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Original Article

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An evaluation of prognostic factors, oncologic outcomes, and management for primary and recurrent squamous cell carcinoma of the vulva

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ABSTRACT

Objective: To evaluate prognostic factors, outcomes, and management patterns of patients treated for squamous cell carcinoma of the vulva.
Methods: One hundred sixty-four women were retrospectively identified with primary squamous cell carcinoma of the vulva treated at our institution between 1/1996–12/2018. Descriptive statistics were performed on patient, tumor, and treatment characteristics. The χ^2 tests and t-tests were used to compare categorical variables and continuous variables, respectively. Recurrence free survival (RFS), overall survival (OS), and disease-specific survival (DSS) were analyzed with Kaplan-Meier estimates, the log-rank test, and Cox proportional hazards.
Results: Median follow-up was 52.5 months. Five-year RFS was 67.9%, 60.0%, 42.1%, and 20.0% for stage I–IV, respectively. Five-year DSS was 86.2%, 81.6%, 65.0%, and 42.9% for stage I–IV, respectively. On multivariate analysis, positive margins predicted overall RFS (hazard ratio [HR]=3.55; 95% confidence interval [CI]=1.18–10.73; p=0.025), while presence of lichen sclerosus on pathology (HR=2.78; 95% CI=1.30–5.91; p=0.008) predicted local RFS. OS was predicted by nodal involvement (HR=2.51; 95% CI=1.02–6.13; p=0.043) and positive margins (HR=5.19; 95% CI=2.03–13.26; p=0.001). Adjuvant radiotherapy significantly improved RFS (p=0.016) and DSS (p=0.012) in node-positive patients. Median survival after treatment of local, groin, and pelvic/distant recurrence was 52, 8, and 5 months, respectively.
Conclusion: For primary treatment, more conservative surgical approaches can be considered with escalation of treatment in patients with concurrent precursor lesions, positive margins, and/or nodal involvement. Further studies are warranted to improve risk stratification in order to optimize treatment paradigms for vulvar cancer patients.

Keywords: Vulvar Cancer; Squamous Cell Carcinoma; Lichen Sclerosus; Radiotherapy

Synopsis

Vulvar cancer is a rare malignancy with limited prospective data to provide definitive clinical guidance. Here, we evaluate our experience with SCC of the vulva with respect to prognostic factors, outcomes, and management patterns. More conservative surgical approaches may be considered with treatment escalation in patients with concurrent precursor lesions, positive margins, and/or nodal involvement.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Data availability
Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Author Contributions
Conceptualization: L.J.Y., A.C.K., M.G.; Data curation: L.J.Y., A.C.K.; Formal analysis: L.J.Y.; Investigation: L.J.Y.; Methodology: L.J.Y., A.C.K.; Supervision: M.G.; Writing - original draft: L.J.Y., A.C.K.; Writing - review & editing: L.J.Y., A.C.K., T.R.J., W.E., S.P., D.S., M.G.

INTRODUCTION

Squamous cell carcinoma (SCC) of the vulva is a rare malignancy with an annual incidence of 2–3 per 100,000 women, accounting for only 5% of gynecologic cancers in the United States [1,2]. Surgery is the cornerstone of management, though the standard treatment of radical vulvectomy with either sentinel node or inguinofemoral lymphadenectomy (IFLD) may cause significant morbidity. As a result, there has been interest in a more individualized approach which minimizes surgical morbidity without compromising overall oncological outcome [3]. Even with aggressive treatment, the risk of recurrence remains high, with prior studies reporting this risk to be as high as 43% among vulvar cancer patients. [4-6]. Thus, we are left to find a delicate balance between reducing treatment-related morbidity and preventing the baseline-high risk of recurrence. This is challenging, as the rarity of vulvar cancer often precludes prospective data to provide definitive clinical guidance. Ideally, better risk stratification based on specific prognostic factors should identify patients who are most likely to benefit from treatment escalation while sparing those who would not necessarily benefit. Lymph node status is a clear prognostic factor in vulvar cancer, with 5-year survival rates declining from 80%–90% in early stage disease to 20%–40% when nodal involvement is present [2,7]. However, data regarding other prognostic factors remains unclear.

Management of recurrent disease is additionally challenging, as the patient population largely consists of older women, many with multiple comorbidities. There remains no standardized treatment for recurrent disease. Local recurrence accounts for more than 50% of recurrences and is primarily treated surgically, though with high rates of re-recurrence from 30% to 68% [4]. Management of groin and distant recurrence is much less clear, and even with treatment, prognosis is extremely poor [4,5]. The poor outcomes of recurrent disease highlight the need to continue optimizing management for this population.

The primary objective of this retrospective study is to evaluate our institutional experience managing 164 vulvar cancer patients over 22 years with regards to prognostic factors, oncologic outcomes, and management of primary and recurrent disease.

MATERIALS AND METHODS

A retrospective review was conducted of patients with primary invasive SCC of the vulva who were treated at our institution from January 1996 to December, 2018. This study was approved by the Institutional Review Board (IRB protocol number 2000023676).

1. Oncologic treatment

Patients were staged according to the 2009 International Federation of Gynaecology and Obstetrics (FIGO) staging system. Patients diagnosed before 2009 were re-staged. A modified Charlson comorbidity index (MCCI) [8] excluding malignancy criteria quantified patient comorbidities. Surgical treatment consisted of primary resection of the tumor with or without IFLD and/or sentinel node dissection (SND). All pathological specimens were reviewed by our institution's expert gynecological pathologists.

Adjuvant pelvic radiotherapy was delivered with modified segmental boost technique or intensity-modulated radiotherapy technique, given in 25–28 fractions for a total dose of 45–50.4 Gy with or without boosts to the vulva or groins with doses ranging from 5.4–21.6 Gy. Select patients in the early study period (1996–2004) received brachytherapy.

Chemotherapy regimens in the early study period (1996–2004) included cisplatin/5-fluorouracil (5-FU), 5-FU/mitomycin, gemcitabine, and paclitaxel. Following this period, chemotherapy largely consisted of weekly cisplatin or carboplatin concurrent with radiation for 4–6 weeks.

Patients had routine follow-up appointments with a gynecologic oncologist as per National Comprehensive Cancer Network (NCCN) guidelines [9], where they underwent routine clinical examination and/or biopsies. Recurrences were identified by imaging and/or biopsy and were categorized as local, groin, pelvic, or distant.

2. Statistical methods

Descriptive statistics were performed on patient, tumor, and treatment characteristics. The χ^2 tests or Fisher's Exact and t-tests or Wilcoxon rank sum tests were used to compare categorical variables and continuous variables, respectively. Overall survival (OS), disease-specific survival (DSS), and recurrence free survival (RFS) curves were generated using the Kaplan-Meier methods. RFS and OS time was counted from the date of initial treatment until the date of first recurrence/date of death or date of last follow-up. Kaplan-Meier curves were compared using the log-rank test. Univariate and multivariate Cox proportional hazards regression models were used to ascertain predictors of RFS and OS. Statistical analyses were performed using Stata version 16.

RESULTS

1. Patient, tumor, and treatment characteristics

One hundred sixty-four patients with invasive SCC of the vulva treated at our institution were retrospectively identified. **Table 1** details patient characteristics, **Table 2** details treatment, and **Table 3** details pathologic characteristics. Briefly, median age at diagnosis was 72 years (interquartile range [IQR]=58–80). Sixty-two (37.8%) patients were stage I, 47 (28.7%) were stage II, 43 (26.2%) were stage III, and 11 (6.7%) were stage IV. Histologically, 38 (25.0%) patients had grade 1 (well-differentiated), 92 (60.5%) had grade 2 (moderately-differentiated), and 22 (14.5%) had grade 3 (poorly-differentiated). Depth of invasion (DOI) was less than 1 mm for 4 patients (3.1%), between 1 and 5 mm for 64 (49.2%), and over 5 mm for 63 (47.7%). Lichen sclerosus (LS) was present in 28 patients (22.0%), low-grade squamous intraepithelial lesion in 7 (5.5%), high-grade squamous intraepithelial lesion in 57 (44.9%), and differentiated vulvar intraepithelial neoplasia (dVIN) in 7 (5.5%).

