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Prognostic factors in vulvar cancer patients: a single center experience

Vulvar kanserli hastalarda prognostik faktörler: tek merkez deneyimi

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Abstract

Purpose: Many prognostic factors have been investigated in vulvar cancer patients. In our study, we aimed to compare clinical and pathological prognostic factors and investigate the factors that affect the recurrence and survival in patients with recurrent and non-recurrent squamous cell vulvar cancer.

Materials and methods: This retrospective study was conducted in Tepecik Research Hospital, Izmir, Turkey between 1999-2020. The descriptive features, prognostic factors and survival in recurrent patients were evaluated.

Results: Tumor invasion depth, surgical margin positivity, lymphovascular space invasion (LVSI), are statistically significant for recurrence (p=0.03, p=0.00, p=0.04). Variables such as age, tumor size, surgical margin distance (mm), tumor localization, presence of metastatic lymph node, operation type (surgery with lymph node dissection) and adjuvant therapy were not found to be statistically significant in terms of recurrent patients with vulvar cancer. There was correlation between recurrence, LVSI, surgical margin positivity, stage and survival in Kaplan Meier survival analysis.

Conclusion: As in other studies, many prognostic factors like tumor invasion depth, surgical margin positivity, LVSI are risk factors for recurrence in our study. Stage, LVSI, recurrence, surgical margin positivity were significant factors for survival as well.

Key words: Vulvar cancer, adjuvant therapy, recurrence.

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Öz

Amaç: Vulvar kanserli hastalarda birçok prognostik faktör araştırılmıştır. Çalışmamızda nüks ve nüks olmayan skuamöz hücreli vulvar kanserli hastalarda klinik ve patolojik prognostik faktörleri karşılaştırmayı, nüks ve sağkalımı etkileyen faktörleri araştırmayı amaçladık.

Gereç ve yöntem: Bu prospektif çalışma 1999-2020 yılları arasında İzmir, Tepecik Araştırma Hastanesi'nde yapıldı. Tekrarlayan hastalarda tanımlayıcı özellikler, prognostik faktörler ve sağkalım değerlendirildi.

Bulgular: Tümör invazyon derinliği, cerrahi sınır pozitifliği, lenfovasküler boşluk invazyonu (LVSI) nüks açısından istatiksel olarak anlamlıdır (p=0,03, p=0,00, p=0,04). Yaş, tümör boyutu, cerrahi sınır mesafesi (mm), tümör lokalizasyonu, metastatik lenf nodu varlığı, operasyon tipi (lenf nodu diseksiyonlu cerrahi) ve adjuvan tedavi gibi değişkenler nüks vulvar kanseri hastaları açısından istatiksel olarak anlamlı bulunmadı. Kaplan Meier sağkalım analizinde nüks, lenfovasküler boşluk invazyonu, cerrahi sınır pozitifliği, evre ve sağkalım arasında korelasyon vardı.

Sonuç: Diğer çalışmalarda olduğu gibi bizim çalışmamızda da tümör invazyon derinliği, cerrahi sınır pozitifliği, lenfovasküler boşluk invazyonu gibi birçok prognostik faktör nüks için risk faktörüdür. Evre, lenfovasküler boşluk invazyonu, nüks, cerrahi sınır pozitifliği de sağkalım için önemli faktörlerdendir.

Anahtar kelimeler: Vulva kanseri, adjuvan tedavi, nüks.

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Introduction

Vulvar cancer is the fourth most common gynecologic malignancy with approximately 3-5% incidence [1, 2] . Squamous cell carcinoma is the most common type of vulvar cancer and squamous cell vulvar carcinomas devided into two main categories; usual and differentiated types [3]. Usual type is human papilloma virus (HPV) related type. Differentiated type does not have an assocation with HPV. Basal cell carcinoma, Paget's disease and vulvar melanomas are the other types of vulvar carcinomas [4]. The most common prognostic factor is lymph node metastasis [5]. Surgery is the gold standart treatment in patients with early stages. Butterfly excision with separate inguinal lymphnode dissection is preferred to wide local excisons. In decades, although the surgical morbidity decreased local and distant recurrences still have a high ratio [6].

Lesion size, depth of stromal invasion, lymphovascular space invasion (LVSI), and the pathological resection margin, positive groin nodes are considered to be associated with local and distant recurrences [7]. The 5-year survival rate of vulvar cancer was reported as 60-70% [8]. The reported incidence of recurrence in vulvar cancers is approximately 25% [9]. In surgical treatment removal of the tumor with a tumor margin of at least 8 mm is recommended to prevent local recurrences [10].

