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Surgical-Pathologic Variables Predictive of Local Recurrence in Squamous Cell Carcinoma of the Vulva

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One hundred and thirty-five patients with squamous carcinoma of the vulva were treated at UCLA and City of Hope Medical Centers between 1957 and 1985. Sixty-two cases were stage I, 48 stage II, 18 stage III, and 7 stage IV. Twenty-one patients developed a local vulvar recurrence after primary radical resection. Ninety-one patients had a surgical tumor-free margin ≥8 mm on tissue section and none had a local vulvar recurrence. Forty-four patients had a margin <8 mm; 21 had a local recurrence and 23 did not ($P < 0.0001$). Of the 23 patients with a margin <8 mm who did not recur locally, 14 remained free of disease, and 9 had either advanced disease, declining health, or short follow-up. Depth of invasion is associated with local recurrence, with a 9.1-mm reference value correctly predicting outcome in 81.5% of cases. Increasing tumor thickness is associated with local recurrence, with a 10-mm reference value predictive of 90% nonrecurrence and 33% recurrences. A pushing border pattern is less likely to recur than an infiltrative growth pattern. Lymph-vascular space invasion has a combined predictive accuracy of 81.5%. Increasing keratin and >10 mitoses per 10 high-power fields correlate with local recurrence. Neither clinical tumor size nor coexisting benign vulvar pathology correlates with local recurrence. Fourteen of twenty-one patients with vulvar recurrence died of metastatic disease, four died of intercurrent disease, and three were alive at 32, 68, and 157 months, with 16 recurring in less than 1 year. Surgical margin is the most powerful predictor of local vulvar recurrence. Combining factors in a stepwise logistical regression does not significantly improve this predictive value. Accounting for specimen preparation and fixation, a 1-cm tumor-free surgical margin on the vulva results in a high rate of local control, whereas a margin <8 mm is associated with a 50% chance of recurrence.

INTRODUCTION

Primary carcinoma of the vulva constitutes 4% of all female genital tract malignancies. Historically, patients presented with locally advanced disease and traditional therapy consisted of radical vulvectomy with bilateral inguinofemoral lymphadenectomy. Since the initial description of this procedure, survival has improved and morbidity has decreased due to advances in both surgical techniques and supportive care [1–3]. Nevertheless, patients' sexual function and body image continue to suffer dramatically after radical vulvectomy [4,5].

With the increasing number of patients presenting with early-stage vulvar carcinomas, alternatives to radical vulvectomy have been developed and successfully employed [4,6–8]. Radical local excisions appear to have local recurrence rates equivalent to those of radical vulvectomy [4,6,7,9–11]. Regardless of the type of resection, the important surgical margin adjacent to the tumor will be the same.

Data comparing the size of a tumor-free margin with the risk and location of vulvar recurrence are, however, lacking. Generally, a 3-cm margin of "normal" skin surrounding the tumor is recommended to ensure adequate clearance and minimize the risk of local recurrence [4,7]. To avoid disfigurement or loss of organ function, lesions in close proximity to the clitoris, urethra, and anus may require compromise of this recommendation. When feasible, modification of the surgical technique to maintain urinary and fecal continence and preserve body image and sexual function is ideal. To assess the risk of local recurrence after primary surgery for vulvar carcinoma, we have reviewed the UCLA experience over a 28-year period.

MATERIALS AND METHODS

One hundred and thirty-five patients with invasive squamous cell carcinoma of the vulva underwent primary surgery at the UCLA Medical Center, Los Angeles, Cal-

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ifornia (119 cases), and the City of Hope Medical Center, Duarte, California (16 cases), between 1957 and 1985. All patients had their primary vulvar lesion treated with a radical vulvectomy or modified radical vulvectomy (117) or a radical local excision (18). One hundred and nine patients had a lymph node dissection, with 32 patients having positive nodes. Patient age ranged from 22 to 90 years (mean, 59 years).

