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Prognostic Factors and Recurrence Patterns of Vulvar Cancer

Vulva Kanserinde Prognostik Faktörler ve Nüks Paternleri

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ABSTRACT

Objective

Vulvar cancer is a rare disease among gynecological cancers, mostly affecting post-menopausal women. The associated prognostic factors are not clear enough and the results in the studies are inconclusive due to rarity. We aimed to determine the impact of clinicopathological and therapeutic prognostic factors on the course of treatment and the patient's survival. The characteristics of recurrences, anatomic localization, and treatment strategies are also described.

Material and Methods

A total of 46 patients with clinicopathological diagnosis of squamous cell carcinoma of vulva who were treated at our tertiary care center between 2004 and 2021 were included in this retrospective cohort analysis study. Data on demographic, clinical and obstetric characteristics of patients at the time of initial diagnosis as well as tumor clinicopathologic features, treatment modalities, and oncological outcomes were recorded. Data were analyzed using Cox proportional hazards regression and Kaplan-Meier methods.

Results

The overall recurrence rate was 34.7% (n=16). The average median overall survival (OS), 5-year OS rate and median 5-year OS was 172 months, 63.6% and 51.9 months, respectively. Five-year progression-free survival rate was 71.7%. Patients experiencing recurrence demonstrating a notably shorter survival duration compared to those without recurrence ($p<0.05$). On logistic regression analysis receiving radiotherapy and neutrophil value were important prognostic factors for recurrence. The risk of recurrence in those who received radiotherapy (RT) was found to be 15 times higher compared to those who did not receive radiotherapy (OR = 15.032). The chance of recurrence rises by 0.05% (OR = 1.0005) for every unit increase in the neutrophil value.

Conclusion

Receiving radiotherapy is an important predictor of vulvar cancer recurrence.

Key Words

Disease free survival, Prognostic factors, Recurrence, Survival Rate, Vulvar cancer

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ÖZ

Amaç

Vulva kanseri, jinekolojik kanserler arasında nadir görülen bir hastalık olup, çoğunlukla postmenopozal kadınları etkilemektedir. İlişkili prognostik faktörler yeterince net değildir ve çalışmalardaki sonuçlar, hastalığın nadir görülmesi nedeniyle kesinlik taşımamaktadır. Klinikopatolojik ve terapötik prognostik faktörlerin tedavi süreci ve hasta sağ kalımı üzerindeki etkisini belirlemeyi amaçladık. Nükslerin özellikleri, anatomik lokalizasyonu ve tedavi stratejileri de detaylandırılmıştır.

Gereç ve Yöntemler

Bu retrospektif kohort analizine, 2004–2021 yılları arasında üçüncü basamak sağlık merkezimizde tedavi edilmiş ve klinikopatolojik olarak vulvar skuamöz hücreli karsinom tanısı almış toplam 46 hasta dahil edilmiştir. Hastaların ilk tanı anındaki demografik, klinik ve obstetrik özelliklerinin yanı sıra tümörün klinikopatolojik özellikleri, tedavi modaliteleri ve onkolojik sonuçlarına ilişkin veriler kaydedilmiştir. Veriler, Cox regresyon analizi ve Kaplan-Meier yöntemleri kullanılarak analiz edilmiştir.

Bulgular

Genel nüks oranı %34,7 (n=16) olarak bulunmuştur. Ortalama medyan genel sağ kalım (OS), 5 yıllık OS oranı ve medyan 5 yıllık OS sırasıyla 172 ay, %63,6 ve 51,9 ay olarak hesaplanmıştır. Beş yıllık progresyonsuz sağ kalım oranı %71,7 olarak belirlenmiştir. Nüks olan hastalar, nüks olmayanlara kıyasla belirgin şekilde daha kısa bir sağ kalım süresine sahiptir ($p<0,05$). Lojistik regresyon analizine göre radyoterapi alımı ve nötrofil değeri, nüks için önemli prognostik faktörler olarak belirlenmiştir. Radyoterapi alan bireylerde nüks riskinin, radyoterapi almayanlara kıyasla 15 kat daha yüksek olduğu tespit edilmiştir (OR = 15,032). Nötrofil değerindeki her bir birimlik artış, nüks olasılığını %0,05 oranında artırmaktadır (OR = 1,0005).

Sonuç

Radyoterapi alımı, vulva kanseri nüksü için önemli bir belirleyicidir.

Anahtar Kelimeler

Hastalıksız sağ kalım, Prognostik faktörler, Nüks, Sağ kalım oranı, Vulva kanseri

INTRODUCTION

Vulvar cancer is a rare but serious gynecologic malignancy representing about 4-5% of malignancies of the female genital tract (1). This neoplasm arises from both human papillomavirus (HPV)-mediated and HPV-independent pathways or crossing over of two pathogenetic pathways (2). Squamous cell carcinoma (SCC) accounts for 85-90% of vulvar cancer and the remaining cases consist of other rare histologic types (3). It is predominantly a disease of postmenopausal women, however there is an increasing incidence among young women due to HPV infection, smoking, screening tests, and changes in sexual behavior (4-6). Although the vulva is an external genital organ and vulvar cancer is curable at early stage, the patients are unfortunately usually diagnosed late due to misdiagnosis of vulvovaginal inflammation, leading to a worsening prognosis (7).