For primary treatment, 151 patients (92.1%) were treated surgically. Fourteen (8.5%) patients underwent wide local excision (WLE) or simple vulvectomy, 137 (83.5%) underwent radical vulvectomy. Unilateral and bilateral IFLD was performed for 64 (39.0%) and 81 (49.4%) patients, respectively. SND was completed in 22 patients (13.4%). Positive inguinal lymph nodes were observed in 49 patients (32.9%). For adjuvant therapy, 26 patients (15.9%) received adjuvant chemoradiation, 11 (6.7%) received adjuvant radiation alone, and 2 (1.2%) received adjuvant chemotherapy alone. One patient (0.6%) received neoadjuvant chemotherapy due to extensive involvement of the tumor.

Among patients who did not undergo surgery as primary treatment, 9 (5.5%) received chemoradiation, and 2 (1.2%) received radiation alone, 1 received chemotherapy alone (0.6%), and 1 (0.6%) received palliative care only.

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Table 1. Patient characteristics

Characteristic		Value
Age (yr)		
	<40	6 (3.7)
	40–49	17 (10.4)
	50–59	20 (12.2)
	60–69	30 (18.3)
	>70	91 (55.5)
Race		
	Non-Hispanic white	144 (87.8)
	Non-Hispanic black	8 (4.9)
	Hispanic	10 (6.1)
	Other	2 (1.2)
Menopause status (n=162)		
	Premenopausal	18 (11.0)
	Postmenopausal	143 (87.2)
MCCI		
	0	17 (10.4)
	1	19 (11.6)
	2	20 (12.2)
	3	45 (27.4)
	4	36 (22.0)
	5+	27 (16.5)
Smoking status (n=158)		
	Never	93 (58.9)
	Previous smoker	34 (21.5)
	Current smoker	30 (19.0)
Past surgical history		
	None	58 (35.4)
	Open	49 (30.0)
	Laparoscopic	22 (13.4)
	Hysteroscopic/vaginal	7 (4.3)
	Multiple	27 (16.5)
	Unknown	1 (0.6)
History of groin/vulvar surgery		
	No	148 (90.2)
	Yes	15 (9.1)
	Unknown	1 (0.6)
Presenting symptoms		
	New/growing lesion	70 (42.4)
	Irritation/pain	59 (35.8)
	Pruritis	46 (27.9)
	Groin symptoms	3 (1.8)
	Urinary symptoms	7 (4.2)
HPV status		
	Negative	11 (6.8)
	Positive	10 (6.1)
	Unknown	144 (87.3)
Immunocompromised status		
	No	160 (97.0)
	Yes	5 (3.0)
Cancer history		
	None	145 (87.9)
	Breast cancer	8 (4.9)
	Endometrial cancer	4 (2.4)
	Cervical cancer	2 (1.2)
	Other	6 (3.6)

Values are presented as number (%).
MCCI, modified Charlson comorbidity index.

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Table 2. Surgical management and adjuvant treatment

Characteristic	All patients (n=164)	Stage I (n=62)	Stage II (n=47)	Stage III (n=43)	Stage IV (n=11)	p-value
Primary treatment						<0.001
WLE/simple vulvectomy	14 (8.5)	9 (14.7)	1 (2.1)	3 (6.8)	0 (0.0)	
Radical vulvectomy	137 (83.5)	53 (85.5)	43 (91.5)	33 (76.7)	5 (50.0)	
Chemo/radiation	12 (7.3)	0 (0.0)	1 (2.1)	8 (18.6)	3 (30.0)	
Palliation	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	
Nodal dissection		(n=62)	(n=47)	(n=43)	(n=10)	0.048
None	19 (11.6)	11 (17.7)	2 (4.3)	3 (7.0)	3 (30.0)	
Unilateral	64 (39.0)	26 (41.9)	21 (44.7)	13 (30.2)	2 (20.0)	
Bilateral	81 (49.4)	25 (40.3)	24 (51.1)	27 (62.8)	4 (50.0)	
Sentinel node dissection						0.032
No	142 (86.6)	52 (83.9)	45 (95.7)	33 (76.7)	10 (100.0)	
Yes	22 (13.4)	10 (16.1)	2 (4.2)	10 (23.3)	0 (0.0)	
Nodes removed	9.5 (1–34)	7.3 (1–22)	9.2 (1–21)	11.8 (1–34)	14.9 (1–37)	0.004
Adjuvant therapy						<0.001
Radiation only	11 (6.7)	1 (1.6)	1 (2.1)	9 (20.9)	0 (0.0)	
Chemotherapy only	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (18.2)	
Chemoradiation	26 (15.9)	2 (3.2)	2 (4.3)	19 (44.2)	3 (27.3)	

Values are presented as median (interquartile range) or number (%).
WLE, wide local excision.

Table 3. Pathology characteristics

Characteristic	All patients (n=164)	Stage I (n=62)	Stage II (n=47)	Stage III (n=43)	Stage IV (n=11)	p-value
Staging (n=162)						
IA	18 (11.1)					
IB	44 (27.2)					
II	47 (29.0)					
IIIA	30 (18.5)					
IIIB	7 (4.3)					
IIIC	6 (3.7)					
IVA	8 (4.9)					
IVB	2 (1.2)					
Tumor laterality	(n=161)	(n=60)	(n=47)	(n=43)	(n=10)	0.226
Unilateral right	43 (26.7)	11 (18.3)	13 (27.7)	16 (37.2)	3 (30.0)	
Unilateral left	57 (35.4)	25 (41.7)	19 (40.4)	11 (25.6)	1 (10.0)	
Bilateral	36 (22.4)	13 (21.7)	9 (19.1)	9 (20.9)	5 (50.0)	
Midline	25 (15.5)	11 (17.7)	6 (12.7)	7 (16.3)	1 (10.0)	
Gross tumor involvement	(n=161)	(n=60)	(n=47)	(n=43)	(n=10)	0.108
Labia	132 (82.0)	44 (73.3)	41 (87.2)	35 (81.4)	10 (100.0)	
Clitoris/periclitoral	59 (36.7)	22 (36.7)	20 (42.6)	14 (32.6)	3 (30.0)	
Vagina	7 (4.3)	0 (0.0)	1 (2.1)	4 (9.3)	2 (20.0)	
Periurethral/urethra	19 (11.8)	3 (5.0)	5 (10.6)	8 (18.6)	3 (30.0)	
Posterior fourchette	5 (3.1)	4 (6.7)	0 (0.0)	1 (2.3)	0 (0.0)	
Perineum	11 (6.8)	5 (8.3)	3 (6.4)	3 (7.0)	0 (0.0)	
Mons	1 (0.6)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	
Perianal	7 (4.3)	1 (1.7)	1 (2.1)	4 (9.3)	1 (10.0)	
Histologic tumor Involvement	(n=132)	(n=50)	(n=40)	(n=36)	(n=6)	<0.001
None	118 (89.4)	50 (100.0)	35 (87.5)	30 (83.3)	3 (50.0)	
Vagina	4 (3.0)	0 (0.0)	1 (2.5)	2 (4.5)	1 (16.7)	
Urethra	4 (3.0)	0 (0.0)	3 (7.5)	1 (2.3)	0 (0.0)	
Anus	2 (1.5)	0 (0.0)	0 (0.0)	2 (4.5)	0 (0.0)	
Multiple	4 (3.0)	0 (0.0)	1 (2.5)	1 (2.3)	2 (33.3)	
Grade	(n=152)	(n=57)	(n=45)	(n=41)	(n=8)	0.038
1	38 (25.0)	22 (38.6)	9 (20.0)	5 (12.2)	1 (12.5)	
2	92 (60.5)	26 (45.6)	32 (71.1)	28 (68.3)	6 (75.0)	
3	22 (14.5)	9 (15.8)	4 (8.7)	8 (19.5)	1 (12.5)	