In this study, we aim to investigate the prognostic factors and the effects of recurrence on survival.

Materials and methods

This retrospective study was conducted in Tepecik Research and Education Hospital, Izmir in between 1999-2020. The medical records of all patients who were operated in our hospital with vulvar squamous cell carcinoma diagnosis were retrieved from the hospital database. Approvals of the study were obtained from the Tepecik Research and Education Hospital Ethics Board. 92 patients' records were examined and analysed by the same author. From records, 90 cases had available records. Two were excluded from the study because of unavailable medical records or being operated in other hospitals. 90 patients were included into the study. FIGO 2009 staging was used for classification and patients classified with the FIGO 1988 were restaged based on the FIGO 2009 staging. The following variables were evaluated; age, operation type (only excision or excision plus inguinal lymph node dissection), recurrence, tumor localization, tumor size, surgical margin, surgical margin tumor free distance, LVSI, adjuvant therapy, lymph node metastasis, overall survival (OS) and disease free survival (DFS). Patients were followed every 3 months for the first 2 years, every 6 months for the next 3 years, and then annually.

Statistical analysis was performed with SPSS version 22 (SPSS for Mac Inc., Chicago, IL, USA). *P*-value <0.05 was considered statistically significant. For descriptive analyses frequency counts, percentages and 95% confidence interval (CI) were used. Binary logistic regression analyses were used to define the risk factors for recurrence. Kaplan Meier graphics were used to analyse survival. Cox regression analyses were used to define factors that affected the OS and DFS.

Results

All patients had vulvar squamous cell carcinoma. Mean age was 65.5±11.2 years. 60.0% (n=54) of the patients were at stage 1, 37.8% (n=34) were at stage 3, 2.2% (n=2) were at stage 4, 83.3% of the patients underwent tumor excisition and bilateral lymph node dissection. In 28.9% (n=26) of the patients recurrence occured. In 83 (92.2%) patients tumor locations were < 2 cm from midline and in 7 (7.8%) patients >2 cm from midline. In 24 (26.7%) (n=24) patients tumor involved the surgical margins. 12 (13.3%) patients had LVSI. Adjuvant treatment was administered to 59 (65,6%) patients. 5 (19.2%) patients had surgical intervention and adjuvant chemoradiotherapy (CRT). 9 (34,6%) patients were treated with chemotherapy. In 2 (7.7%) chemoradiotherapy, and in 6 (23.1%) radiotherapy was used. In 14 (53.8%) patients local recurrence, in 9 (34.6%) patients inguinal recurrence was occured (Table 1). Between recurrent and non recurrent groups the mean tumor size was statistically significant (p=0.03) (Table 2). Binary logistic regression analyses revealed that surgical margin positivity and LVSI were independent risk factors for recurrence (p=0.00, p=0.04) (Table 3). Univariate and Multivariate Cox Regression Analyses revealed

that recurrence, surgical margin, tumor size and adjuvant treatment were significant for overall survival and for disease free survival surgical margin, tumor size and adjuvant teratment were significant (Table 4, 5).

Discussion

In this study we investigated the clinicopathologic prognostic factors and risk factors for recurrence and survival. 90 patients with squamous cell vulvar carcinoma underwent

Table 1. The descriptive features of patients

	n (%)	95% CI	Mean ± STD
Age	90 (100%)		65.5±11.2
Operation			
Tumor Excision(Radical or local excision)	7 (7.8%)	2.2-13.3	
Tumor Excision+Unilateral lymph node dissection	8 (8.9%)	3.3-15.6	
Tumor Excision+Bilateral lymph node dissection	75 (83.3%)	75.6-90.0	
Recurrence			
Positive	26 (28.9%)	20.0-38.9	
Negative	64 (71.1%)	61.1-80.0	
Stage			
1	54 (60.0%)	48.9-71.1	
3	34 (37.8%)	27.8-48.9	
4	2 (2.2%)	0.0-5.6	
Tumor Localization			
<2 cm from Midline	83 (92.2%)	86.7-97.8	
>2 cm from midline	7 (7.8%)	2.2-13.3	
Tumor Size			3.04±1.42
Surgical Margin			
Positive	24 (26.7%)	17.8-35.6	
Negative	66 (73.3%)	64.4-82.2	
Surgical Margin distance (mm)			5.71±5.03
LVSI			
No	78 (86.7%)	78.9-93.3	
Yes	12 (13.3%)	6.7-21.1	
Adjuvant Treatment			
No	31 (34.4%)	25.6-43.3	
Yes	59 (65.6%)	56.7-74.4	
Nux Location			
Local	14 (53.8%)	34.6-73.1	
Inguinal	9 (34.6%)	15.4-53.8	
Systemic	3 (11.5%)	0-23.1	
Recurrence Treatment			
Surgical	4 (15.4%)	3.8-30.8	
RT	6 (23.1%)	7.7-38.5	
CRT	2 (7.7%)	0-19.2	
CT	9 (34.6%)	15.4-53.8	
Surgery+CRT	5 (19.2%)	7.7-34.6	

RT: Radiotherapy, CRT: Chemoradiotherapy, CT: Chemotherapy

Table 2. Comparision of means between recurrent and non-recurrent groups.

