Prognostic Factors in Squamous Cell Carcinoma of the Vulva: a Retrospective Multicenter Study

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ABSTRACT

The study aim to determine the clinicopathological factors for disease-free survival (DFS) and overall survival (OS) in women with vulvar cancer and to analyze the the possible effect of metformin on survival of the patients. From 2011 to 2017, medical records of 142 patients who underwent primary radical surgery for VC at 6 referral centers in Turkey were collected, retrospectively. The median age of the cohort was 67.0 years. 124 patients underwent radical surgery and inguinofemoral lymphadenectomy. The overall recurrence rate was 33.8% within a median follow-up time of 22 months. Five-year DFS and OS rates were 55.8% and 62.6%, respectively. Multivariate analysis showed surgical margin (HR:6.4, p= 0.017 for DFS; HR:13.6, p=0.009 for OS) and lymph node metastasis (HR: 4.1, p= 0.014 for DFS; HR: 6.3, p= 0.020 for OS) were the independent prognostic factors. There was no statistically difference in DFS and OS for patients who had used metformin.

Keywords: Metformin, Prognosis, Recurrence, Survival, Vulvar cancer

ÖZET

Vulva Skuamöz Hücreli Kanserinde Prognostik Faktörler: Retrospektif Çok Merkezli Bir Çalışma

Bu çalışma vulva kanserinde klinikopatolojik faktörlerin ve metforminin hastalıksız sağkalım (DFS) ve genel sağkalım (OS) üzerine etkilerini olan ortaya koymayı amaçlamaktadır. Çalışmada ülkemizde 2011-2017 yılları arasında, 6 referans merkezde vulva kanseri nedeniyle primer radikal cerrahi uygulanan 142 hastanın tıbbi kayıtları retrospektif olarak incelendi. Median yaşı 67.0 olan hastalardan 124'üne radikal cerrahi ve inguinofemoral lenfadenektomi yapıldı. 22 aylık median takip süresince rekürrens oranı %33.8 olarak saptandı. Beş yıllık DFS ve OS oranları sırasıyla % 55.8 ve % 62.6 olarak gösterildi. Çok değişkenli analizlerde cerrahi sınır (HR: 6.4, p= 0.017; DFS için; HR: 13.6, p= 0.009 OS için) ve lenf nodu metastazı (HR: 4.1, p= 0.014 için DFS; HR: 6.3, p = 0.020 OS için) bağımsız prognostik faktörler olarak saptandı. Vulva kanserinde metformin kullanımın DFS ve OS'a istatistiksel olarak etkisi olmadığı görüldü.

Anahtar Kelimeler: Metformin, Prognoz, Rekürrens, Survival, Vulvar kanser

INTRODUCTION

Vulvar cancer (VC) is the fourth most common gynecologic cancer in developed countries and comprises 5% of all female genital tract cancers.[1] It is thought to be a disease of postmenopausal women with the median age at diagnosis is 69 years.[2] Squamous cell carcinoma (SCC) represents vast majority (90%) of the histologic subtypes.[3] The traditional treatment of vulvar cancer has been surgery including radical vulvectomy (RV) and inguinofemoral lymphadenectomy (IFL), which would destroy the psychosexual life of women and cause short-long term surgical complications like wound dehiscence and lymphedema.[4] To minimize the associated morbidities, less radical excision of the primary lesion by radical local excision (RLE) and less radical evaluation of lymph nodes by sentinel lymph node biopsy (SLNB) has been accepted as alternative treatment modalities with similar oncologic outcomes, especially in early stage disease.[5,6]

Because of the rare incidence of the disease and heteregoneous treatments among the different centers, which mostly operate limited number of cases per year, data regarding prognostic factors for recurrence and survival is limited, inconclusive, and based on retrospective studies.[7-9] Generally, the presence of regional lymph node metastasis is accepted as the most important prognostic factor. Also, positive surgical margin has been associated with local recurrence in most of the studies.[10,11] The other possible prognostic factors consist of stage, older age, surgical margin distance, tumor size, lymphovascular space invasion (LVSI), depth of stromal invasion (DSI), and degree of nodal involvement.[7-12]

In this retrospective multicenter study, we aimed to determine the clinicopathological variables in the recurrence and survival of women with SCC of the vulva. Secondarily, we analyzed the the possible effect of metformin in VC.