All patients were staged according to the current International Federation of Gynecology and Obstetrics (FIGO) criteria after thorough record review. Sixty-two patients were clinical stage I, 48 stage II, 18 stage III, and 7 stage IV. The clinical records were reviewed for clinical lesion size, primary site of tumor, recurrence of disease, type of therapy, and follow-up status.

The histopathology of the original and subsequent operative specimens was reviewed by one pathologist (Y.S.F.). Surgical margins, depth of invasion, tumor thickness, cell type and grade (Broder's), growth patterns, lymph-vascular invasion, and mitotic activity were obtained on hematoxylin and eosin-stained (H&E) slides.

The distance between the tumor and the surgical margin was uniformly measured on tissue section on H&E slides using a ruler. The closest tumor-free margin was recorded taking into account both skin surface and deep tissue margins. Depth of stromal invasion and tumor thickness were measured from the most superficial adjacent dermal papilla and the top of the granular layer, respectively, to the deepest vertical extent of tumor growth. Three growth patterns were used. Pushing margins formed well-defined, rounded nests with smooth pushing borders and a minimal desmoplastic reaction. The infiltrative pattern, so called "spray" pattern, had discontinuous nests, cords, and single tumor cells with a desmoplastic stromal response. The mixed pattern consisted of mostly pushing borders with foci of tonguelike processes combined with small nests and/or isolated cells.

Statistical analysis of the frequency distribution of each parameter in relation to local vulvar recurrence was analyzed first by one-way analysis of variance (ANOVA) to calculate the F statistics and probabilities. This identified individual parameters that influence local vulvar recurrence. Then a stepwise logistic regression model (BMDP LR program) [12] was used to compute the probabilities of vulvar recurrence at different cutpoints. From this analysis, optimal thresholds for classification into recurrent and nonrecurrent groups were calculated to achieve the highest predictive accuracy.

RESULTS

Of the 135 patients, 21 had a local recurrence of invasive squamous vulvar carcinoma; 13 of these patients had simultaneous vulvar and other recurrences. All patients with a vulvar recurrence had their primary lesion treated with a radical vulvectomy. Only 18 patients with stage I lesions were treated using a local radical excision and none recurred. Table 1 lists the F statistics and probabilities of the measured parameters in relation to local vulvar recurrence. The closest surgical margin was measured as stated above on H&E slides. Several cuts at the closest margin were taken to ensure an accurate measurement. The exact location of the closest surgical margin was identified on the vulva and local recurrence occurred in that vicinity in all cases.

TABLE 1
Local Recurrence versus No Local Recurrence

Variable	F	P
Stage	41.47	0.0000
Margin	34.49	0.0000
Depth of invasion	17.42	0.0001
Tumor thickness	17.37	0.0001
Growth pattern	14.93	0.0002
Vascular invasion	9.06	0.0031
Amount of keratin	5.41	0.0215
Mitotic activity	5.18	0.0244
Tumor size	3.90	0.0505
Nucleoli	3.68	0.0573
Grade	1.75	0.1876

Increasing tumor-free distance was statistically significantly associated with decreasing local recurrence ($P < 0.0001$). Seven women had a positive margin and four had local vulvar recurrence. Two of these patients died of metastatic disease prior to local recurrence and the other patient had a microscopic deep margin and did not recur locally. None of 91 women with a surgical tumor-free margin $\geq$8 mm had a local vulvar recurrence. Of 44 women with a margin <8 mm, 21 (48%) had a local vulvar recurrence and 23 (52%) did not (Table 2). The highest overall predictive accuracy of 87% (117/135) correct was reached using a margin of 4.8 mm, with 91% (104/114) of the nonrecurrent and 62% (13/21) of the recurrent groups correctly identified.

The 23 women with a tumor-free surgical margin <8 mm who did not have a local recurrence consisted of two groups. One group (14 patients) had early-stage disease that did not recur and the other group (9 patients) had either advanced disease and thus short follow-up or poor health resulting in death from other causes.

The presence of local vulvar recurrence correlated with disease stage: two (3%) patients with stage I disease, six (12.5%) with stage II, eight (44%) with stage III, and five (71%) with stage IV disease recurred. All women with a local vulvar recurrence had a margin <8 mm. The proportion of women per stage with a margin <8 mm that did not recur locally can be seen in Table 3.

