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Original Articles

Pathologic factors are poorly associated with local recurrence of vulvar cancer

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Summary

Objective: To evaluate factors associated with an increased risk of local recurrence of squamous cell carcinoma (SCCA) of the vulva. *Materials and Methods:* Sixty-seven pathologic specimens of vulvar SCCA from 1991-2010 were retrospectively reviewed by a gynecologic pathologist. Medical records were reviewed for demographic, treatment, disease, and follow-up information. Risk of local recurrence was analyzed using Wilcoxon rank sum test and Fisher's analysis. Recurrence-free survival (RFS) was calculated with the Log Rank test and Cox regression. *Results:* Stage distribution in the 67 patients was: four (6.0%) Stage IA, 48 (77.6%) Stage IB, three (4.5%) Stage II, 11 (16.4%) Stage III, and one (1.5%) Stage IV. Overall five-year survival was 84% and median RFS was 84.8 months. Thirty-seven percent of patients (25/67) presented with a local recurrence at their initial re-presentation after initial treatment, accounting for 92.6% of initial recurrences. Rates of local recurrence were lower in non-Caucasians ($p = 0.047$) and when carcinoma in situ was present at the margin ($p = 0.03$). RFS was not affected by stage ($p = 0.60$), lymph node status ($p = 0.55$), tumor size (p=0.45), or pathologic factors. In particular, tumor distance from the surgical margins as a continuous variable or at any cut-off was not associated with either risk of local recurrence or shortened recurrence-free survival; however, there was a trend between prolonged RFS with increasing disease-free pathologic margin ($p = 0.09$). *Conclusion:* Risk of local recurrence and RFS of vulvar SCCA following surgical excision were not affected significantly by most clinical or pathologic variables, including lymph node status, and disease-free margin size.

Key Words: Vulvar neoplasm; Local neoplasm recurrence; Cancer-free margin; Surgical pathology.

Introduction

Vulvar cancer is a rare malignancy that accounts for about 4% of all gynecologic cancers with an estimated 4340 new cancers and 940 deaths from disease annually in the USA [1]. Ninety percent are squamous in origin. Treatment involves surgical excision with or without groin lymph node dissection or radiation. Overall survival exceeds 70% in operable cases [2] and is over 90% in cases without nodal involvement [3]. However, local vulvar/perineal recurrence rates of 15% to 35% are reported [4].

Although groin lymph node status is the strongest predictor for overall survival in vulvar squamous cell carcinoma (SCCA) [5-11], factors associated with local recurrence are less well defined [5, 8-10, 12-15]. As the radicality of vulvar excision of the primary vulvar tumor has decreased over the past 25 years in an effort to lessen morbidity, concern has focused on surgical margin status with respect to local recurrence rates associated with more modified radical or wide local excisions [2, 13, 16, 17]. Several studies have demonstrated a correlation between margin status and risk of local recurrence, but they have not determined how small a disease-free margin can be without increasing the risk of recurrence [13-15, 18]. Additionally, smaller vulvar excision margins have been associated with proximity to adjacent organs, such as the urethra, and may, therefore, be a non-modifiable factor [19]. How much margin status, as well as other clinico-pathologic factors affect local recurrence of vulvar cancer is still under investigation.

The present study objective was to examine the demographic, clinical, and pathologic factors, with particular emphasis on surgical margin status, for an association with local recurrence of squamous cell carcinoma of the vulva.

Materials and Methods

After obtaining Institutional Review Board approval, 83 vulvar squamous cell carcinoma specimens from 1991 to 2010 were identified from a comprehensive vulvar pathology database. Sixteen cases were excluded: nine whose final pathology was not invasive SCCA, nine with biopsies only, two with initial distant recurrence, and three whose follow-up information was not available. Information about patient characteristics (age, race, BMI, menopausal

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Table 1. — *Demographics and treatment history.*