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Table 3. (Continued) Pathology characteristics

Characteristic	All patients (n=164)	Stage I (n=62)	Stage II (n=47)	Stage III (n=43)	Stage IV (n=11)	p-value
Precursor lesion on pathology	(n=127)	(n=48)	(n=38)	(n=36)	(n=5)	
Lichen sclerosis	28 (22.0)	9 (18.8)	9 (23.7)	7 (19.4)	2 (40.0)	0.758
LSIL	7 (5.5)	3 (6.3)	3 (7.9)	1 (2.8)	0 (0.0)	0.736
HSIL	57 (44.9)	28 (58.3)	16 (42.1)	10 (27.8)	3 (60.0)	0.039
dVIN	7 (5.5)	3 (6.3)	1 (2.6)	3 (8.3)	0 (0.0)	0.683
Maximum depth	(n=130)	(n=51)	(n=40)	(n=33)	(n=6)	0.035
<1 mm	4 (3.1)	3 (5.9)	0 (0.0)	1 (3.0)	0 (0.0)	
1–5 mm	64 (49.2)	33 (64.7)	18 (45.0)	11 (33.3)	2 (33.3)	
>5 cm	62 (47.7)	15 (29.4)	22 (55.0)	21 (63.6)	4 (66.7)	
Tumor size	(n=148)	(n=56)	(n=46)	(n=38)	(n=8)	0.002
<2 cm	31 (20.9)	22 (39.3)	6 (13.0)	3 (7.9)	0 (0.0)	
2–4 cm	85 (57.4)	25 (44.6)	31 (67.4)	24 (63.2)	5 (62.5)	
>4 cm	32 (21.6)	9 (16.1)	9 (19.6)	11 (28.9)	3 (37.5)	
LVSI	(n=114)	(n=41)	(n=36)	(n=34)	(n=3)	0.057
Negative	89 (78.1)	35 (85.4)	30 (83.3)	23 (67.6)	1 (33.3)	
Positive	25 (21.9)	6 (14.6)	6 (16.7)	11 (32.4)	2 (66.7)	
PNI	(n=21)	(n=4)	(n=10)	(n=6)	(n=1)	0.270
Negative	12 (57.1)	3 (75.0)	7 (70.0)	2 (33.3)	0 (0.0)	
Positive	9 (42.9)	1 (25.0)	3 (30.0)	4 (66.7)	1 (100.0)	
Tumor margins	(n=133)	(n=54)	(n=38)	(n=36)	(n=6)	0.007
Negative	83 (62.4)	35 (64.8)	28 (73.7)	18 (50.0)	3 (50.0)	
Positive	20 (15.0)	2 (3.7)	4 (10.5)	12 (33.3)	2 (33.3)	
Close (<5 mm)	30 (22.6)	17 (31.5)	6 (15.8)	6 (16.7)	1 (16.7)	
Precursor lesion at margin	(n=124)	(n=49)	(n=36)	(n=34)	(n=5)	0.686
Lichen sclerosis	2 (1.6)	1 (2.0)	0 (0.0)	1 (2.9)	0 (0.0)	
LSIL	2 (1.6)	1 (2.0)	0 (0.0)	1 (2.9)	0 (0.0)	
HSIL	29 (23.4)	14 (28.6)	9 (25.0)	4 (11.8)	2 (40.0)	
dVIN	3 (2.4)	1 (2.0)	0 (0.0)	1 (2.9)	0 (0.0)	
Groin lymph node involvement	(n=149)	(n=52)	(n=46)	(n=42)	(n=8)	<0.001
No	100 (67.1)	52 (100.0)	46 (100.0)	0 (0.0)	1 (12.5)	
Yes	49 (32.9)	0 (0.0)	0 (0.0)	42 (100.0)	7 (87.5)	

Values are presented as number (%).
dVIN, differentiated vulvar intraepithelial neoplasia; HSIL, high grade squamous intraepithelial lesion; LSIL, low grade squamous intraepithelial lesion; LVSI, lympho-vascular invasion; PNI, perineural invasion.

2. Treatment outcomes

Median follow-up time was 52 months (IQR=13–116). Five-year RFS and DSS for the entire cohort was 63.0% and 76.4%, respectively. Sixty-eight patients (41.2%) had evidence of recurrence. Median time to recurrence was 24 months (IQR=7–83). Five-year RFS was 67.9%, 60.0%, 42.1%, and 20.0% for stage I, II, III, and IV, respectively. Median OS was 63 months (IQR=19–127), and 5-year DSS was 86.2%, 81.6%, 65.0%, and 42.9% for stage I–IV, respectively. Of the patients with recorded date of death, 36 (39.6%) were attributed to vulvar cancer, while for 55 (60.4%), the cause of death was unrelated (n=17) or unknown (n=38).

Patterns of recurrence are described in **Table 4**. Forty-seven (28.7%) had isolated local recurrence, 1 (0.6%) had local and groin recurrence, 10 (6.1%) had isolated groin recurrence, 1 (0.6%) had groin and pelvic recurrence, 2 (1.2%) had groin and distant recurrence, 3 (1.8%) had isolated pelvic recurrence, 2 (1.2%) had pelvic and distant recurrence, and 2 (1.2%) had distant recurrence only.

Table 5 summarizes the unadjusted hazard ratios for RFS, local RFS, OS, and DSS. On univariate analysis, increased MCCI (p=0.010), stage III (p=0.023) and stage IV (p=0.002), locally advanced disease involving the vagina/anus/urethra (p=0.013), nodal involvement (p=0.009), and number of positive nodes (p=0.012) were associated with poorer overall

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Table 4. Patterns of recurrence