Because of the concomitant comorbidities and the patient's relatively advanced age at diagnosis, patient survival may differ dramatically between stages. The associated prognostic factors are not clear enough and the results in the studies are inconclusive due to rarity (1). Tumor size, depth of invasion, lymph node status, extension of tumor to adjacent or distant structures are the most important prognostic factors mentioned in new International Federation of Gynecology and Obstetrics (FIGO 2021) staging classification and treatment modalities are applied according to these parameters to prevent a recurrence (8). Surgery together with primary chemoradiation depending on the extension of the disease, play a prominent role in the treatment of this cancer.

Prognosis depends mainly on the metastatic status of the groin lymph nodes and stage (9). Other clinicopathological factors including age, tumor size, and depth of invasion, free surgical margin, lymphovascular space invasion (LVSI), accompanying premalignant lesions are less important in defining prognosis (10). Age was found to be a statistically significant progrostic factor in some studies but not in others (1, 11, 12). There is continuing debate regarding the ideal tumor-free margin to lower the risk of local recurrences (7, 13-15). The results of the studies on the other factors mentioned are also controversial (1, 9, 16, 17).

In this study, we aimed to determine the impact of clinicopathological and therapeutic prognostic factors on the course of treatment and the patient's survival. The characteristics of recurrences, anatomic localization, and treatment strategies are also described.

MATERIAL and METHODS

A total of 46 patients with clinicopathological diagnosis of squamous cell carcinoma of vulva who were treated at our tertiary care center (Department of Gynecological Oncology, Akdeniz University Faculty of Medicine, Antalya, Turkey) between 2004 and 2021 were included in this retrospective cohort analysis study. The study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the institutional ethics committee (Akdeniz University Clinical Research Ethics Committee - KAEK-854; date: 01.12.2021). Informed consent was obtained from each subject or their first-degree relatives (for the deceased ones).

Demographic, clinical and obstetric characteristics of patients at the time of initial diagnosis and tumor clinicopathologic features were retrieved from paper- and electronic medical records. Data on age, body mass index (BMI), reproductive history, clinical manifestations at the time of diagnosis, smoking, menopausal status, preoperative systemic immune-inflammation index (SII) (defined as platelets × neutrophils/lymphocytes), tumor characteristics (histopathological subtype, grade when available, tumor size, anatomic location, depth of invasion, surgical margin status, tumor-free distance, LVSI and stage according to the FIGO 2021 staging classification, co-test results when available, tumor size, treatment characteristics regarding the primary treatment modality, type of surgical interventions, number of surgically removed lymph nodes, number of positive lymph nodes, accompanying preneoplastic lesions, chemoradiotherapy (regimen, setting and the number of cycles), recurrence status, treatment protocols in case of recurrence, overall survival (OS), disease-free survival (DFS) were recorded (8). Patients with histologic types other than squamous cell carcinoma, those with insufficient data or lack of attendance to follow-up, and those with metastasis originating from gynecologic or non-gynecologic primary sites were excluded from the study.

Follow-up visits for recurrence assessment were performed at 3-month intervals for the first 2 years and every 6 months in the following years. Data on symptoms, tumor markers, and pelvic examination findings were recorded at each visit. Imaging modalities used in relapse detection were chest X-ray, pelvic ultrasound, and computed tomography (CT) or Positron Emission Tomography–Computed Tomography (PET/CT). OS was defined as the time from initial diagnosis to death. DFS was defined as the interval between the date of remission and the date of the first recurrence detected. In the case of recurrent disease, its anatomic localization, characteristics, and treatment strategies were analyzed. Recurrent disease regardless of anatomical localization, death, or last follow-up were the endpoints for this study. Variables such as age, BMI, gravidity and parity, preoperative systemic immune-inflammation index, menopausal status, mode of delivery, comorbidity, smoking, initial complaint, anatomic location of lesion, palpable inguinal lymphadenopathy, LVSI, size of the tumor, depth of invasion, tumor-free distance, number of malign lymph nodes, tumor stage, treatment modality, type of surgical intervention, surgical margin status, accompanying preinvasive lesions in surgical margin and chemoradiotherapy were chosen to be tested regarding their potential value as prognostic factors for recurrence of patients with squamous cell carcinoma of vulva.