	Recurrent group mean ± SD	Non-Recurrent Group mean ± SD	*p* Value (2 -tailed)
Tumor Size (cm)	3.23±1.42	2.98±1.39	0.45
Invasion Depth(mm)	6.40±5.71	4.39±4.50	0.03
Surgical Margin Distance(mm)	4.53±5.28	6.18±4.88	0.16

Independent T- test, $p<0,05$ is significant

Table3. Risk Factors for recurrence. Binary Logistic Regression Analyses

	p Value	OR	95% CI
Age	0.24	1.03	0.97-1.08
Surgical Margin positivity	0.00	6.80	1.60-29.2
LVSI	0.04	0.11	0.01-0.90
Adjuvant treatment	0.84	0.86	0.19-3.85
Tumor localization	0.63	0.60	0.07-4.83
Lymph node metastasis	1.00	0.00	0.00-0.93
Operation Type(excision and Lymph node dissection groups)	0.08	0.10	0.00-1.40

LVSI: Lymphovascular space invasion

Table 4. Univariate and Multivariate Cox Regression Analyses of OVS

	Univariate Analyses			Multivariate Analyses		
	p Value	OR	95% CI	*p* Value	OR	95% CI
Recurrence	0.00	0.30	0.15-0.60	0.00	0,24	0.11-0.52
Stage	0.06			0.91		
Surgical margin	0.00	0.30	0.14-0.63	0.48		
Lymph node metastasis	0.07			0.91		
Tm size	0.00	1.32	1.08-1.62	0.81		
Adjuvant Treatment	0.02	0.39	0.17-0.87	0.36		

OVS: Overall survival

Table 5. Univariate and Multivariate Cox Regression Analyses of DFS

	Univariate Analyses			Multivariate Analyses		
	p Value	OR	95% CI	*p* Value	OR	95% CI
Stage	0.06	7.27	0.87-60.8	0.50		
Surgical margin	0.00	0.32	0.16-0.67	0.05	0.44	0.19-1.01
Lymph node metastasis	0.14	0.59	0.29-1.19	0.93	0.00	
Tumor size	0.01	1.30	1.05-1.60	0.64	0.78	0.27-2.22
Adjuvant Treatment	0.04	0.43	0.19-0.97	0.32	1.12	0.88-1.43

DFS: Disease free survival

vulvectomy ± lymph node dissection. In line with literature, this study revealed that there are several risk factors and clinicopathologic prognostic factors associated with recurrence and survival in this rare gynecologic malignancy.

The reported rate for recurrence in a study was 25%- 33% [6]. In this study 28.9% of patients had a recurrent disease. In literature, the most significant factor was described as lymph node metastasis [11]. Although in literature it was described that lymphnode metastasis was the most significant factor, in our study, lymph node metastasis was not found to be statistically significant for recurrence (Figure 1) . Zach et al reported the recurrence rate as 22.3% in their study [12]. They also reported that stage 1 patients had an excellent prognosis. Similarly in our study for stage 1 patients had statistically significant overall survival than stage 3 and 4 patients (Figure 2).

In this study independent t-test analysis between recurrent and non-recurrent group revealed that, mean tumor size, invasion depth and tumor free surgical margin, was statistically significant in the recurrent group (p=0.00, p=0.03, p=0.04).

In literature, pathologic tumor free surgical margin distance is described as a predictor factor for local vulvar recurrence. In our study tumor free surgical margin distance (mm) mean was not statistically significant between two groups. Heaps et al emphasized <8 mm tumor free surgical margin as a risk factor for recurrence [7]. Perez et al reported that post operative RT improves the local control at the primary site