Variables	No recurrence	Local recurrence	Groin recurrence	Pelvic recurrence	Distant recurrence	Total number who recurred
Total (n=164)	96 (58.5)	48 (29.3)	14 (8.5)	6 (3.7)	6 (3.7)	68 (41.5)
Stage (n=163)						
I (n=62)	40 (64.5)	18 (29.0)	4 (6.5)	1 (1.6)	1 (1.6)	22 (35.5)
II (n=47)	29 (61.7)	17 (36.2)	1 (2.1)	0 (0.0)	0 (0.0)	18 (38.3)
III (n=43)	22 (51.2)	10 (23.3)	7 (16.3)	4 (9.3)	4 (9.3)	21 (48.8)
IV (n=10)	4 (40.0)	2 (20.0)	2 (20.0)	1 (10.0)	1 (10.0)	6 (60.0)
Nodal status						
Negative (n=100)	64 (64.0)	30 (30.0)	5 (5.0)	2 (2.0)	1 (1.0)	36 (36.0)
No radiation (n=91)	59 (64.8)	28 (30.8)	4 (4.4)	1 (1.1)	0 (0.0)	32 (35.2)
Adjuvant radiation +/− chemo (n=7)	4 (57.1)	1 (14.3)	1 (14.3)	1 (14.3)	1 (14.3)	3 (42.9)
Primary chemoradiation (n=1)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
Neoadjuvant chemo (n=1)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Positive (n=49)	24 (49.0)	11 (22.4)	9 (18.4)	4 (8.2)	5 (10.2)	25 (51.0)
No radiation (n=11)	5 (45.5)	2 (18.2)	2 (18.2)	1 (9.1)	2 (18.2)	6 (54.5)
Adjuvant radiation +/− chemo (n=30)	17 (56.7)	7 (23.3)	5 (8.3)	1 (3.3)	2 (6.7)	13 (43.3)
Primary chemoradiation (n=8)	2 (25.0)	2 (25.0)	2 (25.0)	2 (25.0)	1 (12.5)	6 (75.0)
Margin status						
Negative (n=83)	50 (60.2)	24 (28.9)	5 (28.9)	3 (3.6)	5 (6.0)	33 (39.8)
No adjuvant therapy (n=64)	40 (62.5)	20 (31.3)	3 (4.7)	1 (1.6)	0 (0.0)	24 (37.5)
Adjuvant radiation +/− chemo (n=16)	9 (56.3)	4 (25.0)	2 (12.5)	0 (0.0)	2 (12.5)	7 (42.8)
Primary chemoradiation (n=2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)	1 (50.0)	2 (100.0)
Neoadjuvant chemo (n=1)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Close (<5 mm) (n=30)	17 (56.7)	11 (36.7)	2 (6.7)	0 (0.0)	0 (0.0)	13 (43.3)
No adjuvant therapy (n=22)	13 (59.1)	8 (36.4)	1 (4.5)	0 (0.0)	0 (0.0)	9 (40.9)
Adjuvant radiation +/− chemo (n=8)	4 (50.0)	3 (37.5)	1 (12.5)	0 (0.0)	0 (0.0)	4 (50.0)
Positive (n=20)	10 (50.0)	3 (15.0)	5 (25.0)	3 (15.0)	1 (5.0)	10 (50.0)
No adjuvant therapy (n=7)	3 (42.9)	2 (28.6)	2 (28.6)	1 (14.3)	0 (0.0)	4 (57.1)
Adjuvant radiation +/− chemo (n=13)	7 (53.8)	1 (7.7)	3 (23.1)	2 (15.4)	1 (7.7)	6 (46.2)
Lichen sclerosus						
Negative (n=99)	60 (60.6)	21 (21.2)	11 (11.1)	6 (6.1)	6 (6.1)	39 (39.4)
No radiation (n=69)	44 (63.8)	17 (24.6)	6 (8.7)	2 (2.9)	2 (2.9)	25 (36.2)
Adjuvant radiation +/− chemo (n=26)	15 (57.7)	3 (11.5)	5 (19.2)	2 (7.7)	3 (11.5)	11 (42.3)
Primary chemoradiation (n=4)	1 (25.0)	1 (25.0)	0 (0.0)	2 (50.0)	1 (25.0)	3 (75.0)
Positive (n=28)	14 (50.0)	14 (50.0)	1 (7.1)	0 (0.0)	0 (0.0)	14 (50.0)
No radiation (n=20)	9 (45.0)	11 (55.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (55.0)
Adjuvant radiation +/− chemo (n=7)	4 (57.1)	3 (42.9)	1 (14.3)	0 (0.0)	0 (0.0)	3 (42.9)
Neoadjuvant chemo (n=1)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Values are presented as number (%).

RFS. Local RFS was predicted by the presence of LS on pathology (p=0.017) or at the margin (p=0.03). DSS was predicted by more advanced age (p=0.001), increased comorbidity index (p=0.003), stage III (p=0.015) or stage IV (p=0.001) disease, grade 3 disease (p=0.028), DOI greater than 5 mm (p=0.029), nodal involvement (p=0.004), and positive margins (p < 0.001). On multivariate analysis (**Table 6**), increased MCCI (p=0.029) and positive margins (p=0.025) remained significant predictors for overall RFS. For local RFS, the presence of LS (p=0.008) on pathology remained a significant predictor. DSS was predicted by DOI greater than 5 mm (p=0.010) and positive margins (p=0.011).

Margin status

Surgical margins were negative for malignancy in 83 patients (62.4%), positive in 20 (15.0%), and within 5 mm in 30 (22.6%). Overall recurrence rates in patients with positive, close, and negative margins were 43.3%, 50.0%, and 39.8%, respectively, while local recurrence rates were 15.0%, 36.7%, and 28.9%, respectively (**Table 4**). Among the 20 patients with positive surgical margins, 13 (65%) were treated with adjuvant radiation +/− chemotherapy. Six

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Table 5. Univariate analysis for factors associated with RFS, OS, and DSS

