P R A C E  O R Y G I N A L N E
*ginekologia*

# Characteristic features of recurrences of squamous cell carcinoma of the vulva

## Charakterystyczne cechy wznów raka płaskonabłonkowego sromu

Sznurkowski Jacek J., Emerich Janusz

Department of Gynecology of Medical University Gdansk, Poland

**Abstract**

***Aim:*** *The objective of this study was to find prognostic factors for the development of recurrences in patients who had undergone surgical treatment of vulvar cancer.*

***Methods:*** *The records of patients with primary vulvar cancer (n=104) treated at the Department of Gynaecological Oncology of the Medical University of Gdańsk between 1998 and 2001 were reviewed to identify those with squamous histology. Of the 93 thus identified 27 were excluded because of lack of standard treatment and 7 because of lack of radical surgery. A total number of 59 patients with squamous cell carcinoma were finally analyzed. For each record the age of the patient, size of the lesion, depth of invasion, margins of resection and lymph node status were analyzed. All patients were staged according to FIGO (1996). Recurrences were recorded by localization, whether local, groin or distant, and compared with a group of patients without any recurrences after radical surgery (n=59).*

***Results:*** *Recurrence was recorded in 19 cases (28.8%). A local (vulvar/perineal) recurrence was diagnosed in 10 patients (10/59, 16.9%), while 5 (5/59, 8.5%) developed groin recurrence and 4 (4/59, 6.8%) had distant recurrences. Multifocality of the primary tumour is an independent risk factor for local recurrence (HR: 3.12; 95% CI: 0.84–11.6). A metastatic node was the only independent prognostic risk factor for groin or distant recurrence (HR: 3.16; 95% CI: 0.94–10.2).*

***Conclusion:*** *Close follow-up of patients treated for vulvar cancer is recommended to detect recurrences at an early and potentially curable stage. Deep inguinal-femoral lymphadenectomy could be replaced with superficial inguinal groin dissection.*

Key words: **vulvar cancer** / **local neoplasm recurrence** / / **squamous cell carcinoma - SCC** /

**Corresponding author:**
Jacek J. Sznurkowski,
Department of Gynecology of Medical University Gdansk
80-401 Gdańsk, Kliniczna 1a str., Poland
tel. +48583493436
e-mail: jacek.sznurkowski@amg.gda.pl

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## Streszczenie

***Cel pracy:*** *Celem pracy było określenie czynników prognostycznych dla powstawania wznów raka płaskonabłonkowego sromu u pacjentów leczonych chirurgicznie.*

***Materiał i metoda:*** *Przeanalizowano historie chorób pacjentek leczonych z powodu pierwotnego raka sromu w Klinice Ginekologii i Ginekologii Onkologicznej w latach 1998-2001(n=104) w celu identyfikacji przypadków raka płaskonabłonkowego (n=93). Z dalszej analizy wyłączono 27 kobiet, u których wystąpiły odstępstwa od standardowego schematu leczenia chirurgicznego oraz 7 kobiet, których nie udało się zoperować w sposób radykalny.*

*Ostatecznie analizie poddano 59 chorych, u których oceniono: wiek w momencie rozpoznania choroby, średnicę zmiany pierwotnej, głębokość nacieku podścieliska, margines tkanek wokół guza, wieloogniskowość zmian na sromie oraz stan regionalnych węzłów chłonnych.*

*Zaawansowanie choroby określono zgodnie z FIGO (1996). Odnotowane wznowy podzielono na podstawie ich lokalizacji na: miejscowe, węzłowe i odległe. Porównano cechy kliniczne pacjentek w poszczególnych typach wznowy z cechami klinicznymi pozostałych chorych zoperowanych radykalnie.*