MATERIALS AND METHODS

This multi-center retrospective study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant. Ethics Committee approval was also obtained for the study. And the work has been reported in line with the STROCSS criteria.[13]

Study Population

From January 2011 to December 2017, medical records of all patients who underwent primary surgery for SCC of vulva at 6 Gynecologic Oncology Centers in Turkey were collected, retrospectively. Patients who had distant metastasis and concomitant malignancies at the time of diagnosis, were excluded from the study. None of the patients have had neo-adjuvant therapy.

Surgery and Adjuvant Treatment

In the study period, general acceptance of VC management was to treat the patients with radical surgery (RS) including radical vulvectomy or radical local excision. All operations were performed by at least one gyne-oncologists. RLE without IFL was selected just for the Stage IA lesions. IFL was performed for stage ≥ IB lesions. In case of IFL, it was done mostly bilateral. SLNB was not used in any surgery.

RV was defined as the excision of the whole vulva down to the deep fascia of the thigh, the periosteum of the pubis, and the deep fascia of the urogenital diaphragm. RV was performed through triple incision technique with 1-2 cm tumor free margin. RLE was defined as excision of the tumoral lesion with 1-2 cm of surrounding tissue. For RLE, the deep margin of the excision corresponds to the deep fascia of urogenital diaphragm. IFL included both superficial and deep inguinofemoral lymph nodes.

All pathologic specimens were reviewed by specialized gynecologic pathologist at these centers. Fresh specimens were fixed with formalin then processed with hematoxylin and eosin staining. Pathologic information such as grade, tumor size, DSI, LVSI, surgical margin, margin distance, presence and features of lymph node metastasis (lymph node count, extracapsular spread, diameter of the metastatic node), location of the tumor (midline, ≤ 2 cm or > 2 cm to midline structures) was collected from pathology reports. DSI was measured from the superficial adjacent dermal papilla to the vertical extension of the tumor. Margin distance was measured, after formalin fixation has been completed (pathologic margin). Pathological tumor size was classified into 2 groups: ≤ 3 cm and > 3 cm. Stages were defined according to FIGO 2009 surgical staging system.[14]

Table 1. Clinicopathological characteristics of the study population (Totally 142 patients)

Characteristics	Values
Age, years (median)	67 (35-85)
Age group, years	
≤ 65	63 (44.4%)
> 65	79 (55.6%)
Surgery :	
RV+BIFL	70 (49.3%)
RLE+BIFL	48 (33.8%)
RLE+UIFL	6 (4.2%)
RLE	18 (12.7%)
Tumor Size, cm (median)	3 (0.3-15)
Tumor size:	
≤ 3 cm	84 (59.2%)
> 3 cm	58 (40.8%)
Grade:	
1	47 (33.1%)
2	32 (22.5%)
3	13 (9.2%)
Missing	50 (35.2%)
LVSI,	
Positive	45 (31.7%)
Negative	70 (49.3%)
Missing	27 (19%)
Localization:	
Midline	46 (32.4%)
≤ 2 cm	57 (40.1%)
> 2 cm	34 (23.9%)
Missing	5 (3.5%)
Surgical margin	
Positive	21 (14.8%)
≤ 1 cm	50 (35.2%)
> 1 cm	68 (47.9%)
Missing	3 (2.1%)
DSI, mm (median)	1.2 (0.1-20)
DSI	
≤ 1 mm	58 (41.1%)
>1 mm	63 (44.7%)
M issing	20 (14.2%)
LN metastasis	
Positive	40 (32.3%)
Negative	84 (67.7%)
Total LN count, median	15 (4-42)
Metastatic lymph node count	
0	84 (64.7%)
1	14 (11.3%)
≥ 2	26 (21%)
Diabetes Mellitus, n	
Present	37 (26.1%)
Absent	105 (73.9)
Antidiabetic medication	
Metformin	25 (67.6%)
Insulin	7 (18.9%)
Metformin + insulin	3 (8.1%)
Other	2 (5.4%)
Extracapsular spread	
Present	11 (8.9%)
Absent	113 (91.1%)
StStage, n	
IA	18 (12.7%)
IB	82 (57.7%)
II	2 (1.4%)
IIIA	14 (9.9%)
IIIB	15 (10.6%)
IIIC	9 (6.3%)
IVA	2 (1.4%)
Adjuvant treatment	
Observation	86 (60.6)
RT	20 (14.1%)
CRT	36 (25.4%)
Median follow-up, months	22 (4-90)
Recurrence, n	
Yes	48 (33.8%)
No	94 (66.2%)
Recurrent site	
Local	16 (33.3%)
Regional	17 (35.4 %)
Distant	15 (31.3 %)
Status	
Alive	106 (74.6%)
Dead	36 (25.4%)