Characteristic	Overall RFS		Local RFS		OS		DSS	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.02 (1.00–1.04)	0.056	1.02 (0.99–1.04)	0.115	1.07 (1.05–1.09)	<0.001	1.05 (1.02–1.08)	0.001
Race								
Non-Hispanic white	Reference							
Non-Hispanic black	0.86 (0.27–2.75)	0.794	0.75 (0.18–3.11)	0.690	0.16 (0.02–1.17)	0.072	0.44 (0.06–3.25)	0.424
Hispanic	1.28 (0.40–4.13)	0.679	1.57 (0.48–5.12)	0.453	1.25 (0.39–4.04)	0.705	2.39 (0.72–7.94)	0.156
Menopausal vs. Premenopausal	1.00 (0.48–2.09)	0.995	1.12 (0.47–2.66)	0.790	6.57 (2.06–20.93)	<0.001	7.61 (1.04–55.90)	0.046
MCCI	1.21 (1.05–1.40)	0.010	1.20 (1.01–1.42)	0.036	1.41 (1.24–1.60)	<0.001	1.34 (1.10–1.64)	0.003
Stage								
I	Reference							
II	1.22 (0.65–2.28)	0.529	1.43 (0.74–2.79)	0.289	1.37 (0.80–2.34)	0.250	1.52 (0.62–3.77)	0.363
III	2.01 (1.10–3.66)	0.023	1.11 (0.51–2.41)	0.789	1.83 (1.07–3.15)	0.028	2.83 (1.23–6.57)	0.015
IV	4.19 (1.68–10.48)	0.002	1.25 (0.28–5.41)	0.769	4.04 (1.82–8.96)	0.001	6.80 (2.26–20.50)	0.001
Tumor location								
Unilateral right	Reference							
Unilateral left	1.03 (0.53–1.98)	0.935	1.51 (0.65–3.53)	0.341	1.01 (0.60–1.73)	0.951	0.91 (0.39–2.13)	0.828
Bilateral	1.30 (0.65–2.61)	0.460	1.77 (0.72–4.33)	0.212	0.81 (0.43–1.52)	0.506	0.93 (0.36–2.43)	0.879
Midline	1.11 (0.51–2.42)	0.796	1.91 (0.74–4.98)	0.183	0.86 (0.43–1.75)	0.685	1.17 (0.43–3.16)	0.755
Presence of precursor lesion								
Lichen sclerosis	1.12 (0.61–2.07)	0.582	2.29 (1.16–4.51)	0.017	1.19 (0.70–2.01)	0.523	0.83 (0.34–2.04)	0.687
LSIL	1.04 (0.33–3.35)	0.942	1.11 (0.27–4.65)	0.883	1.41 (0.51–3.90)	0.511	0.75 (0.10–5.51)	0.774
HSIL	1.00 (0.58–1.72)	0.999	0.77 (0.39–1.53)	0.453	0.95 (0.59–1.54)	0.847	1.23 (0.59–2.55)	0.577
dVIN	0.66 (0.16–2.72)	0.564	0.56 (0.08–4.08)	0.563	0.53 (0.07–3.85)	0.528	0.83 (0.11–6.18)	0.857
Grade								
Grade 1	Reference							
Grade 2	1.18 (0.59–2.34)	0.119	1.66 (0.81–3.37)	0.165	1.35 (0.82–2.25)	0.241	2.47 (0.94–6.47)	0.066
Grade 3	1.47 (0.60–3.61)	0.395	0.22 (0.03–1.75)	0.154	1.66 (0.81–3.39)	0.165	3.65 (1.15–11.58)	0.028
Depth of invasion								
≤5 mm	Reference							
>5 mm	1.71 (0.99–2.96)	0.053	1.39 (0.73–2.66)	0.320	1.58 (0.99–2.51)	0.053	2.44 (1.09–4.63)	0.029
Tumor size								
<2 cm	Reference							
2–4 cm	1.18 (0.59–2.34)	0.638	0.75 (0.36–1.55)	0.436	0.95 (0.54–1.67)	0.863	1.57 (0.59–4.17)	0.364
>4 cm	1.70 (0.78–3.70)	0.185	0.77 (0.30–1.98)	0.582	1.70 (0.89–3.25)	0.109	2.77 (0.95–8.14)	0.063
Vaginal, anal, or urethral involvement	2.81 (1.25–6.32)	0.013	1.83 (0.55–6.09)	0.326	3.35 (1.62–6.92)	0.001	1.98 (0.59–6.65)	0.271
LVSI	0.88 (0.42–1.83)	0.732	0.55 (0.19–1.59)	0.272	1.17 (0.66–2.08)	0.582	1.43 (0.63–3.27)	0.395
PNI	2.64 (0.74–9.46)	0.137	0.52 (0.05–5.16)	0.578	1.84 (0.58–5.78)	0.298	2.91 (0.68–12.43)	0.150
Number of nodes removed	0.99 (0.95–1.02)	0.472	0.99 (0.95–1.03)	0.649	0.99 (0.97–1.02)	0.617	0.99 (0.95–1.04)	0.686
Presence of positive node	2.00 (1.19–3.36)	0.009	1.00 (0.50–2.12)	0.984	1.53 (0.97–2.41)	0.067	2.54 (1.34–4.83)	0.004
Number of positive nodes	1.37 (1.07–1.75)	0.012	1.15 (0.82–1.62)	0.416	1.10 (0.89–1.35)	0.397	1.25 (0.94–1.66)	0.131
Sentinel node dissection	0.72 (0.33–1.58)	0.411	0.47 (0.14–1.51)	0.204	0.93 (0.39–2.19)	0.866	1.06 (0.37–3.08)	0.913
Tumor margin status								
Negative	Reference							
Positive	1.87 (0.92–3.81)	0.084	0.76 (0.23–2.54)	0.658	2.96 (1.68–5.22)	<0.001	3.05 (1.37–6.77)	0.006
Close (<5 mm)	1.31 (0.69–2.51)	0.411	1.73 (0.83–3.58)	0.143	1.30 (0.67–2.51)	0.435	0.80 (0.27–2.36)	0.675
Precursor lesion at margin								
Lichen sclerosis	5.33 (0.71–40.07)	0.104	9.77 (1.24–76.78)	0.030	6.46 (0.85–48.77)	0.071	9.96 (1.27–78.06)	0.029
LSIL	5.31 (1.24–22.71)	0.024	3.72 (0.49–28.21)	0.204	4.16 (0.98–17.55)	0.053	3.69 (0.48–28.22)	0.208
HSIL	5.22 (0.70–39.22)	0.108	0.82 (0.31–2.15)	0.688	1.40 (0.75–2.59)	0.286	2.14 (0.33–19.48)	0.370
dVIN	1.75 (0.42–7.34)	0.446	1.42 (0.19–10.68)	0.731	1.46 (0.20–10.82)	0.281	2.54 (0.33–19.48)	0.370
Adjuvant therapy								
None	Reference							
Adjuvant radiation alone	2.00 (0.84–4.73)	0.115	1.25 (0.38–4.10)	0.713	1.01 (0.46–2.23)	0.981	0.70 (0.16–3.01)	0.635
Adjuvant chemotherapy alone	8.85 (2.08–37.70)	0.003	4.58 (0.60–34.73)	0.141	3.12 (0.42–22.94)	0.263	5.34 (0.71–40.37)	0.104
Adjuvant chemoradiation	0.99 (0.48–2.03)	0.972	0.63 (0.25–1.61)	0.332	1.10 (0.57–2.09)	0.779	1.59 (0.68–3.70)	0.286
Time period								
1996–2007	Reference							
2008–2018	1.26 (0.77–2.06)	0.364	1.06 (0.58–1.93)	0.858	1.09 (0.66–1.80)	0.743	1.28 (0.62–2.67)	0.507

CI, confidence interval; DSS, disease-specific survival; dVIN, differentiated vulvar intraepithelial neoplasia; HR, hazard ratio; HSIL, high grade squamous intraepithelial lesion; LSIL, low grade squamous intraepithelial lesion; LVSI, lympho-vascular invasion; MCCI, modified Charlson comorbidity index; OS, overall survival; PNI, perineural invasion; RFS, recurrence free survival.

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Table 6. Multivariate analysis for factors associated with RFS and OS

Characteristic	Overall RFS		Local RFS		OS		DSS	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age					1.04 (0.99–1.09)	0.097		
Race								
Non-Hispanic white					Reference		Reference	
Non-Hispanic black					0.7 (0.006–1.00)	0.050	0.8 (0.5–1.34)	0.080
Hispanic					7.84 (1.94–31.65)	0.004	11.74 (2.40–57.43)	0.002
MCCI	1.30 (1.03–1.65)	0.029			1.28 (0.88–1.86)	0.190	1.38 (0.95–2.00)	0.089
Lichen sclerosis			2.78 (1.30–5.91)	0.008				
Stage								
I	Reference							
II	0.73 (0.33–1.62)	0.439						
III	1.06 (1.03–1.27)	0.072						
IV	2.78 (0.26–29.26)	0.075						
Depth of invasion >5 mm					1.93 (0.98–3.83)	0.059	3.64 (1.36–9.68)	0.010
Grade								
1	Reference							
2	1.89 (0.73–4.91)	0.190	1.29 (0.57–2.90)	0.540				
3	1.07 (0.31–3.74)	0.914	0.21 (0.02–1.89)	0.164				
Tumor size								
<2 cm	Reference							
2–4 cm	0.86 (0.33–2.22)	0.756			0.44 (0.21–0.94)	0.034	0.43 (0.14–1.37)	0.154
>4 cm	0.49 (0.14–1.64)	0.246			0.33 (0.12–1.03)	0.056	0.27 (0.05–1.33)	0.107
Presence of positive node	12.07 (0.69–212.00)	0.088			2.51 (1.02–6.13)	0.043	3.02 (0.84–10.82)	0.090
Margin status								
Negative	Reference		Reference					
Positive	3.55 (1.18–10.73)	0.025	2.51 (0.61–10.40)	0.204	5.19 (2.03–13.26)	0.001	4.96 (1.44–17.13)	0.011
Close (<5 mm)	1.91 (0.85–4.29)	0.116	2.21 (0.98–4.97)	0.055	1.85 (0.87–3.93)	0.107	1.33 (0.40–4.42)	0.642
Treatment								
None	Reference		Reference		Reference		Reference	
Surgery + adjuvant radiation	1.9 (0.55–6.67)	0.312	0.57 (0.07–4.67)	0.602	0.97 (0.34–2.75)	0.947	0.586 (0.11–3.19)	0.536
Surgery + adjuvant chemotherapy	0.28 (0.02–3.23)	0.306	3.05 (0.38–24.52)	0.295	2.85 (0.32–25.22)	0.346	4.35 (0.39–48.20)	0.231
Surgery + adjuvant chemoradiation	0.62 (0.17–2.19)	0.456	0.62 (0.23–1.71)	0.361	0.38 (0.10–1.38)	0.141	2.93 (0.06–1.35)	0.115

CI, confidence interval; DSS, disease-specific survival; HR, hazard ratio; MCCI, modified Charlson comorbidity index; OS, overall survival; RFS, recurrence free survival.

patients (30%) who were treated had a recurrence, with only 1 (5%) having a local recurrence. Among the 8 patients (40%) with positive margins who did not receive adjuvant therapy, 5 had a recurrence (62.5%), with 2 patients (25.0%) experiencing a local recurrence.