TABLE 2
Margin versus Vulvar Recurrence

Margin (mm)	Vulvar recurrence	No vulvar recurrence	Total
<8	21	23	44
≥8	0	91	91
Total	21	114	135
≤4.8	13	10	23
>4.8	8	104	112
Total	21	114	135

	Predicted (4.8 mm)		
	No recurrence	Recurrence	Total
No recurrence	104	10	114 (91.2%)
Recurrence	8	13	21 (61.9%)
Total	112	23	135 (86.7%)

$P = 1/(1 + e^{-y})$ $y = -1.25 + 0.444x$ (margin in mm)

If margin is ≤ 4.8 mm, a case is predicted to be in the recurrence group. If margin is > 4.8 mm, a case is predicted to be in the no recurrence group.

Depth of invasion was associated significantly ($P < 0.0001$) with local recurrence. Using a 9.1-mm reference value, an overall accuracy of 81.5% was achieved. The nonrecurrent group was correctly classified in 90% of patients and the recurrent group in 33%. None of 52 patients with a depth of stromal invasion <2.5 mm had a local vulvar recurrence. As depth of invasion increased to 10 mm, the recurrence rate increased to 30% (Table 4).

Increasing tumor thickness was associated significantly ($P < 0.0001$) with local vulvar recurrence. Overall, the highest predictive accuracy was seen with a cutoff of 10 mm, which identified 90% of the nonrecurrent and 33% of the recurrent lesions. None of 47 patients with a tumor thickness <2.5 mm had a local recurrence. As tumor thickness increased from 2.5 to 10.0 mm, the recurrence rate increased from 15 to 30% (Table 5).

Three types of growth patterns—pushing, pushing intermixed with infiltrative, and infiltrative—were examined. None of 44 women with a pushing border tumor had a local recurrence, whereas 13 (28%) of 46 with an infiltrative tumor pattern and 8 (17%) of 45 with a mixed tumor pattern recurred locally ($P = 0.0002$) (Table 6).

Lymph-vascular invasion was defined as a tumor-filled space lined by a distinct endothelium. Seven (39%) of eighteen patients with lymph-vascular invasion had a local recurrence, and 14 (12%) of 117 without invasion recurred on the vulva ($P = 0.0031$) (Table 7). The overall accuracy of lymph-vascular invasion in the prediction of local vulvar recurrence was 81.5%: 90% for the locally nonrecurrent group and 33% in the recurrent group.

TABLE 3
Patients with Margins <8 mm

Stage	All patients Total	<8 mm Total	Vulvar recurrence	No vulvar recurrence
I	62	7	2	5
II	48	20	6	14
III	18	11	8	3
IV	7	6	5	1
Total	135	44	21	23

The amount of laminated, acellular keratin material in the tumor correlated significantly ($P = 0.0215$) with local recurrence. This was quantified as none, low (0–25% of the tumor area), moderate (25–50%), and high (>50%). In 33 patients with greater than 25% keratin, 10 (30%) had a local recurrence, whereas 11 (11%) of 102 patients with <25% keratin recurred (Table 8). Seventy-five percent of the outcomes could be predicted using only the amount of keratin.

Mitotic activity correlated with outcome ($P = 0.0244$). This was examined using at least 20 high-power-fields (400×). Sixty-six patients had >10 mitoses per 10 high-power fields (HPF) and 16 (24%) of these recurred lo-

TABLE 4
Depth of Stromal Invasion and Local Recurrence

Depth (mm)	Recurrence	No recurrence	Total
<2.5	0	52	52
2.5–5.0	6	30	36
5.1–7.5	6	14	20
7.6–10.0	5	11	16
10.1–12.5	2	3	5
12.6–15.0	1	3	4
15.1–17.5	1	0	1
17.6–20.0	0	1	1
Total	21	114	135
≤9.1	14	103	117
>9.1	7	11	18
Total	21	114	135

	Predicted		
	No recurrence	Recurrence	Total
No recurrence	103	11	114 (90.4%)
Recurrence	14	7	21 (33.3%)
	117	18	135 (81.5%)

$P = 1/(1 + e^{-y})$ $y = 2.85 - 0.207x$ (depth of invasion in mm)

If depth of invasion is >9.1 mm, a case is predicted to be in the recurrence group. If depth of invasion is ≤9.1 mm, a case is predicted to be in the no recurrence group.