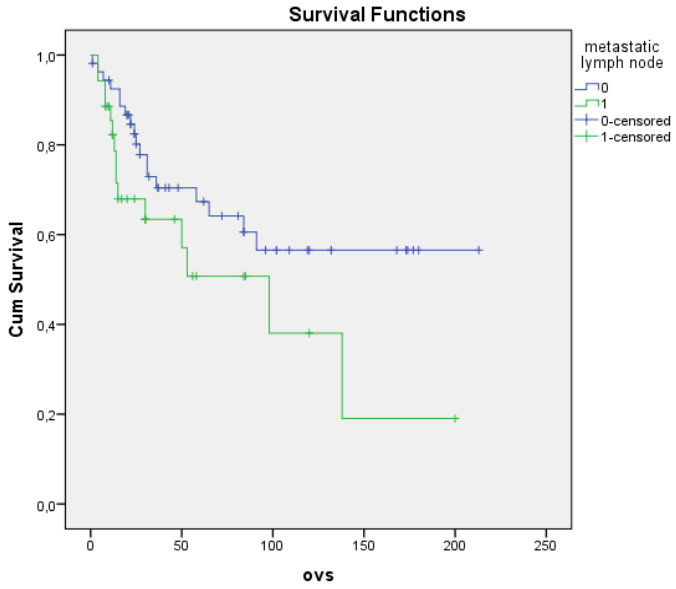

Figure 1. Kaplan-Meier survival analyses of lymph node metastasis (p=0.06)

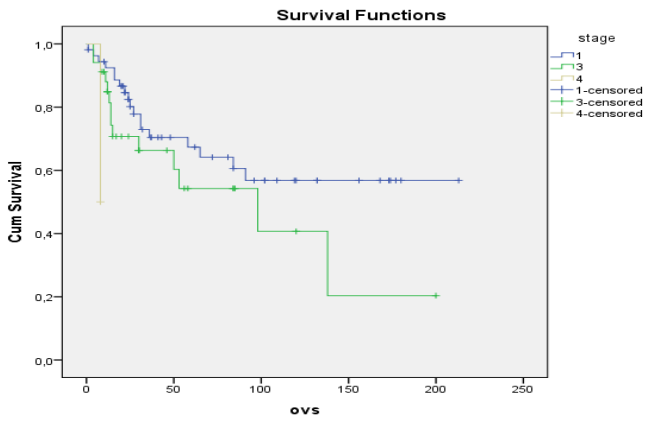

Figure 2. Kaplan-Meier survival analyses of stages (p=0.03)

[13]. In this study authors stated that irridation is an alternative treatment to radical vulvectomy and when used postoperatively it improves tumor control at the primary site. In our study, adjuvant RT was not statistically significant for recurrence but in the univariate and multivariate cox regression analysis it improved OS and DFS.

In this study in the univariate cox regression analysis surgical margin, tm size, adjuvant treatments were independent risk factors both for OS and DFS. In a study reported by Imoto, age > 70 years, close surgical resection margin were found as independent prognostic factors for OS but not for DFS [14].

In a study age, nodal status, tumor classification, depth of invasion, surgical margin involvement were found to be statistically significant parameters that affecting OS and DFS [11]. The authors also found that survival parameters decreased with tumor size, depth of invasion and margin involvement. In our study tumor size, recurrence, stage, LVSI, surgical margin, adjuvant treatment were statistically significant for survival parameters (Figure 3, 4, 5, 6).

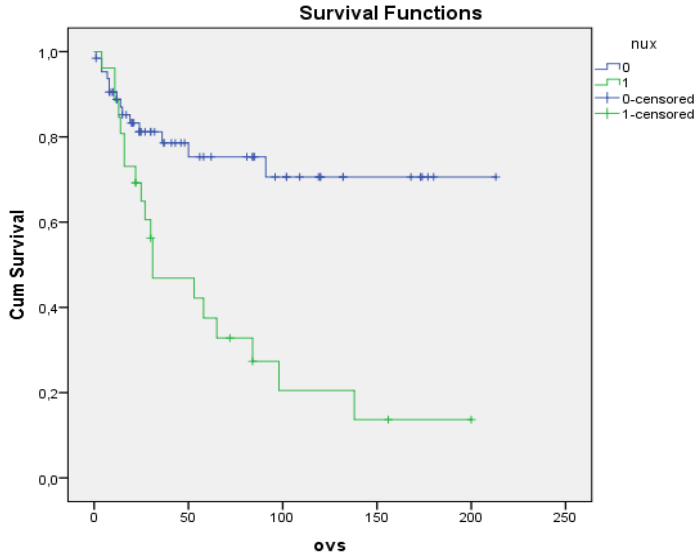

Figure 3. Kaplan-Meier survival analyses of recurrent and non-recurrent groups (p=0.00)