***Wyniki:*** *Wznowy wystąpiły w 19 przypadkach (19/59, 28,8%). Wznowę miejscową rozpoznano u 10 pacjentek, wznowę węzłową u 5 pacjentek (5/59, 8,5%) natomiast wznowa odległa wystąpiła u 4 kobiet (4/59, 6,8%). Wieloogniskowość zmiany pierwotnej jest niezależnym czynnikiem ryzyka wznowy miejscowej (HR: 3,12; 95% CI: 0,84–11,6). Przerzut do węzła chłonnego pachwinowego był jedynym niezależnym czynnikiem prognostycznym ryzyka wznowy węzłowej oraz odległej (HR: 3,16; 95% CI: 0,94–10,2).*

***Wniosek:*** *Stała opieka pooperacyjna nad kobietami poddanymi leczeniu chirurgicznemu z powodu raka sromu jest niezbędna dla wczesnego wykrywania niepowodzeń leczenia. Głęboka limfadenektomia pachwinowo-udowa może być zastąpiona przez powierzchowną limfadenektomię pachwinową.*

Słowa kluczowe: **rak sromu** / **wznowa raka sromu – miejscowa** / / **rak płaskonabłonkowy** /

## Introduction

Vulvar cancer has an incidence of 1–2 per 100,000 women per year and represents 3–5% of all gynaecological malignancies [1–3]. Squamous cell carcinoma (SCC) accounts for approximately 85–90% of vulvar cancers [4, 5]. Other vulvar neoplasms are melanoma 2.4–5% [4–6] and Bartholin gland carcinoma 1–3% [4, 7, 8]. Basal cell carcinoma [9], invasive Paget's disease and intraepithelial Paget's disease with underlying adenocarcinoma [10], sarcoma [11] and metastatic tumours of the vulva [12] are extremely rare, while endodermal sinus tumours [13, 14] and primary breast carcinoma developing within ectopic breast tissue [15] are exceptional. Verrucous carcinoma is a low aggressive variant of squamous cell carcinoma with a very low propensity for lymphatic spread [16].

The FIGO nomenclature and stage grouping for vulvar cancer are shown in Table I [17].

Tumour size, depth of invasion, lymph-vascular space involvement and lymph node status are the most important prognostic variables for SCC [17–23].

The incidence of positive groin nodes is mainly related to tumour size, depth of the stromal invasion, histological grade and lymph-vascular space involvement. The depth of stromal invasion measured from the most superficial dermal papilla adjacent to the tumour to the deepest focus of invasion is the strongest predictive factor for lymph node involvement in patients with T1 disease [24]. Pooled data from the literature revealed lymph node metastases in 10.7% of 578 patients with T1 squamous cell carcinoma, and positive node rates were 0%, 7.7%, 8.3%, 26.7%, and 34.2% for stromal invasion of depths of <1, 1.1–2, 2.1–3, 3.1–5, and >5mm, respectively. Positive contralateral groin nodes were found in 0.4% of 476 patients with lateral T1 tumours and negative ipsilateral nodes.

In the early 1950s Stanley Way introduced the radical vulvectomy with *"en bloc"* bilateral inguinal-femoral lymphadenectomy as standard treatment for all operative vulvar cancers [25, 26]. This strategy resulted in excellent survival rates with up to 90% of patients without lymph node metastases (stages I and II) achieving five-year survival and an overall survival rate of about 70% [27]. However, the complication rate was high because of the extent of the operation. Most of the early complications were infections and wound breakdown [28]. The main late postoperative complication was chronic leg oedema.

Over the last 30 years major modifications have been introduced to the standard surgical treatment to reduce morbidity without compromising the prognosis. These modifications are as follows: wide local excision instead of radical vulvectomy, no lymph node dissection in the case of a micro-invasive tumour (invasion <1mm), unilateral lymph node dissection in the case of a lateral tumour (a unilateral lesion with the medial margin >1cm from the midline, provided that the contralateral side of the vulva is histologically free of a second primary tumour) [29] and either superficial or deep inguinal-femoral lymphadenectomy by separate incisions instead of *"en bloc"* inguinal-femoral lymph node excision. All modifications introduced to the *"new standard"* surgical treatment in our Department are presented in Tables II and III.