RV= Radical vulvectomy; BIFL= Bilateral inguinofemoral lymphadenectomy; UIFL= Unilateral inguinofemoral lymphadenectomy; RLE= Radical local excision; DSI= Deep stromal invasion; LVSI= Lymphovascular space invasion; LN= Lymph node; RT= Radiotherapy; CRT= Chemoradiotherapy

Patients with one macrometastasis (> 5 mm diameter) or two micrometastasis (≤ 5 mm diameter), or any evidence of extracapsular spread received adjuvant radiotherapy (RT) to the groins and pelvis including the primary site. Concurrent cisplatinum-based chemotherapy (CT) was given with the clinician's preference. Adjuvant RT of the vulva alone was performed if the surgical margin was positive or < 8 mm without any lymph node metastases.

Information regarding the medication use in DM was reached from the private patient's files or by calling the patient. Follow-up was planned every 3 months in the first 2 years, then every 6 months for the subsequent 3 years, annually thereafter. Recurrences were classified as local (primary tumor bed or residual vulva), regional (nodal), or distant.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software (version 22; SPSS Inc., Chicago, IL, USA). The data was expressed as median and range for continuous variables. Binary variables were reported as

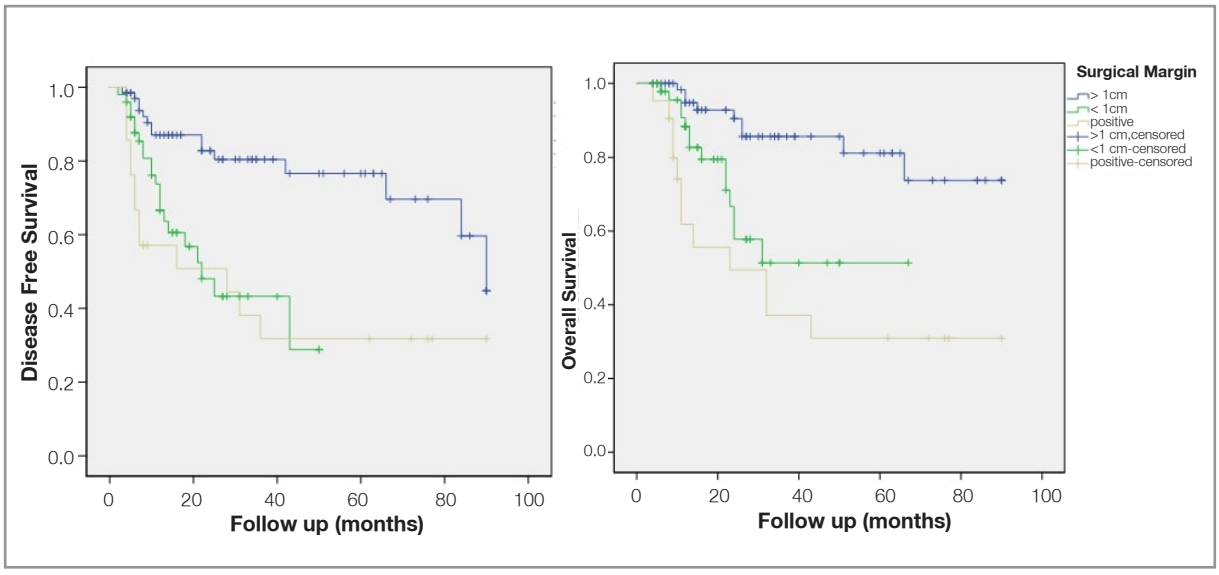

Figure 1. Survival by surgical margin. Five-year disease-free and overall survivals