Of the 30 patients with close margins, 8 (26.7%) received adjuvant therapy, and 22 (73.3%) did not. Overall recurrence rates in untreated and treated patients with close margins was 40.9% and 50.0%, respectively, and local recurrence rates were 36.4% and 37.5%, respectively. OS and DSS stratified by margin status are shown in **Figs. S1** and **S2**, respectively.

Outcomes after adjuvant therapy in node-positive patients

Overall recurrence rates in node-negative and node-positive patients were 37% and 50%, respectively. The local recurrence rate in node-negative and node-positive patients was 30.0% and 22.4%, the groin recurrence rate was 5.1% and 18.8%, and the pelvic/distant recurrence rate was 3.1% and 14.6%, respectively.

In total, 40 patients received adjuvant therapy following surgery, of which 32 were node-positive patients (stage III or IV). Eight node-negative patients received adjuvant therapy due to positive surgical margins or other high risk pathological factors such as large tumor size. Within the node-positive cohort (n=49), 21 received adjuvant chemoradiation, 9 received adjuvant radiation alone, 2 received chemotherapy alone, and 8 received primary

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chemoradiation. Nine node-positive patients did not receive any adjuvant therapy due to extensive medical comorbidities.

Among node-positive patients, 5-year RFS and DSS for those who received no adjuvant radiation were 18.0% and 31.6%, respectively. In comparison, those treated with adjuvant radiation +/− chemotherapy had 5-year RFS and DSS of 51.0% (p=0.016) and 78.0% (p=0.012), respectively. The addition of adjuvant chemotherapy to radiation did not have a significant effect on RFS (p=0.296) or DSS (p=0.518). OS and DSS among node-positive patients stratified by adjuvant therapy is shown in **Figs. S3** and **S4**, respectively.

3. Treatment of recurrence

Amongst the 47 patients with isolated local recurrence, median time to recurrence was 19 months. Regarding treatment, 39 underwent surgery, with 1 receiving adjuvant radiation, and 1 receiving adjuvant chemoradiation. Surgery included WLE/simple vulvectomy (n=12), radical vulvectomy (n=24), and pelvic exenteration (n=3). Five patients underwent groin nodal dissection. Specifically, regarding the 3 patients treated with pelvic exenteration, one died from surgical complications, and the remaining 2 patients had re-recurrence. Among these patients treated surgically, 26 (65%) had an additional recurrence. Of the 8 patients with isolated local recurrence who were not surgically managed, 2 received radiation, of which 1 had an additional recurrence, and 6 underwent chemoradiation, of which 2 had an additional recurrence. Median time to second recurrence was 18 months (IQR=10–45). Median survival after treatment was 52 months (IQR=22–95), and 3-year DSS after treatment was 79%.

Ten patients had an isolated groin recurrence, and 1 patient had a concurrent local and groin recurrence. Median time to recurrence was 8 months (IQR=5–13). Regarding treatment, 5 patients underwent secondary surgery, after which 2 received adjuvant radiotherapy and 1 received adjuvant chemoradiation. Of the remaining patients who did not undergo surgery, 2 received chemoradiation, 3 received palliative chemotherapy, and 1 received palliative care only. Of these patients, 7 had an additional recurrence, with median time to second recurrence of 5 months (IQR=2–6). Median survival after treatment was 8 months (IQR=6–15), and 3-year DSS was 33%.

Ten patients had pelvic or distant recurrence, of which 3 patients had concurrent groin recurrences. Distant recurrence sites included bone (n=2), lung (n=4), and liver (n=1). Median time to recurrence was 8 months (IQR=6–15). For treatment, 1 patient with isolated pelvic recurrence underwent surgery, 5 received chemotherapy alone, 3 were treated with palliative therapy only, and 1 was lost to follow up. Among the patients treated, only one treated with chemotherapy had a complete response, while 1 had stable disease on chemotherapy and 3 progressed on chemotherapy. Median survival after recurrence was 5 months (IQR=1–6). Eight of the 9 patients with known cause of death died from disease.

Additional specific details regarding the treatment and course of disease for each patient with recurrence are presented in **Table S1**.

DISCUSSION

Oncologic outcomes at our institution are largely in agreement with the literature, with a 5-year RFS and DSS of 56.3% and 76.5%, respectively. Overall and local recurrence rate

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was 41.5% and 29.3%, respectively. Similar to a key finding of the GROINSS-V-I long-term follow-up [6], local recurrence translated into a significant decrease in DSS in our series. This highlights a need to focus on risk factors to triage patients to treatment escalation when deemed appropriate. Treatment outcomes at our institution have remained similar as in the previous decade, a phenomenon also seen in the literature [4,10]. With limited data to provide definitive clinical guidance, treatment often varies widely by institution. Our goal was to evaluate our institution's experience with vulvar cancer over a 22-year time period to contribute to this discussion.

Surgery is the cornerstone for management, with 92% of patients in our series undergoing surgery for primary treatment. The traditional gold standard of en bloc radical vulvectomy with bilateral ILFD has since been replaced with more conservative surgical methods to reduce surgical morbidity [3]. Standard recommendations for clear surgical margins is 1–2 cm, with close tumor margins historically defined as less than 8 mm [9-11]. However, these recommendations have been challenged given recent studies demonstrating a less clear picture regarding tumor-free margins and local recurrence [12]. Grootenhuis et al. [11] reported that tumor-free margins were not associated with local recurrence risk at cutoffs of 3, 5, and 8 mm. Our findings were similar, as margins less than 5 mm were not found to predict recurrence. The implications are highly relevant, given that large surgical margins contribute to high morbidity and may not actually reduce risk of local recurrence. Interestingly, Grootenhuis et al. [11] also demonstrated that the presence of precursor lesions, LS and dVIN, at the margin predicted risk of local recurrence. Indeed, we also found that the presence of LS was an independent risk factor for local recurrence on multivariate analysis (HR=2.78; 95% CI=1.30–5.91; p=0.008). Precursor lesions are not currently considered to be an indication for adjuvant therapy according to NCCN guidelines [13]. Certainly, this warrants further research as a specific risk factor that may be incorporated into future treatment paradigms.

Positive surgical margin was an independent risk factor on multivariable analysis for overall RFS (HR=3.55; 95% CI=1.18–10.73; p=0.025) and DSS (HR=4.96; 95% CI=1.44–17.13; p=0.011). Interestingly, it was not a risk factor for local recurrence. Compared to a local recurrence rate of 28.9% and 36.7% in patients with negative and close margins, only 15.0% of patients with positive surgical margins had a local recurrence. As 60% of margin-positive patients received adjuvant radiation +/– chemotherapy, this may reflect the benefit of adjuvant radiation for localized control, which is supported by several other retrospective studies [14,15].

Nodal involvement is the most important prognostic factor for patients with vulvar cancer [7,16,17], with 5-year survival declining from 70%–95% in node-negative patients to 25%–41% in node-positive patients. In our series, 5-year OS and DSS in node-negative patients was 76.8% and 81.1%, and in node-positive patients was 51.7% and 61.8%, respectively. The addition of adjuvant radiation +/- chemotherapy made a significant difference in both RFS and DSS among node-positive patients. The 5-year RFS and DSS of 18.0% and 36.0% in untreated patients increased to 51.0% (p=0.016) and 78.0% (p=0.012), respectively, in patients treated with adjuvant therapy. The use of adjuvant radiotherapy in node-positive patients is supported by GOG 37, which demonstrated a benefit to the nodal regions of high-risk, node-positive patients [18]. A SEER analysis further demonstrated a benefit of adjuvant radiotherapy in survival of patients with single node involvement [19].