A potential disadvantage of surgical treatment of SCC of the vulva is the possibility of recurrence. The most common site of recurrence is the vulvar region [30]. There may also be a second primary tumour (*de novo*), especially in patients with multifocal premalignant vulvar disease. Groin recurrences are less frequent but mostly develop earlier than vulvar recurrences or second primaries, and the prognosis is much worse than that for patients with a recurrence on the vulva [28, 31, 32].

**Table I.** FIGO nomenclature and Stage grouping of the carcinoma of the vulva.

| FIGO | | UICC |
|---|---|---|
| **Stage 0** | Carcinoma in situ, intraepithelial neoplasia grade III | TisN0M0 |
| **Stage I** | Tumour ≤2cm. confined to the vulva or perineum, no node metastasis | |
| | Ia- stromal invasion ≤1mm | T1aN0M0 |
| | Ib- stromal invasion >1mm | T1bN0M0 |
| **Stage II** | Tumour >2cm, confined to the vulva or perineum, no node metastasis | T2N0M0 |
| **Stage III** | Tumour with spread to lower urethra and/or vagina and/or anus [T3], and/or unilateral [N1] regional (inguinal-femoral nodes) node metastasis | T3N0M0<br>T1BN1M0<br>T2N1M0 |
| **Stage IV** | IVA - tumour with spread to upper urethra and/or bladder mucosa and/or rectal mucosa and/or pelvic [T4] and/or bilateral regional node metastases [N2]. | T4 AnyNM0<br>T1BN2M0<br>T2N2M0<br>T3N2M0 |
| | IVB- tumour with any distant metastasis including pelvic nodes | AnyTAnyNM1 |

**Table II.** Type of surgical treatment depended on primary vulvar tumor.

| Primary vulvar tumor | Type and extent of vulvar surgery | | |
|---|---|---|---|
| | wide local excision | vulvectomy (partial/total; superficial/deep) | vulvectomy with "en bloc" bilateral inguinofemoral lymphadenectomy |
| **T1A** | X | | |
| **T1B** | | X | |
| **T2** | | X | |
| **T2 >4 cm** | | | X |
| **T3** | Partial vaginectomy or uretherectomy combined with radical vulvectomy (to obtain adequate surgical margins) with bilateral groin dissection. | | |
| **T4** | Partial or total pelvic exenteration combined with radical vulvectomy and "en bloc" bilateral inguinofemoral lymphadenectomy. | | |

**Table III.** Type and extent of lymphadenectomy depended on primary vulvar tumor and it's localization.

| Primary vulvar tumor | Type and extent of lymphadenectomy | | |
|---|---|---|---|
| | unilateral | bilateral separate groin incisions | bilateral "en bloc" with vulva |
| **T1A** | | | |
| **T1B (unilateral lesion with the medial margin >1cm from the midline)** | X | | |
| **T1B (unilateral lesion with the medial margin <1cm from the midline)** | | X | |
| **T2 <4cm** | | X | |
| **T2 >4cm** | | | X |
| **T3, T4** | | | X<br>Combined with pelvic lymphadenectomy |

While local recurrences may be controlled with a new wide local excision and/or radiotherapy, groin recurrences are usually fatal [32].

The objective of this study was to analyze the patterns and frequency of recurrence of SCC of the vulva after *"new standard"* surgical treatment and to identify prognostic factors for the development of recurrences.

## Material and methods

Between January 1998 and December 2001 at the Department of Gynaecological Oncology of the Medical University of Gdańsk all 104 consecutive patients with primary vulvar cancer were treated by the same surgeons, the authors of this study (J.E and J.J.S). The records of these patients were reviewed to find cases with squamous histology strictly treated according to the rules described as *"new standard"* surgery (Tables II and III).