counts and percentages. Categorical variables were evaluated using the χ^2 test or Fisher's Exact test as appropriate for the group size. DFS was calculated from the time of diagnosis to the time of disease recurrence, death or last follow-up. Overall survival (OS) was calculated as the time period between initial diagnosis of VC to the date of death or the last contact. Survival curves were generated using the Kaplan-Meier method, and the differences between survival curves were calculated using the log-rank test. In order to evaluate the prognostic factors for DFS and OS, a Cox-regression model was used. A p-value < 0.05 was considered as statistically significant.

RESULTS

A total of 181 patients fulfilled inclusion criteria. Of these, 39 patients were lost to follow-up and were excluded. The remaining 142 patients were included in the final study cohort. The clinicopathological characteristics of the study population were summarized in Table 1.

The median age of the cohort was 67.0 years (range; 35-85). 37 patients had Diabetes Mellitus (DM), of them 25 has used metformin as the medication. The median tumor size was 3.0 cm (range, 0.3-15), and the median DSI was 1.2 mm (range,0.1-20). 72.5% (103/142) of the tumors located at or close (≤ 2 cm) to the midline structures.

RS and bilateral IFL was performed in most of the cases (83.1%, 118/142), whereas RLE without IFL was performed in only 18 cases (12.7%). 21 patients (14.8%) had tumor on the resection margin whereas ≤ 1 cm and > 1 cm tumor free margin were found in 50 (35.2%) and 68 (47.9%) patients, respectively. 124 patients underwent IFL (118 bilateral and 6 unilateral). Among them, 40 patients (32.3%) had lymph node metastasis; extracapsular spread was detected in 11 of them (27.5%). The median number of lymph nodes dissected was 14 (range, 4-42). According to 2009 FIGO staging; Stage IA, IB, II, IIIA, IIIB, IIIC, IVA were determined in 18 (12.7%), 82 (57.7%), 2 (1.4%), 14 (9.9%), 15 (10.6%), 9 (6.3%), and 2 (1.4%) patients, respectively. 56 patients (39.4%) received adjuvant RT, of those 36 also received concurrent CT.

The overall recurrence rate was 33.8% (48/142) within a median follow-up time of 22 months (range, 4-90). Recurrence sites were as follows: local in 16 cases (33.3%), regional in 17 cases (35.4%), and distant in 15 cases (31.3%).

Five-year DFS rate was 55.8% with a median time of 84 months (SE:20.26, 95% CI, 44.28-123.72). The univariate analysis showed tumor size (5-year DFS 65.0% for tumor size ≤ 3 cm vs. 41.2% for > 3 cm, p= 0.021), DSI (5-year DFS 76.6% for stromal invasion ≤ 1mm vs. 38.5% for > 1 mm, p= 0.05), LVSI (5-year DFS 46.9% for LVSI present vs.