	No local recurrence (n=42)	Local recurrence (n=25)	*p*-value for recurrence	*p*-value for recurrence free survival
Age (years)	66.8 ± 13	65.5 ± 15	0.76	0.78
Follow up (months) mean ± SD	63 (0.2 – 265)	76 (6 – 236)	0.41	-
Race			0.052	0.047
Caucasian	31 (77.5%)	25 (100%)		
African-American	6 (15.0%)			
Latina	2 (5%)			
Unknown	3 (7.1%)			
BMI	28.5 ± 6.3	31.6 ± 9.8	0.43	0.19
Menopausal status			0.10	0.36
Premenopausal	1 (2.4%)	4 (16%)		
Post-menopausal	35 (83.3%)	19 (76%)		
Unknown	2 (4.8%)	2 (8%)		
Smoking history			0.13	0.85
Yes	10 (23.8%)	13 (52%)		
No	21 (50.0%)	10 (40%)		
Unknown	11 (26.2%)	2 (8%)		
Abn Pap history			0.94	0.45
Yes	8 (19.0%)	5 (20%)		
No	22 (52.4%)	14 (56%)		
Unknown	12 (28.6%)	6 (24%)		
VIN history			0.58	0.22
Yes	4 (9.5%)	1 (4%)		
No	28 (66.7%)	20 (80%)		
Unknown	10 (23.8%)	4 (16%)		

VIN = vulvar intraepithelial neoplasia.

Table 2. — *Disease stage and treatment.*

	No local recurrence (n=42)	Local recurrence (n=25)	Recurrence odds ratio	*p*-value for recurrence	*p*-value for RFS
Stage				0.60	0.88
I	34 (82%)	18 (72%)	1.00	-	
II	2 (5%)	1 (4%)	0.94	0.71	
III	5 (12%)	6 (24%)	2.30	0.33	
IV	1 (2%)	0 (0%)	0	-	
Procedure				0.67	
Radical vulvectomy	19 (45%)	14 (56%)	1.96	0.35	
Modified radical vulvectomy	15 (36%)	8 (32%)	1.42	0.98	
Wide local excision	8 (19%)	3 (12%)	1.00	-	
Radiation before recurrence			0.39	0.27	
No	31(74%)	15 (60%)	1.00	-	
Yes	7 (17%)	8 (32%)	2.36	0.22	
Unkown	4 (10%)	2 (8%)	1.03	0.66	
Lymph node status			0.55	0.88	
LAD Pathology					
- Negative	21 (50%)	14 (56%)	1.00	-	
- Positive	6 (14%)	7 (24%)	1.50	0.29	
No LAD	11 (26%)	4 (16%)	0.55	0.33	
Unknown	4 (10%)	1 (4%)	-	-	

LAD: lymphadenectomy. RFS: recurrence-free survival.

status, smoking history, prior lower genital tract intraepithelial neoplasia), and stage based on the 2009 International Federation of Gynecology and Obstetrics (FIGO) guidelines, follow-up, and disease status were obtained from paper and electronic medical records for the 67 included patients. A local recurrence was defined as first re-presentation after initial treatment with vulvar or perineal disease.

A single gynecologic pathologist (AP) reviewed all of the hematoxylin and eosin (H&E) stained slides for tumor size, depth of invasion as measured from the most superficial dermal papilla, distance from the invasive tumor border to the closest lateral and deep specimen margins, histologic differentiation, lymphovascular space involvement (LVSI), and surrounding precursor lesion (differentiated or usual type vulvar intraepithelial neoplasia).

STATA and SAS software were used for statistical analysis. To describe risk of local recurrence, Wilcoxon rank sum test was used for continuous variables and Fisher's exact test for categorical variables. Recurrence-free survival was calculated using the Log Rank test for categorical variables and the Cox regression for continuous variables.

Results

Patient demographics with respect to local recurrence are presented in Table 1. There were no differences in age, BMI, menopausal status, smoking history, or prior lower genital tract neoplasia between patients who developed or did not develop a local recurrence. Of the 25 patients who presented with a local recurrence, all were Caucasian (p = 0.05). African American patients tended to be younger (mean age ± SD = 50 ± 11 years) compared to Caucasian (mean age = 68 ± 14 years), and Hispanic (mean age 70 ± 13 years) patients (p = 0.02).

Median follow-up was 65 months (range 0.2 − 265). Ten patients (14.9%) were lost to follow up within six months, and 38 patients (56.7%) were followed for more than five years. Twenty-five patients (37.3%) recurred. Nineteen patients (28.4%) died; six from progression to metastatic cancer, five of unknown causes, and eight from other causes. None died from locally recurrent disease. Overall survival was 84% at five years and 58% at ten years. Recurrence-free survival was 68% at five years and 38% at ten years.