Of the 104 patients 11 had vulvar tumor with non-squamous cell carcinoma (one had adenocarcinoma, three had basal cell carcinomas, two melanomas, one sarcoma and four other tumours). Two of 93 patients with primary squamous cell carcinoma received chemoradiation before surgery because of very extensive vulvar cancer, and 25 patients did not undergo lymph node dissection because of extensive vulvar cancer or poor general condition. These were excluded. A total of 66 patients with SCC were finally analyzed in the study. All patients were staged according to the surgical and pathological staging system for vulvar cancer of the International Federation of Gynaecology and Obstetrics (FIGO) [33].

Between 1998 and 2001 sentinel node mapping, using blue dye and $^{99m}$Tc-labelled colloid was under evaluation in our Department, and we did not modify groin node dissection.

Radiotherapy (45-50Gy) was given to all patients with positive inguinal lymph nodes, unless there was only one intranodal lymph node metastasis in combination with well differentiated vulvar cancer.

The surgical treatment was not radical in 7 cases, and these were recommended for palliative treatment. The remaining 59 patients received regular follow-up every 3 months during the first two years, every 6 months for the subsequent three years and then once every 12 months. When a recurrence was diagnosed, the localization of the recurrence was recorded as local, groin or distant. Local recurrences were treated with wide local excision, whereas recurrences in the groin were treated with surgery and radiotherapy. Distant recurrences were treated with chemotherapy and/or radiotherapy.

Clinical and histopathological data were obtained from medical records. If not available from these, the data were obtained from questionnaires completed personally by the patients or by their relatives. Paraffin-embedded samples from all the patients analyzed were retrieved from the archives and prepared for central histopathological revision according to diameter, depth of invasion, the unifocality or multifocality of the tumour, the presence of lichen sclerosis, vulvar intraepithelial neoplasia and the width of the free surgical margins of the carcinoma. All the histopathological reports were made by the same pathologist.

### *Statistical methods*

Endpoints for this study were: local recurrences, groin recurrences and distant recurrences. Progression-free survival was defined as the time from the date of primary treatment to the date of diagnosis of the first recurrence, the death or the last date of follow-up. All clinical and histopathological factors included in this study (for an overview, see Table IV) were related to recurrence risk.

Univariate Cox regression analyses were performed for each prognostic factor separately, taking into account local, groin and distant recurrences. Hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated. Multivariate Cox regression analyses were performed, including all factors with an HR exceeding the value of 1.3 in the univariate model. With these variables a model was constructed using a stepwise procedure [34].

**Table IV.** FIGO and TNM classification of primary SCC of the vulva (n=66).

| FIGO | | No / % | No | % | UICC |
|---|---|---|---|---|---|
| Stage I | I A | 19 / 28.79% | 10 | 15.15 | T1aN0M0 |
| | I B | | 9 | 13.64 | T1bN0M0 |
| Stage II | | 21 / 31.82% | 21 | 31.82 | T2N0M0 |
| Stage III | | 11 / 16.67% | 1 | 1.52 | T3N0M0 |
| | | | 1 | 1.52 | T3N1M0 |
| | | | 9 | 13.64 | T2N1M0 |
| Stage IV | IV A | 6 / 9.1% | 2 | 3.03 | T4N1M0 |
| | | | 4 | 6.06 | T1BN2M0 |

To test the assumption of proportional hazards, an interaction term of a prognostic variable and a time-dependent covariate was added. A significant effect of this interaction term is that it denotes the presence of a time-dependent effect and thus a violation of the proportional hazards assumption. P values less than 0.05 were considered to be statistically significant. All analyses were performed with the program XLSTAT for Microsoft Excel.