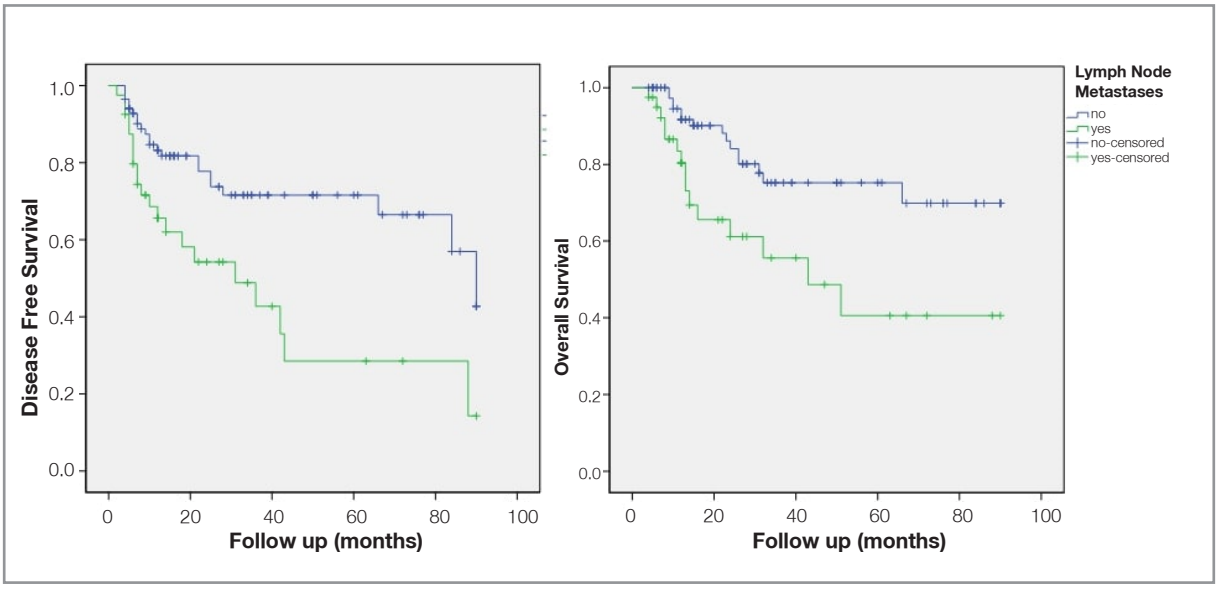

Figure 2. Survival by lymph node involvement. Five-year disease-free and overall survivals

66.0% for absent, p= 0.009), surgical margin (5-year DFS 31.7% for surgical margin positive vs. 28.8% for tumor free distance ≤ 1cm vs 76.6% for tumor free distance > 1cm, p< 0.001), extracapsular spread (5-year DFS 0% for extracapsular spread positive vs. 62.3% for absent, p= 0.033), lymph node metastasis (5-year DFS 28.5% for nodal metastasis present vs. 71.6% for absent, p= 0.001) were significantly related to DFS, although surgical margin (HR:6.4, 95% CI:1.39-29.74) and lymph node metastasis (HR:4.1, 95% CI:1.33-12.87) were found to be independent prognostic factors after multivariate analysis (Figure 1-2 and Table 2).

Five-year OS rate was 62.6% (not reached median yet). 74.6% of the patients were alive when this paper was written. The univariate analysis showed localization (5-year OS 37.2% for midline localization vs 68.9% for localized within 2 cm vs 65.8% for localized beyond 2 cm, p= 0.013), tumor size (5-year OS 70.0% for tumor size ≤ 3 cm vs. 46.6% for > 3 cm, p= 0.047), DSI (5-year OS 79.6% for stromal invasion ≤ 1 mm vs. 50.9% for > 1 mm, p= 0.016), LVSI (5-year OS 51.7% for LVSI present vs. 77.4% for absent, p= 0.012), surgical margin (5-year OS 30.9% for surgical margin positive vs. 51.3% for tumor free distance ≤ 1cm vs 81.1% for tumor free distance >1cm, p< 0.001), lymph node metastasis (5-year OS 40.6% for nodal metastasis present vs. 75.2% for absent, p= 0.005) were significantly related to OS. Among them, surgical margin (HR: 13.6, 95% CI: 1.94-96.05) and lymph node metastasis (HR: 6.3, 95% CI: 1.33-29.94) were found to be independent prognostic factors after multivariate analysis (Figure 1-2 and Table 3).

Specifically, we analyzed the effect of DM and metformin as a prognostic factor in terms of survival. There was no statistically difference in DFS and OS (5-year DFS 34.3% for DM and metformin users vs 55.6% for DM and non-metformin users vs 61.8% for non-DM, p= 0.16) (5-year OS 52.6% for DM and metformin users vs 62.2% for DM and non-metformin users vs 65.5% for non-DM, p= 0.74).

DISCUSSION

In the present study, we retrospectively analyzed 142 patients with primary SCC of the vulva who underwent radical surgery at 6 referral centers in Turkey. In our study, surgical margin and lymph node status appeared as independent prognostic factors for DFS and OS.

