large tumor who are being considered for SLN biopsy only should be counselled about the possible increased risk of a false negative result. However, a subset of patients, specifically those who are poor surgical candidates, would still benefit from SLN rather than no groin staging.

The limitations of this study include the relatively small number of patients in each subgroup analyzed, the retrospective nature of the data collected, and missing information, mainly in patients receiving follow-up care at institutions closer to their home. This contributed to our relatively short medium follow-up of 31 months despite the data being collected over 8 years.

Because of the low incidence of vulvar cancer, a randomized trial to address these important questions about management of patients with positive SLNs may not be achievable, and thus practice will have to be guided by the results gained from multicenter and single center observational studies. Our study suggests that it may be safe to take a less aggressive approach in certain situations (micrometastasis, unilateral positive SLN, larger tumors in a patient who is a poor surgical candidate). We anxiously await the results of GROINS-V-II and other larger long-term studies needed to ensure that oncologic safety is not sacrificed.

## Conflict of interest

None of the authors have any conflict of interest to declare.

## CRediT authorship contribution statement

**Andra Nica:** Data curation, Formal analysis, Writing - original draft. **Allan Covens:** Writing - review & editing. **Danielle Vicus:** Writing - review & editing. **Rachel Kupets:** Writing - review & editing. **Ray Osborne:** Writing - review & editing. **Matthew Cesari:** Data curation. **Lilian T. Gien:** Conceptualization, Supervision, Formal analysis, Writing - review & editing.

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