## Results

### *Primary treatment and staging*

The age of the 66 patients at the time of the primary diagnosis was in the range 30–85 years, with a median age of 67 years. Wide local excision was performed in 7 cases (10.6 %) and superficial hemivulvectomy in 3 cases (4.6%). A total of 52 (78.8%) patients were treated with total radical vulvectomy and 4 (6.1%) with radical vulvectomy combined with partial (n=3) and total (n=1) exenteration. In 56 (84.9%) patients the margins were free of cancer after surgical treatment of a vulvar tumour, and 10 (15.1%) had cancer-positive margins, of whom 8/10 (80%) received postoperative radiotherapy, while 2/10 (20%) underwent re-excision.

In 46 of 66 (69.7%) patients bilateral inguinal-femoral lymphadenectomy was performed, while 10 (15.2%) patients underwent unilateral inguinal-femoral lymph node dissection. In 21 cases inguinal-femoral lymphadenectomy was extended to resection of enlarged pelvic nodules. In 10/66 (15.2%) cases (stage IA) no lymph node dissection was performed.

In 51 of 56 (91.1%) groin dissections separate incisions were performed, while 5/56 (8.9%) cases underwent *"en bloc"* inguinal-femoral lymph node excision. The average number of nodules received for histopathological examination from these lymphadenectomies, of which 46 were bilateral and 10 unilateral, was 6.7 (SD 5.0) for each side. In 21/56 (37.5%) cases metastatic nodules were found, the number of metastatic nodules for a groin-positive patient averaging 3.8 (SD 2.6). Extra-peritoneal pelvic lymphadenectomy was performed on all patients in this category. Metastases to the pelvic nodules were confirmed in 7/21 (33.3%) cases. These patients did not receive radical surgery and they were recommended for palliative treatment (radiotherapy combined with single-agent chemotherapy 5-FU). Five of them died during or shortly after treatment as a result of pneumonia, heart failure and sequelae of an avascular hip necrosis. Two deaths occurred before 11 months after primary treatment. Postoperative radiotherapy (45-50Gy) was given to 14 patients with positive inguinal-femoral lymph nodes.

See Table IV for an overview of the FIGO and TNM classifications within our group (n=66).

**Table V.** Characteristics of follow-up and recurrences in 66 patients with primary squamous vulvar cancer.

| Patients vulvar SCC (n=66) | |
|---|---|
| Radical surgical treatment | 59 (89.4%) |
| First recurrences | 19 (32.2%) |
| Local recurrences | 10 (16.9%) |
| Groin recurrences | 5 (8.5%) |
| Distant recurrences | 4 (6.8%) |
| Second local recurrence after first local recurrence (n=10) | Yes - 2 (20.0%) |
| | No - 8 (80.0%) |
| Overall median follow-up | 48 (range 4-200 months) |
| Median interval primary therapy to recurrence in months | 35 (range 4-192 months) |
| Median interval to first 1oca1 recurrence in months | 40 (range 5-100 months). |
| Median interval to groin recurrence in months | 11 (range 2,5-18 months) |
| Median interval to distant recurrence in months | 15 (range 2,5-18 months) |
| Overall relapse-free survival at 5 years | 52% |
| Local relapse-free survival at 5 years | 67% |

### *Recurrences*

See Table V (characteristics of follow-up and recurrences in 66 patients with primary squamous vulvar cancer). Analysis was made of recurrent disease only in those patients who had received radical surgical treatment (n=59). Recurrence was diagnosed in 19 (32.2%) of patients. Local recurrent disease was diagnosed in 10/59 (16.9%) patients and was treated with wide local excision in 7/10 patients and with radical vulvectomy in 3/10 patients. The interval from primary treatment to the first local recurrence ranged from 5 to 100 months with a median interval of 40 months (range 5–100 months). A second local recurrence developed in 2 (20.0%) out of 10 patients. The interval from first to second recurrence ranged from 2 to 24 months with a mean of 13 months.

In this group 2/2 (100 %) patients had lichen sclerosis. They were again treated with wide local excision. The site of the local recurrence was not analyzed. Groin recurrences were diagnosed in 5 (8.5 %) of the 59 patients. Three (60%) of these had negative and two (40%) had positive lymph nodes at primary treatment. All patients with positive lymph nodes at primary treatment underwent bilateral inguinal-femoral lymph node dissection completed with pelvic groin dissection (negative in all cases).