Stage and treatment information are presented in Table 2. Rates of local recurrence did not differ by stage. Fifteen patients (22.4%) did not undergo inguinal-femoral lymphadenectomy: six were thought to be Stage IA, three planned for neoadjuvant radiation, three were too sick to undergo surgery, and three had no documented reason. These patients were staged by the appearance of lymph nodes on imaging or exam. One patient who did not have a lymphadenectomy had a fine needle aspiration positive for malignancy. No sentinel lymph nodes were performed. There was no difference in local recurrence rates based on type of local tumor resection or performance of inguinal lymphadenectomy. However, the recurrence rate was

Table 3. — *Pathologic factors.*

	No local recurrence (n=39)	Local Recurrence (n=25)	*p*-value for recurrence	*p*-value for recurrence free survival
Depth of invasion (mm) mean ± SD	5.8 ± 5.1	6.1 ± 4.8	0.41	0.88
Greatest dimension (cm) mean ± SD	2.5 ± 1.5	2.0 ± 0.89	0.28	0.67
Closest lateral margin (mm) mean ± SD	8.4 ± 6.6	7.0 ± 4.6	0.44	0.09
Closest deep margin (mm) mean ± SD	7.2 ± 4.6	11.8 ± 16.5	0.26	0.054
Differentiation			0.96	0.29
Well	2 (5%)	1 (4%)		
Well-moderate	28 67%)	17 (68%)		
Moderate	7 (17%)	5 (20%)		
Moderate-poor	4 (10%)	1 (4%)		
Poor	1 (2%)	1 (4%)		
Tumor type			0.10	0.11
Basaloid	3 (7%)	0 (0%)		
Keratinizing	34 (81%)	25 (100%)		
Non-keratinizing	5 (12%)	0 (0%)		
CIS at margin	6 (14%)	0 (0%)	0.08	0.03
LVSI	5 (12%)	2 (8%)	0.60	0.93

CIS: carcinoma in situ, LVIS: lymphovascular space invasion.

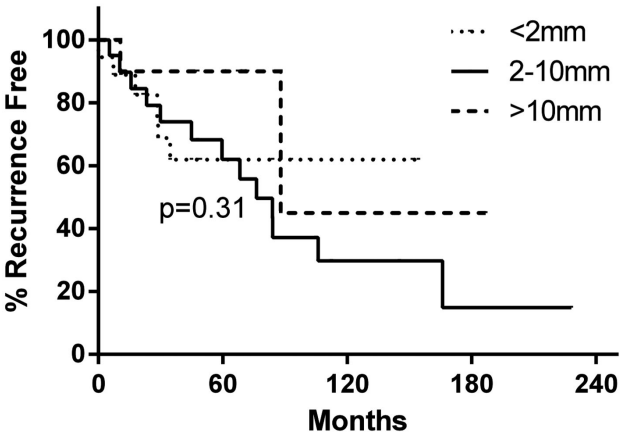

Figure 1. — Kaplan-Meier curve for recurrence based on disease-free margin size. Deaths due to causes other than disease were censored.

higher for patients with positive nodes (53%), in comparison to the group of patients with either pathologically or clinically negative nodes (36%) (OR 1.5, p = NS). Post-operative radiation treatment was given to 15 patients: six for positive nodes, four for close margins, and five for other reasons [concurrent vaginal cancer (two), Stage IV disease (one), no documented reason (one)]. Recurrence-free survival was shorter in the patients who received radiation (30 months *vs.* 85 months, $p = 0.27$).

Pathologic results are detailed in Table 3. Tumor size, depth of invasion, distance of the tumor from the lateral and deep margins, tumor differentiation, type of SCCA, and LVSI were not associated with rate of local recurrence; however, carcinoma in situ at the resection margin was associated with a lower rate of local recurrence. Tumor distance from the surgical margins as a continuous variable did not correlate with local recurrence rate or recurrence-free survival. Receiver operator characteristic (ROC) curves did not provide a tumor-free margin cut-off predictive of recurrence, and evaluation of three- and eight-mm cut-offs did not show a difference in RFS or recurrence rates; however, there did seem to be a trend toward longer RFS with larger tumor-free lateral margins (Figure 1).