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The role of adjuvant chemotherapy in vulvar cancer is less clear, though there has been increasing application of adjuvant chemotherapy [20], drawing on robust data gleaned from other gynecologic sites, especially cervical cancer [20-24]. In our series, the majority of our treated node-positive patients received adjuvant chemoradiation (n=21). Only 9 node-positive patients were treated with adjuvant radiation alone. While the chemoradiation cohort had improved 5-year RFS and DSS of 58.5% and 81.8% compared to 41.7% and 55.6%, respectively, in the radiation alone cohort, there was not enough power to detect a significant difference. Retrospective studies have suggested benefit of adjuvant chemoradiation over radiation alone in node-positive patients [25,26]. Most convincingly, an NCDB population-based analysis of node-positive patients who received adjuvant radiotherapy found a 38% reduction in all-cause mortality risk [20]. While there may exist hesitation to adopt adjuvant chemotherapy in a population with competing comorbidities, it should be considered in node-positive patients with appropriate performance status.

Treatment of recurrent vulvar cancer is challenging, especially given avoidance of aggressive treatment in an older population. Additionally, literature regarding treatment of recurrent vulvar cancer remains limited. Five-year survival for patients with recurrence has been reported to be 25%–50%, compared to 50-90% of patients without recurrence [4,27,28]. Among our patient cohort, 5-year OS was 80% and 53% and 5-year DSS was 98% and 62% for patients without and with recurrence, respectively. Though the majority of patients recurred within 2 years following treatment, 28% of patients with recurrence recurred after 2 years and 14.7% after 5 years. Thus, lifelong follow-up with careful examinations is important for this patient population.

Patients with isolated local recurrence typically are good candidates for surgery [5,29]. This is reflected in our patient cohort, as 40 of 47 patients with isolated local recurrence were treated surgically. Most received WLE, simple vulvectomy, or radical vulvectomy with or without groin lymph node dissection. In addition, pelvic exenteration has been used as a curative treatment option in some cases with extensive local recurrent disease [30-32]. Unfortunately, the 3 patients in our series with extensive local recurrent disease who underwent exenteration did not ultimately achieve a positive outcome. Radiation with or without concurrent chemotherapy is considered in lieu of surgery due to comorbidities, extent of disease, or extensive previous surgery. This applied to 7 patients with isolated local recurrence. Re-recurrence rate after isolated local recurrence overall remained high at 62%. Of note, though patients with isolated local recurrence are at high risk for re-recurrence, 3-year DSS after recurrence treatment remained high at 79%.

Patients with groin recurrence historically have had poor survival [4,33-35]. However, one study with 30 patients with groin recurrence reported a 50% survival rate after 7 years, suggesting that these patients can potentially be candidates for more aggressive treatment beyond sole palliation [36]. In our series, the 11 patients with groin recurrence had varied treatment, with only one patient receiving palliative care alone and 3 receiving palliative chemotherapy. Indeed, our patients with groin recurrence had poor survival, as 8 of the 11 died of disease. There is some evidence that surgery with adjuvant therapy may lead to better outcomes in this population compared to single mode therapy [36]. Though only 3 patients in our cohort received adjuvant therapy, multimodality therapy in the setting of groin recurrence should be explored more thoroughly in the future.

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Distant and/or pelvic recurrence has a very poor prognosis, and patients are almost exclusively treated palliatively [4,27]. In the few retrospective studies evaluating treatment in the setting of metastatic disease, chemotherapy has been shown to have low response rates with median survival 2–7 months [4,27,37]. In accordance, only one of five patients with distant recurrence treated with chemotherapy in our cohort had a complete response.

Our study has several limitations in addition to being a single-institution, retrospective study. This study spans a large time period, and some clinicopathologic data was unavailable. In addition, treatment decisions were individualized, and institutional treatment paradigm changed over the course of the studied time period, resulting in heterogeneous treatment. Additionally, human papillomavirus and p16 status was available in only a minority of patients, as recent findings have indicated this as an important prognostic factor that also may confer sensitivity to chemoradiation [38,39]. Lastly, the study period preceded the availability of checkpoint inhibitors, which have been shown to have a role in treating squamous cell skin cancers [40]. Despite these limitations, our study is strengthened by its grounding at a tertiary care center with high volume and multi-disciplinary teams with extensive experience caring for vulvar cancer patients. All pathology was reviewed by a specialized gynecologic pathologist. Lastly, our patient cohort represents a comparatively large single-institution cohort for this rare disease.

In summary, SCC of the vulva is a rare disease that poses considerable challenges due to limited prospective data. That outcomes have not improved across the last few decades highlights a great need to continue studying this disease to improve treatment paradigms. Surgical management remains the mainstay of treatment, though methods to reduce morbidity should be considered, such as smaller tumor-free margins and SNDs. Patients with positive nodes and positive margins have been shown to benefit from adjuvant therapy; however, further studies are needed to identify additional risk factors that can dictate optimal management escalation. Based on our results, the presence of precursor lesions may represent a risk factor that can benefit from treatment escalation. Additionally, the high re-recurrence rates and catastrophic prognosis of patients with groin recurrence demonstrate the need for optimizing management for recurrent disease.

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SUPPLEMENTARY MATERIALS

Table S1

Disease course in patients with recurrence

Click here to view

Fig. S1

OS by margin status.

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Fig. S2
DSS by margin status.

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Fig. S3
OS in node-positive patients by adjuvant treatment.

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Fig. S4
DSS in node-positive patients by adjuvant treatment.

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30.
PUBMED | CROSSREF
2. National Cancer Institute. Cancer STAT facts: vulvar cancer. Bethesda, MD: National Cancer Institute; 2021.
3. Rogers LJ, Cuello MA. Cancer of the vulva. Int J Gynaecol Obstet 2018;143 Suppl 2:4-13.
PUBMED | CROSSREF
4. Nooij LS, Brand FA, Gaarenstroom KN, Creutzberg CL, de Hullu JA, van Poelgeest MI. Risk factors and treatment for recurrent vulvar squamous cell carcinoma. Crit Rev Oncol Hematol 2016;106:1-13.
PUBMED | CROSSREF
5. Coulter J, Gleeson N. Local and regional recurrence of vulval cancer: management dilemmas. Best Pract Res Clin Obstet Gynaecol 2003;17:663-81.
PUBMED | CROSSREF
6. Te Grootenhuis NC, van der Zee AG, van Doorn HC, van der Velden J, Vergote I, Zanagnolo V, et al. Sentinel nodes in vulvar cancer: long-term follow-up of the GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V) I. Gynecol Oncol 2016;140:8-14.
PUBMED | CROSSREF
7. Gadducci A, Cionini L, Romanini A, Fanucchi A, Genazzani AR. Old and new perspectives in the management of high-risk, locally advanced or recurrent, and metastatic vulvar cancer. Crit Rev Oncol Hematol 2006;60:227-41.
PUBMED | CROSSREF
8. Roffman CE, Buchanan J, Allison GT. Charlson comorbidities index. J Physiother 2016;62:171.
PUBMED | CROSSREF
9. Greer BE, Koh WJ. New NCCN guidelines for vulvar cancer. J Natl Compr Canc Netw 2016;14:656-8.
PUBMED | CROSSREF
10. Dudley S, Viswanathan A. Margins in vulvar cancer: challenges to classical clinicopathologic vulvar recurrence risk factors. Gynecol Oncol 2019;154:253-4.
PUBMED | CROSSREF
11. Te Grootenhuis NC, Pouwer AW, de Bock GH, Hollema H, Bulten J, van der Zee AG, et al. Margin status revisited in vulvar squamous cell carcinoma. Gynecol Oncol 2019;154:266-75.
PUBMED | CROSSREF
12. Baiocchi G, Mantoan H, de Brot L, Badiglian-Filho L, Kumagai LY, Faloppa CC, et al. How important is the pathological margin distance in vulvar cancer? Eur J Surg Oncol 2015;41:1653-8.
PUBMED | CROSSREF
13. Koh WJ, Greer BE, Abu-Rustum NR, Campos SM, Cho KR, Chon HS, et al. Vulvar cancer, version 1.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2017;15:92-120.
PUBMED | CROSSREF
14. Viswanathan AN, Pinto AP, Schultz D, Berkowitz R, Crum CP. Relationship of margin status and radiation dose to recurrence in post-operative vulvar carcinoma. Gynecol Oncol 2013;130:545-9.
PUBMED | CROSSREF