One of two patients with negative lymph nodes at primary treatment underwent unilateral inguinal-femoral groin dissection, while the second underwent bilateral inguinal-femoral groin dissection.

The average number of nodules received for histopathological examination in the five lymphadenectomies performed (two unilateral and three bilateral) was 7.5 (ranging from 4 to 15) for each side. The average number of positive lymph nodes at primary treatment was 2.5 (range 2 to 3) for each case. Radiotherapy (45-50Gy) was given to all patients with positive inguinal lymph nodes at primary treatment.

The median interval from primary treatment to groin recurrence was 11 months (ranging from 2.5 to 18 months). Of 5 patients with groin recurrences 4 received surgery and postoperative radiotherapy, while one patient received surgery and radiotherapy combined with single-agent chemotherapy (5-FU).

All patients with a groin recurrence died of vulvar cancer. The number of lymph nodes removed was analyzed. In patients without a groin recurrence the mean number of lymph nodes removed was 11.1 (SD=5.1) for each case of inguinal-femoral lymphadenectomy. In patients who developed a groin recurrence after negative lymph nodes the mean number of lymph nodes removed was 11 (SD=4.2). This difference is not significant (t=2.04: DF=40: *P*=0.984).

Distant recurrences were diagnosed in 4/59 (6.8%) patients. The median interval from primary treatment to the distant recurrence was 15 months (ranging from 9 to 40 months). Two patients received radiotherapy combined with single-agent chemotherapy (5-FU), while two others received only single-agent chemotherapy (5-FU). All died within 8 months of recurrence. The overall median follow-up time was 48 months (in a range of 4–200 months). The median interval between primary therapy and recurrence was 35 months (in a range of 4–192 months). Patients with tumours that recurred in the vulva had a longer median interval to recurrence of 40 months (in a range of 5–100 months) compared to those with distant recurrences, for whom the interval averaged 15 months (in a range of 9–40 months) and those with groin recurrences, for whom it averaged 11 months (in a range of 2.5–18 months)

The local relapse-free survival was 67% at 5 years. The overall relapse-free survival was 52% at 5 years.

**Table VI.** Clinical and histopathological characteristics related to the course of disease.

| Clinical and histopathological characteristics | Without any recurrence n=40 | Local recurrence n=10 | Groin recurrence n=5 | Distant recurrence n=4 |
|---|---|---|---|---|
| Age in years; median (range) | 68 (40-85) | 69 (57-74) | 57 (49-70) | 60 (30-73) |
| Multifocality present | 9 (22.5%) | 5 (50%) | 1 (20%) | 0 (0%) |
| Lichen sclerosis present | 17 (42.5%) | 8 (80%) | 1 (20%) | 0 (0%) |
| Maximum tumor width in mm; median (range) | 3 (0.4-7.5) | 1,75 (05-5.0) | 3 (2.2-8.0) | 3,25 (0.4-3.5) |
| Maximum depth invasion in mm; median (range) | 10 (1.0-30.0) | 6 (1.0- 25.0) | 13 (5.0-30.0) | 9 (4.0- 12.0) |
| Low differentiation grade present | 10 (25%) | 1 (10%) | 3 (60%) | 1 (25%) |
| Free Margins width in cm median (range) | 1 (0- 2.5) | 0.85 (0-2.0) | 1.5 (0.7-1.5) | 1.0 (0.8- 2.0) |
| Stadium I/II | 25 (62.5%) | 9 (90%) | 3 (60%) | 2 (50%) |
| Stadium III/IV | 14 (35%) | 1 (10%) | 2 (40%) | 2 (50%) |
| Inguinal-femoral groin index | 4.8 (SD 8.3)* | 3.3 (SD 10.5) | 6.6 (SD 9.2) | 25.6 (SD 37.8) |