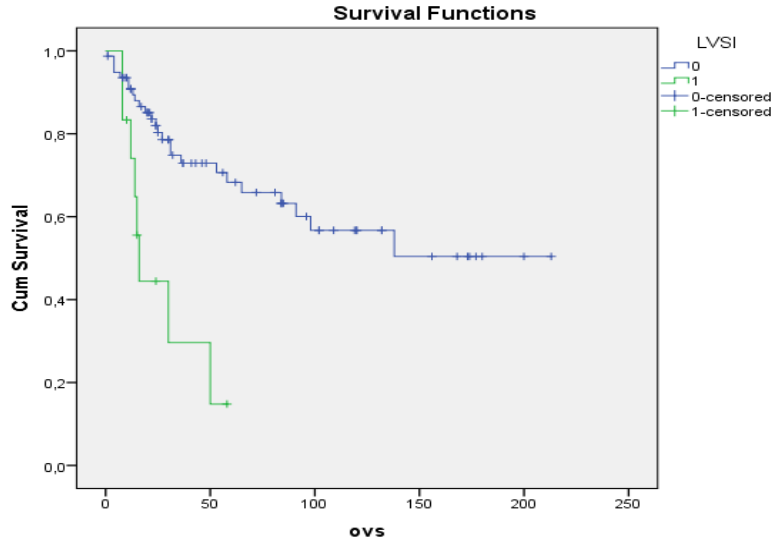

Figure 4. Kaplan-Meier survival analyses of LVSI (p=0.00)

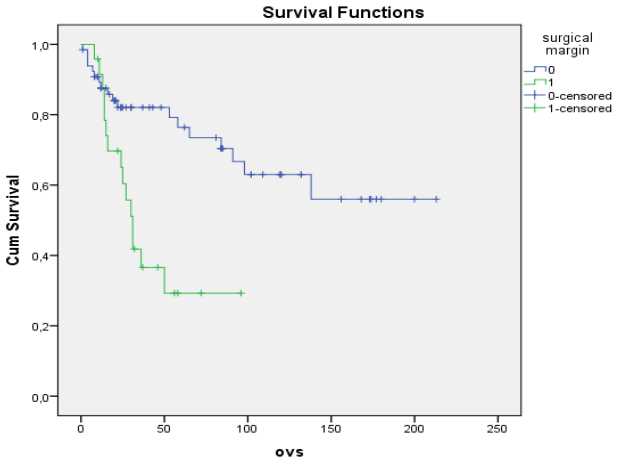

Figure 5. Kaplan-Meier survival analyses of surgical margin (p=0.00)

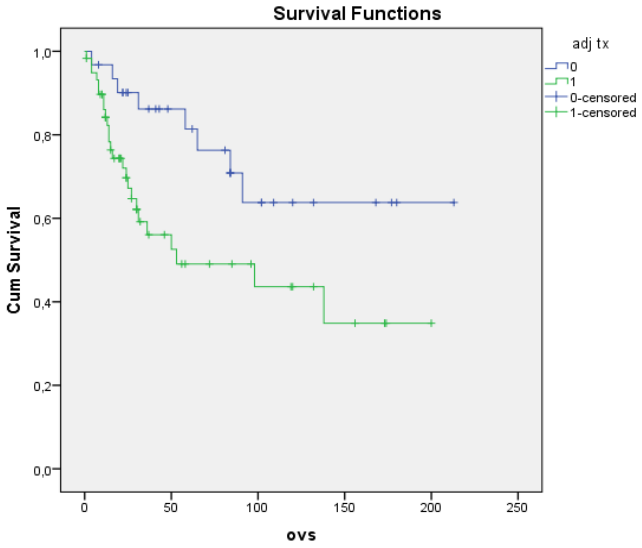

Figure 6. Kaplan-Meier survival analyses of adjuvant treatment (p=0.01)

Although there were several risk factors mentioned in literature Stankevica et al revealed that midline involvement was a risk factor for vulvar cancer recurrence [15]. However in this study we found that tumor localization (<2 cm from midline, >2cm from midline) was not statistically significant for recurrence (p=0.63). The main limitations of this study are retrospective design and small sample size.

In conclusion, vulvar cancer is a rare gynecologic malignancy. The present study demonstrated that stage, LVSI, recurrence, surgical margin positivity were significant factors for survival in this rare malignacy. Larger prospective series are needed to further evaluate women with vulvar cancer.

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Conflict of interest: No conflict of interest was declared by the authors.

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Ethics Committee Aproval: The study was conducted in accordance with the declaration of Helsinki, and the protocol was approved by the ethics committee of number 2020/10-13 on 12.08.2020.

Author Contribution

G.S.D.: Designed the study, analysed the data, wrote the study.

F.D.: Analysed the data

G. G.: Collected the data, analysed the data

M. S. : Analysed the data

S. S.: Analysed the data