In the last FIGO staging system, a cut-off value of > 2 cm has been determined, as the larger tumors have poorer prognosis even regardless of nodal metastasis.[14] Aragona et al. investigated the prognostic factors in patients with scc of the vulva who had Stage ≥ IB, large (> 2 cm) tumors with tumor-free

Table 2. Univariate and multivariate analyses for disease free survival

	DFS*	Univariate	Multivariate		
		p	HR	CI 95%	p
Age, y, (n)		0.88			
≤ 65 (63)	54.1 %				
> 65 (79)	57.2 %				
Surgery		0.16			
RS + BIF	57.7 %				
RLE + UIF	83.3 %				
RLE	41.4 %				
Grade		0.15			
1	38.5 %				
2	21.0 %				
3					
Localization		0.059			0.54
Midline	37.2 %				
≤ 2 cm	68.9 %				
> 2 cm	65.8 %				
Tumor size		0.021			0.75
≤ 3 cm	65.0 %				
> 3 cm	41.2 %				
Depth of stromal invasion		0.05			0.68
≤ 1 mm	76.6 %				
> 1 mm	38.5 %				
LVSI		**0.009**			0.57
Yes	46.9 %				
No	66.0 %				
Surgical margin		**< 0.001**	**6.4**	1.39-29.74	**0.017**
Positive	31.7 %				
≤ 1 cm	28.8 %				
> 1 cm	76.6 %				
Extracapsular spread		**0.033**			0.17
Yes	0%				
No	62.3 %				
LN metastasis		**0.001**	**4.1**	1.33-12.87	**0.014**
Yes	28.5 %				
No	71.6 %				
DM with Metformin	34.3 %	0.16			
DM with non-metformin	55.6 %				
No DM	61.8 %				

*= 5-year disease free survival rate

RV= Radical vulvectomy; RLE= Radical local excision; RS= Radical surgery; BIF= Bilateral inguinofemoral lymphadenectomy; UIF= Unilateral inguinofemoral lymphadenectomy; DFS= Disease free survival; LN= Lymph node; LVSI= Lymphovascular space invasion; HR= Hazard ratio; CI= Confidence interval; DM= Diabetes Mellitus

margin (≥ 8 mm). They identified a cut-off value of ≥ 6 cm of diameter plus DSI > 4 mm and ≥ 8 cm of diameter irrespective of any other factor, from which value, survival drops remarkably.[7] This study questioned the management of a sub-group of patients who had primary bulky tumor without nodal metastasis and margin involvement, as there could be an under-treatment without adjuvant treatment suggested by the current guidelines.[15] We also found > 3 cm tumors have less survival in univariate analysis, but it was not statistically significant after multivariate analysis.

There are conflicting results regarding the surgical margin distance in VC. In a large retrospective study (AGO-CaRE-1), solely surgically treated node-negative patients with complete tumour resection (n= 289) were analyzed.[16] They could not show a statistically significant effect of surgical margin

Table 3. Univariate and multivariate analyses for overall survival

	DFS*	Univariate	Multivariate		
		p	HR	CI 95%	p
Age, y, (n)		0.44			
≤ 65 (63)	62.0 %				
> 65 (79)	63.7 %				
Surgery		0.47			
RS + BIF	64.4 %				
RV + UIF	75.0 %				
RLE	53.0 %				
Grade	0.069				
1	68.4 %				
2	58.3 %				
3	27.7 %				
Localization		0.013			0.41
Midline	44.5 %				
≤ 2 cm	79.9 %				
> 2 cm	59.3 %				
Tumor size		0.047			0.76
≤ 3 cm	70.0 %				
> 3 cm	46.6 %				
Depth of stromal invasion		0.016			0.36
≤ 1 mm	79.6 %				
> 1 mm	50.9 %				
LVSI		0.012			0.17
Yes	51.7 %				
No	77.4 %				
Surgical margin		< 0.001	13.6	1.94-96.05	0.009
Positive	30.9 %				
≤ 1 cm	51.3 %				
> 1 cm	81.1 %				
Extracapsular spread		0.40			
Yes	38.9 %				
No	65.5 %				
LN metastasis		0.005	6.3	1.33-29.94	0.020
Yes	40.6 %				
No	75.2 %				
DM with Metformin	52.6 %	0.74			
DM with non-metformin	62.2 %				
No DM	65.5 %				