TABLE 5
Tumor Thickness and Local Recurrence

Thickness (mm)	Recurrence	No recurrence	Total
<2.5	0	47	47
2.5–5.0	6	34	40
5.1–7.5	6	15	21
7.6–10.0	3	7	10
10.1–12.5	4	7	11
12.6–15.0	0	1	1
15.1–17.5	2	2	4
17.6–20.0	0	1	1
Total	21	114	135
≤9.97	14	103	117
>9.97	7	11	18
Total	21	114	135

	Predicted		
	No recurrence	Recurrence	Total
No recurrence	103	11	114 (90.4%)
Recurrence	14	7	21 (33.3%)
	117	18	135 (81.5%)

$P = 1/(1 + e^{-y})$ $y = 2.88 - 0.2x$ (tumor thickness in mm)

If tumor thickness is >9.97 mm, a case is predicted to be in the recurrence group. If tumor thickness is ≤9.97 mm, a case is predicted to be in the no recurrence group.

cally, whereas 69 had <10 mitoses per 10 HPF and only 5 (7%) recurred (Table 9). However, using mitotic activity alone, only a 59% accuracy could be obtained.

Neither clinical size of the tumor, tumor grade, nor coexisting vulvar condyloma, dystrophy, dysplasia, or carcinoma *in situ* showed statistical correlation with local vulvar recurrence. Overall, there were 38 large cell nonkeratinizing and 97 large cell keratinizing tumors, and this did not correlate with recurrence. Forty-nine tumors were well differentiated, 52 moderately differentiated, and 34 poorly differentiated.

With a stepwise logistical model, combinations of factors were examined for their ability to predict local vulvar recurrence. Using margin and depth of invasion, 89% of nonrecurrences and 71% of the recurrences could be predicted accurately for an overall accuracy rate of 87%. The combination of stage and margin yielded an overall accuracy of 90%, 97% nonrecurrences and 76% recurrences. Overall, the ability to predict local vulvar recurrence using surgical margin could not be improved significantly by various combinations.

All 13 women with simultaneous vulvar and distant recurrence and 1 of 8 women with only local vulvar recurrence died of disease. Four women died of intercurrent disease and three were alive at 32, 68, and 157 months (Table 10). As expected, patients presenting with advanced disease and thus closer margins were more likely to recur and had poorer survival. Average time to local recurrence was 15 months; 16 women had a recurrence within 1 year, and 5 others at 24, 30, 42, 60, and 68 months.

TABLE 7
Lymph-Vascular Invasion and Vulvar Recurrence[a]

Lymph-vascular invasion	Vulvar recurrence	Total
Present	7 (39%)	18
Absent	14 (12%)	117
Total	21	135

[a] $P = 0.0031$.

DISCUSSION

Surgical treatment of vulvar squamous cell carcinoma can be modified to obtain less morbidity without sacrificing prognosis. In appropriate clinical settings, the en bloc radical vulvectomy has been successfully modified to local radical excision with or without groin dissections [7]. An array of surgical-pathological variables that would allow for the identification of a subset of patients at low risk for local vulvar recurrence are needed. Surgical resection could then be tailored to that patient's specific tumor location and likelihood of recurrence.

Regardless of the type of resection, traditionally a 2- to 3-cm tumor-free surgical margin has been desired. In our series, no one with a margin ≥8 mm had a local vulvar recurrence, whereas 48% with a margin <8 mm

TABLE 6
Growth Pattern and Vulvar Recurrence[a]

Growth pattern	Vulvar recurrence	Total
Pushing	0	44
Infiltrative	13 (28%)	46
Mixed	8 (17%)	45
Total	21	135

[a] $P = 0.0002$.