Discussion

This study involved a systematic pathologic review of patients with vulvar SCCA by a single dedicated gynecologic pathologist to evaluate pathologic and demographic factors associated with recurrence of vulvar cancer. The present authors found that there were no tumor pathology factors (size, depth of invasion, tumor distance from the margin as a continuous variable or any cut-off between two and ten mm, LVSI, tumor differentiation or tumor type) predictive of patients at increased risk for recurrence.

A 2012 review of tumor pathologic factors found limited correlation with vulvar cancer recurrence. Recurrence was associated with tumor grade in only one of four studies, LVSI in three of seven studies, and depth of invasion in two out of six studies [5]. Likewise, tumor size was shown to be an independent predictor of recurrence in some studies [8, 9, 13, 20], while other studies failed to demonstrate a significant association [10, 12, 14, 15]. Vulvar intraepithelial neoplasia (VIN 3) has been reported to be associated with increased risk for recurrence [21], but surprisingly the present authors found decreased recurrence with VIN 3/ carcinoma-in-situ (CIS) at the specimen margin. Residual CIS within the tumor may be a sign of earlier or better differentiated disease, which would have a better prognosis, although differentiation itself was not associated with improved outcomes, which is consistent with prior studies [22].

In contrast to other pathologic factors, margin size has been considered one of the strongest predictors of recurrence [23]. Studies have found a correlation between recurrence and margin size less than five, eight or 15 mm [13-15], but these results have been challenged [18, 22]. The present study did not determine a particular minimum cancer-free margin, although there appeared to be a trend of prolonged RFS with larger pathologically negative margins. It is likely that this sample size was too small to detect an effect of margin size. However, residual cancer is in fact only found in one-third of patients with positive

margins [24], and up to 15% of vulvar cancers recur at a different site, presumably as a second primary [21]. Additionally, tumor factors not currently evaluated such as p16 and p53 may affect recurrence, independent of gross pathologic factors [5].

The strongest prognostic indicator for vulvar SCCA recurrence has consistently been shown to be lymph node status [5-11], although one study looking specifically at local recurrence did not show a correlation [22]. Aragona *et al.* found a relationship between number of involved lymph nodes and decreased survival in patients with margins > eight mm [21], which is a factor the present authors did not evaluate. Number of lymph nodes evaluated, independent of the number of positive lymph nodes, has also been noted to be associated with survival [25]. The present authors found no statistically-significant correlation between lymph node status and recurrence, although there was a trend towards increased recurrence in patients with surgically-proven positive lymph nodes.

Stage is correlated directly to lymph node status in the FIGO 2009 vulvar SCCA staging [26], and therefore the absence of correlation between stage and local recurrence is likely due to the lack of association with lymph node status. It has been suggested that the 1994 FIGO staging criteria may be more closely associated with recurrence risk [27], which may explain the absence of association in the present small study.

Race was the only demographic factor that correlated with recurrence. In the present study, African American women presented with cancer almost 20 years earlier than Caucasian and Latino women. The present results are similar to those found in the SEER database analysis as reported by Rauh-Hain *et al.* in 2013, where African-American women tended to present with vulvar cancer at a younger age and had lower mortality [28].

The strengths of this study were that a single dedicated gynecologic pathologist re-reviewed all the slides of the patient population treated at a single institution, standardizing the pathologic evaluation. Weaknesses of this study include the biases inherent in a retrospective chart review. The small size of the cohort is comparable to previous cohorts analyzing this rare cancer, but certainly limited the power of the conclusions of this analysis. Additionally, subjects were chosen by a review of surgical pathology specimen, which excluded patients who underwent non-surgical treatment. Loss to follow up was relatively high, and only half of patients were followed more than five years.

This study in which a single pathologist reviewed all pathologic slides, no pathologic factors were found to be predictive of local recurrence of vulvar SCCA. Positive lymph node status did increase the risk of recurrence, although the results are not statistically significant. No minimum disease-free margin size could be determined to help decrease the risk of recurrence. Overall, the present results do not suggest that less radical surgery increases the risk of local recurrence, however given the small sample size, further study is required to further determine the factors associated with vulvar cancer recurrence.

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