15. Ignatov T, Eggemann H, Burger E, Costa SD, Ignatov A. Adjuvant radiotherapy for vulvar cancer with close or positive surgical margins. J Cancer Res Clin Oncol 2016;142:489-95.
PUBMED | CROSSREF
16. Mahner S, Jueckstock J, Hilpert F, Neuser P, Harter P, de Gregorio N, et al. Adjuvant therapy in lymph node-positive vulvar cancer: the AGO-CaRE-1 study. J Natl Cancer Inst 2015;107:dju426.
PUBMED | CROSSREF
17. Woelber L, Eulenburg C, Choschzick M, Kruell A, Petersen C, Gieseking F, et al. Prognostic role of lymph node metastases in vulvar cancer and implications for adjuvant treatment. Int J Gynecol Cancer 2012;22:503-8.
PUBMED | CROSSREF
18. Kunos C, Simpkins F, Gibbons H, Tian C, Homesley H. Radiation therapy compared with pelvic node resection for node-positive vulvar cancer: a randomized controlled trial. Obstet Gynecol 2009;114:537-46.
PUBMED | CROSSREF
19. Parthasarathy A, Cheung MK, Osann K, Husain A, Teng NN, Berek JS, et al. The benefit of adjuvant radiation therapy in single-node-positive squamous cell vulvar carcinoma. Gynecol Oncol 2006;103:1095-9.
PUBMED | CROSSREF
20. Gill BS, Bernard ME, Lin JF, Balasubramani GK, Rajagopalan MS, Sukumvanich P, et al. Impact of adjuvant chemotherapy with radiation for node-positive vulvar cancer: a National Cancer Data Base (NCDB) analysis. Gynecol Oncol 2015;137:365-72.
PUBMED | CROSSREF
21. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999;340:1144-53.
PUBMED | CROSSREF
22. Gaffney DK, Du Bois A, Narayan K, Reed N, Toita T, Pignata S, et al. Patterns of care for radiotherapy in vulvar cancer: a Gynecologic Cancer Intergroup study. Int J Gynecol Cancer 2009;19:163-7.
PUBMED | CROSSREF
23. Peters WA 3rd, Liu PY, Barrett RJ 2nd, Stock RJ, Monk BJ, Berek JS, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000;18:1606-13.
PUBMED | CROSSREF
24. Eifel PJ, Winter K, Morris M, Levenback C, Grigsby PW, Cooper J, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. J Clin Oncol 2004;22:872-80.
PUBMED | CROSSREF
25. Han SC, Kim DH, Higgins SA, Carcangiu ML, Kacinski BM. Chemoradiation as primary or adjuvant treatment for locally advanced carcinoma of the vulva. Int J Radiat Oncol Biol Phys 2000;47:1235-44.
PUBMED | CROSSREF
26. Mulayim N, Foster Silver D, Schwartz PE, Higgins S. Chemoradiation with 5-fluorouracil and mitomycin C in the treatment of vulvar squamous cell carcinoma. Gynecol Oncol 2004;93:659-66.
PUBMED | CROSSREF
27. Tilmans AS, Sutton GP, Look KY, Stehman FB, Ehrlich CE, Hornback NB. Recurrent squamous carcinoma of the vulva. Am J Obstet Gynecol 1992;167:1383-9.
PUBMED | CROSSREF
28. Piura B, Masotina A, Murdoch J, Lopes A, Morgan P, Monaghan J. Recurrent squamous cell carcinoma of the vulva: a study of 73 cases. Gynecol Oncol 1993;48:189-95.
PUBMED | CROSSREF
29. Salom EM, Penalver M. Recurrent vulvar cancer. Curr Treat Options Oncol 2002;3:143-53.
PUBMED | CROSSREF
30. Tan KK, Pal S, Lee PJ, Rodwell L, Solomon MJ. Pelvic exenteration for recurrent squamous cell carcinoma of the pelvic organs arising from the cloaca--a single institution's experience over 16 years. Colorectal Dis 2013;15:1227-31.
PUBMED | CROSSREF
31. Kaur M, Joniau S, D'Hoore A, Vergote I. Indications, techniques and outcomes for pelvic exenteration in gynecological malignancy. Curr Opin Oncol 2014;26:514-20.
PUBMED | CROSSREF
32. Miller B, Morris M, Levenback C, Burke TW, Gershenson DM. Pelvic exenteration for primary and recurrent vulvar cancer. Gynecol Oncol 1995;58:202-5.
PUBMED | CROSSREF

33. Gonzalez Bosquet J, Magrina JF, Gaffey TA, Hernandez JL, Webb MJ, Cliby WA, et al. Long-term survival and disease recurrence in patients with primary squamous cell carcinoma of the vulva. Gynecol Oncol 2005;97:828-33.
PUBMED | CROSSREF
34. Woolderink JM, de Bock GH, de Hullu JA, Davy MJ, van der Zee AG, Mourits MJ. Patterns and frequency of recurrences of squamous cell carcinoma of the vulva. Gynecol Oncol 2006;103:293-9.
PUBMED | CROSSREF
35. Stehman FB, Bundy BN, Ball H, Clarke-Pearson DL. Sites of failure and times to failure in carcinoma of the vulva treated conservatively: a Gynecologic Oncology Group study. Am J Obstet Gynecol 1996;174:1128-32.
PUBMED | CROSSREF
36. Frey JN, Hampl M, Mueller MD, Günthert AR. Should groin recurrence still be considered as a palliative situation in vulvar cancer patients?: a brief report. Int J Gynecol Cancer 2016;26:575-9.
PUBMED | CROSSREF
37. Witteveen PO, van der Velden J, Vergote I, Guerra C, Scarabeli C, Coens C, et al. Phase II study on paclitaxel in patients with recurrent, metastatic or locally advanced vulvar cancer not amenable to surgery or radiotherapy: a study of the EORTC-GCG (European Organisation for Research and Treatment of Cancer--Gynaecological Cancer Group). Ann Oncol 2009;20:1511-6.
PUBMED | CROSSREF
38. Horne ZD, Dohopolski MJ, Pradhan D, Bhargava R, Edwards RP, Kelley JL, et al. Human papillomavirus infection mediates response and outcome of vulvar squamous cell carcinomas treated with radiation therapy. Gynecol Oncol 2018;151:96-101.
PUBMED | CROSSREF
39. Lee LJ, Howitt B, Catalano P, Tanaka C, Murphy R, Cimbak N, et al. Prognostic importance of human papillomavirus (HPV) and p16 positivity in squamous cell carcinoma of the vulva treated with radiotherapy. Gynecol Oncol 2016;142:293-8.
PUBMED | CROSSREF
40. Patel R, Chang ALS. Immune checkpoint inhibitors for treating advanced cutaneous squamous cell carcinoma. Am J Clin Dermatol 2019;20:477-82.
PUBMED | CROSSREF