TABLE 8
Keratinization and Vulvar Recurrence[a]

Amount of keratin	Vulvar recurrence	Total
<25%	11 (11%)	102
≥25%	10 (30%)	33
Total	21	135

[a] $P = 0.0215$.

TABLE 9
Mitotic Activity and Vulvar Recurrence[a]

Mitoses per 10 HPF	Vulvar recurrence	Total
>10	16 (24%)	66
<10	5 (7%)	69
Total	21	135

[a] $P = 0.024$.

recurred locally. This percentage might be higher except for the nine women who died soon after diagnosis with advanced or intercurrent disease. Although a 4.8-mm margin achieved the highest overall predictive accuracy of recurrence, this resulted in a small group of false-negative patients. This is shown by the 8 patients who recurred in the group of 112 patients predicted not to recur (Table 2). If an 8-mm margin is used, none of the 91 patients predicted not to recur did so. Clinically, obtaining a margin that would eliminate recurrences is much more useful and the difference of 3.2 mm is insignificant. Since the measurement was based on formalin-fixed and paraffin-embedded tissue sections, the 8-mm tumor-free distance would approximate 10 mm in the fresh state after adjusting for 25% tissue shrinkage in fixatives. Therefore, the use of a 1-cm surgical margin should successfully prevent local vulvar recurrence and reduce the currently used standard margin by over 50%. The type of vulvar excision can be tailored to the location of the disease on the vulva. When lesions are near the clitoris, urethra, anus, and vagina, this reduction should increase our ability to spare these structures without predisposing to recurrence.

In addition, individualization of treatment can be accomplished by analyzing histopathological variables. In our series, depth of invasion, tumor thickness, tumor growth patterns, lymph-vascular space invasion, and amount of keratin were all significantly associated with local vulvar recurrence. Our data emphasize the importance of local vascular lymphatic involvement on the probability of vulvar recurrence.

No patient with a depth of stromal invasion or a tumor thickness <2.5 mm had a local recurrence. As both of these measurements increased to 10 mm, recurrence rates rose to approximately 30%. Tumors with a pushing border did not recur locally, whereas an infiltrating pattern was associated with recurrence rates of 30%. Lymph-vascular space invasion was seen in 18 tumors and 39% of these recurred after resection. Of 117 tumors without this invasion, only 14 recurred locally. Tumors with <25% keratin had a recurrence rate of only 11% and tumors with <10 mitoses per 10 HPF had a rate of 7%. Clinical tumor size, histologic grade, and coexistent vulvar pathology were not significant.

TABLE 10
Follow-up in 21 Patients with Vulvar Recurrence

Recurrence	Number who died
Vulvar and distant	13/13
Vulvar only	1/8
Total	14/21

Variables were combined in a stepwise logistical regression in an attempt to determine if a more powerful prediction of patients at low risk for recurrence could be found. When margin and depth of invasion were combined, the overall predictive accuracy was 87%, which was identical to that obtained by using margin alone. No combination could improve on the significance of the tumor-free margin.

Tumor stage was significantly associated with recurrence and this could probably be explained on the basis that patients with advanced metastatic disease usually receive smaller, palliative local resections since their outcome is determined by the extent of their metastases. Despite the fact that these patients die of distant disease, avoidance of a local recurrence can significantly improve their quality of life. Adherence to a 1-cm surgical tumor-free margin may reduce the local recurrence rates in this group. All five of our stage IV patients who died of disease suffered with a local recurrence and all had a margin <8 mm.

To reduce local vulvar recurrence after primary surgical treatment for vulvar squamous cell carcinoma, several variables may be studied preoperatively to identify a subgroup of patients at low risk. First, an adequate biopsy should be obtained. Histological evaluation can be used to delineate several of the variables described in this study and aid in the determination of the relative risk for local recurrence. Tumors that invade <2.5 mm, are <2.5 mm thick, have a pushing border, contain <25% keratin, and exhibit no lymph-vascular space invasion are unlikely to recur after excision using a surgical margin of 10 mm. Thus, treatment should be individualized.

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