*= 5-year overall survival rate

RV= Radical vulvectomy; RLE= Radical local excision; RS= Radical surgery; BIF= Bilateral inguinofemoral lymphadenectomy; UIF= Unilateral inguinofemoral lymphadenectomy; OS= Overall survival; LN= Lymph node; LVSI= Lymphovascular space invasion; HR= Hazard ratio; CI= Confidence interval; DM= Diabetes Mellitus

distance on local recurrence. In a study by Arvas et al., the importance of clear surgical margin distance in patients operated for primary SCC of the vulva was investigated. In a sub-group analysis of the 61 patients who had no lymph node metastasis or adjuvant RT, they found > 2 mm tumor-free pathological margin was associated with better local control although ≥ 8 mm pathological margin has been a standard approach in the literature.[10] Our results also showed a significant association between > 1 cm pathological tumor-free margin and survival after multivariate analysis. On the other hand, Höckel et al. introduced a new concept of vulvar field resection based on the ontogenetic anatomy, irrespective of the tumor margin distance.[17] They treated 38 VC with their new technique, and reported no local recurrence in a median follow-up time of 19 months. Prospective randomized trials comparing these dif-

ferent surgical techniques are needed to know the real impact of surgical margin distance on survival.

Lymph node status at initial diagnosis is accepted as the most important independent prognostic factor, although the rest of the clinicopathological variables were controversial.[18] Woelber et al. demonstrated that the only independent prognostic factor in VC was the lymph node involvement. Interestingly, they pointed out the dominance of local recurrence pattern in patients who had nodal metastasis, even in the case of negative surgical margin.[2] Underknown tumor biology or Human Papilloma Virus infection in rest of the vulva could be answer for these local recurrences. We also found LN metastasis was an independent prognostic factor for survival. Patiens with LN metastasis had a four-fold increased risk of recurrence and six-fold increased risk of dead from disease compared to LN negative patients. But just 33.3% of our recurrences were located at the vulva. Different study populations and adjuvant treatment protocols among centers could be the reason for this difference.

Regarding stromal invasion, although most of the authors accepted its relevance on survival, they suggested various cut-off values. FIGO applies 1 mm cut-off to increase the stage from IA to IB, whereas Iacaponi et al. sets > 4 mm value as their DFS was effected in that value (relapse rate of 52.9% for DSI > 4 mm vs 43.5% for DSI < 4 mm).[3,14] In our study, although DSI > 1 mm was associated with recurrence and survival, it could not reach a statistical significance after multivariate analysis. In 2009, FIGO modified VC staging system, as the detailed features of the lymph node metastasis were the greatest innovation. Accordingly, extracapsular spread increases stage to IIIC.[14] Bogani et al. evaluated 101 patients affected by VC, and found that DSI > 2 mm was the only factor predicting for local recurrence whereas extracapsular involvement predicted for regional recurrence.[5] In our study, extracapsular spread was also associated with a higher recurrence rate (62.3%). But it was not statistically significant after multivariate analysis.

Recent clinical studies showed that metformin use is associated with improved survival in gynecologic malignancies and and pre-clinical studies supported its anti-cancer effect in endometrial, ovarian, and cervical cancer.[19,20] But, up to now, there has been no data in the literature, analyzing the possible effect of metformin in VC. Although it was not statistically significant, we found patients using metformin had less 5-year survival rate (34.3%) when we compared with other groups (DM with non-metformin use 55.6% and Non-DM 61.8%, p= 0.16). Possible explanation for this "unexpected" result, could be the higher incidence of advanced stage disease in diabetic group. Further well designed clinical and preclinical studies are needed to better know the real effect of metformin in VC.

Our study had some limitations. Because of the rare incidence of the disease, it is difficult to complete a prospective trial in a reasonable time. That's why, our study has a retrospective design. Also, the specimens were examined by different pathologists at these centers. But the power of our study comes from the high number of patients included and the qualified gyne-oncologic centers participated the study.

In conclusion, surgical margin status and lymph node involvement were the independent prognostic factors in terms of recurrence and overall survival. Metformin had no beneficial effect for patients with VC.

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