* patients with follow up 12 months and longer

**Table VII.** Clinical and histopathological characteristics related to the course of disease: univariate analysis (HR95%CI) n=59.

| Clinical and histopathological characteristics | With local recurrence (n=10) compared to patients without any recurrence (n=40) | With groin and distant recurrence (n=9) compared to patients without any recurrence (n=40) |
|---|---|---|
| Age in years;<br><br><75 years<br>≥75 year | <br><br>1<br>0.35 (0.17 – 0.73) | <br><br>1<br>0.46 (0.22 – 0.94) |
| Multifocality<br><br>No<br>Yes | <br><br>1<br>3.12 (0.84-11.6) | <br><br>1<br>1.08 (0.5 – 2.35) |
| Lichen sclerosis<br><br>No<br>Yes | <br><br>1<br>1.25 (0.65 – 2.38) | <br><br>1<br>0.85 (0.44 – 1.65) |
| Maximum tumor width in mm; | 0.91 (0.65 – 1.28) | 1.1 (0.99 – 1.14) |
| Maximum depth invasion in mm; | 0.98 (0.89 – 1.08) | 1.06 (1.02- 1.10) |
| Low differentiation grade<br><br>No<br>Yes | <br><br>1<br>0.62 (0.29 – 1.28) | <br><br>1<br>0.78 (0.38 – 1.62) |
| Free Margins width in cm<br><br>≥1cm<br><1cm | <br><br>1<br>1.33 (0.65 – 2.60) | <br><br>1<br>0.92 (0.23 – 3.69) |
| Stadium<br>I/ II<br>III/IV | <br>1<br>0.19 (0.04 – 0.93) | <br>1<br>2.8 (0.81 – 6.16) |
| Inguinal-femoral groin<br><br>Negative<br>Positive | <br><br>1<br>0.23 (0.11 – 0.52) | <br><br>1<br>3.16 (0.94 – 1.2) |

***Clinical and histopathological characteristics in relation to recurrence***

Multifocality of the primary tumour and lichen sclerosis were more often present in patients with local recurrences. Multifocal disease was diagnosed in 50% of the patients who developed a local recurrence compared with 22.5% of the patients without a recurrence. A total of 42.5% of the patients without a recurrence had lichen sclerosis in contrast to 80% of the patients who developed a local recurrence. (Table VI).

Univariately, multifocality was the main risk factor for developing local recurrences with an HR of 3.12 (0.84–11.6). (Table VII).

Univariately, a free margin width of less than 1cm and lichen sclerosis were not significant for developing a local recurrence (HR: 1.33; 95% CI: 0.65–2.60; HR: 1.25; 95% CI: 0.65–2.38 respectively). However, these factors showed a trend and were used in multivariate analysis. Multivariately, multifocality was the only independent prognostic factor for local recurrence (HR: 2.98; 95% CI: 1.08–7.26). Univariately, a positive (metastatic) inguinal-femoral groin was the only independent prognostic risk factor for groin or distant recurrences (HR: 3.16; 95% CI: 0.94–10.2). (Table VII).

FIGO-staged II/III carcinoma showed a trend, but multivariate analysis was not performed because positive lymph nodes were a linearly dependent covariate with the FIGO stage.

## Discussion

We analyzed recurrences in a group of patients with SCC of the vulva who received a radical surgical treatment. All the patients were surgically treated strictly in accordance with the same rules (described in Tables II and III) and by the same surgeons. Radiotherapy (45-50Gy) was given to all patients with positive inguinal lymph nodes, unless there was only one intranodal lymph node metastasis in combination with well differentiated vulvar cancer. Paraffin-embedded samples from all the patients analyzed were retrieved from the archives and prepared for central histopathological revision according to diameter, depth of invasion, the unifocality or multifocality of the tumour, the presence of lichen sclerosis and other analyzed histopathological features. We found no retrospective study in the literature with a central histopathological revision of all specimens.

Recurrent disease was diagnosed in 19/59 (32.2%) patients. This is in accordance with the 15–35% reported in the literature [35, 36, 37].

Local recurrent disease was diagnosed in 10/59 (16.9%), in the groin in 5/59 (8.5%) and distant metastases in 4/59 (6.8%) cases. (Table VI).

This proportion of sites of recurrence is in agreement with Cavanagh et al., who provided an overview of different studies and reported recurrences in 15–40%, of whom more than half (55–90%) were local recurrences [38]. Skin bridge recurrences were not noted by us, although most of the groin dissections were performed with separate incisions (51/56, 91.1%). Our results are in accordance with others who also failed to find any skin recurrence after technical modifications in the treatment [39, 40].

The median interval from primary treatment to the first local recurrence was 40 months (in a range of 5–100 months). In the case of groin recurrence it was 11 months (range 2.5–18 months), and where the recurrence was distant it was 15 months (range 2.5–18 months). This is also in agreement with previous reports [41]. We found that multifocality of the tumour is an independent prognostic factor for local recurrences (HR: 2.98; 95% CI: 1.08–7.26). Wide local excision leaves part of the possible abnormal vulva in situ, and it is likely that this vulvar abnormality then becomes a local recurrence. Others have found that the only independent prognostic factor for local recurrences of SCC of the vulva is an age of over 74 years, although multifocality has also shown a strong trend in this analysis [41]. Inguinal-femoral lymphadenectomy was performed in 56 patients. Only in 21 (37.5%) cases metastatic nodules were found. Five (8.9%) women developed groin recurrences after inguinal-femoral lymph node dissection (n=56). Three of these had negative and two had positive lymph nodes at primary treatment. Unexpected groin relapse was found in 8.6% (3/35) of patients with negative inguinal-femoral lymph nodes. This result is of special concern because the relapse rate in patients with negative inguinal-femoral lymphadenectomy in the Gynaecology Oncology Group (GOG) protocols 36 and 37, was less than 1% [42, 43, 44].

In the literature unexpected groin relapses are reported in 5–7% of patients with negative inguinal-femoral lymph nodes after inguinal-femoral lymphadenectomy by separate incisions [31, 45, 46], which appears to be a substantial increase in groin recurrences in comparison with the *"en bloc"* approach [31, 47].

Two main mechanisms might account for groin relapse following negative inguinal-femoral lymphadenectomy. Firstly, there is the possibility of operative failure; some of the nodes that contain metastases were not resected. Secondly, there may be tumour emboli *"in transit"* in the lymphatic channels that are unresected in true node-negative patients. As we have indicated, in our results the mean number of removed lymph nodes was 6.7 (SD 5.0) for each side, similar to the number of groins reported in GOG protocols 36 and 37 [42, 43, 44].

We did not find any difference between the mean number of removed lymph nodes in patients with and without groin recurrence (t=2.04: DF=40: *P*=0.984). These data, and the fact that most groin dissections were performed with separate incisions (51/56, 91.1%), could suggest that the high rate of groin relapse was more likely to be caused by tumour emboli. As expected, patients with positive lymph nodes showed a significantly higher risk for developing a groin or distant recurrence in this study. This is in agreement with others who also found positive lymph nodes as a predictive factor [35, 36, 48]. The primary route of spread in vulvar cancer is by lymphatic embolization to the regional inguinal-femoral lymph nodes. The number of positive lymph nodes and extra-nodal tumour growth are of especially great importance for the patient's prognosis [18, 49].

## Conclusions

Surgical treatment of squamous cell carcinoma of the vulva (according to the rules detailed in Tables II and III) leads to a local recurrence rate of 16.9% and a groin recurrence rate of 8.5%. We did not note any recurrence in the skin bridge, although separate incisions were performed in 91.1% of cases.

Deep inguinal-femoral lymphadenectomy did not decrease the number of patients with lymph node recurrences in our series.

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