Statistical Analysis

Statistical analyses were performed using the SPSS package program (IBM SPSS Statistics 27). Frequency tables and descriptive statistics were used to interpret the results. Parametric methods were used for the measured values suitable for normal distribution. In accordance with the parametric methods, the "independent sample t" test (t-table value) was used to compare the measured values of two independent groups. Non-parametric methods were used for the measured values that did not fit the normal distribution. "Mann-Whitney U" test (Z-table value) was used to compare the measured values of two independent groups. "Pearson-$\chi 2$" cross-tabulations were used to analyze the relationships between two qualitative variables. "Binary Logistic Regression method; Backward LR model" was used to determine the risk factors affecting the recurrence status. All prognostic variables found to be significant in univariate analysis were included in regression analysis. PFS and OS were estimated using the Kaplan-Meier method. p-values ≤ 0.05 in two-sided tests were regarded as significant.

RESULTS

A total of forty-six patients with primary squamous cell carcinoma of the vulva were included in this study. Characteristics of study population by women with or without recurrence of vulvar squamous cell carcinoma are shown in Table I and tumor clinicopathologic features and treatment modalities are shown in Table II. The median age of the non-recurrence group was 60 years, with a BMI of 27.6 kg/m2, while in the recurrence group, the median age and BMI were 63 years and 27.3 kg/m2, respectively. More than half of these patients had other co-morbidities, including chronic hypertension (52% in non-recurrent group, 62.5% in recurrent group), diabetes (23.8% in non-recurrent group, 12.5% in recurrent group) and cardiovascular diseases (4.8% in non-recurrent group), with many having multiple co-morbidities. No statistically significant relationship was found between recurrence status and parity, menopause, mode of delivery, comorbidities, smoking, initial complaint, or lesion anatomical location ($p > 0.05$). Recurrence status was determined to be independent and homogeneous with respect to the specified characteristics. A statistically significant relationship was found between recurrence status and palpable LAP ($p<0.05$). It was determined that 24 individuals (80.0%) without recurrence did not have a palpable LAP while eight individuals (50.0%) with recurrence had a palpable LAP. Leukocyte, neutrophil, and SII values measured at the time of initial

Table I. Characteristics of the study population according to recurrence status of vulvar squamous cell carcinoma

Characteristics	No Recurrence (n=30)	Recurrence (n=16)	P value
Age (years), median	61 (32-86)	63 (42-87)	0.205
BMI (kg/m²), median	27.6 (16-51)	27.3 (22.1-35.4)	0.453
Gravida, median	2.5 (0-6)	3.5 (0-11)	0.054
Parity, median	2.0 (0-5)	3.0 (0-8)	0.086
Menopause,n, %			
No	9 (30)	2 (12.5)	0.185
Yes	21 (70)	14 (87.5)	
Mode of delivery, n, %			
NVD	23(76.7)	14(87.4)	0.669
CS	4 (13.3)	1(6.3)	
None	3 (10.0)	1(6.3)	
Comorbidity n, %			
No	14 (46.7)	6 (37.5)	0.550
Yes	16 (53.3)	10 (62.5)	
Smoking n, %			
No	23 (76.7)	15 (93.8)	0.145
Yes	7 (23.3)	1 (6.2)	
Initial complaint n, %			
Asymptomatic	1 (3.3)	1 (6.3)	0.369
Mass	27 (90)	14 (87.4)	
Itching	2 (6.7)	-	
Bleeding	-	1 (6.3)	
Location n, %			
Labium major	7 (23.3)	3 (18.7)	0.209
Labium minor	12 (40.0)	5 (31.3)	
Clitoris	8 (26.7)	2 (12.4)	
Posterior forchette	3 (10)	5 (31.3)	
Other	-	1 (6.3)	
Palpable LAP n, %			
No	24 (80)	8 (50)	**0.035**
Yes	6 (20)	8 (50)	
Leukocyte	6468.68±2150.63	7886.67±2527.98	**0.030**
Neutrophil (/ml), mean ± SD	3678.75±1693.77	4929.16±1720.35	**0.009**
Lymphocyte (/ml), mean ± SD	2036.87±874.58	1915.67±782.25	0.633
Platelet (/ml), mean ± SD	242843.75± 72751.35	278633.33± 70736.84	0.113
SII, mean ± SD	565.06±516.05	938.80±986.89	**0.022**

SD: Standard deviation, BMI: Body mass index, NVD; normal vaginal delivery, CS; caesarean section, LAP; Lymphadenopathy, SII; systemic immune-inflammation index.

Table II. Tumor clinicopathologic features and treatment modalities according to recurrence status in vulvar squamous cell carcinoma

Characteristics	No Recurrence (n=30)	Recurrence (n=16)	P value
Tumor diameter (mm), median	21 (5-55)	28(40-10)	0.068
Mass size, clinically (cm), median	2.5 (1-8)	3.0 (2-7)	0.165
Depth of invasion (mm), median	0.9 (0.2-1.8)	1.1 (0.2-2)	0.187
Free surgical margin distance (mm), median	6.0 (0-21)	6.5 (0-20)	0.989
LVSI n, %			
None	25 (96.2)	10 (71.4)	**0.024**
Yes	1 (3.8)	4 (28.6)	
Surgical margin n, %			
Negative	24 (92.3)	13 (92.9)	0.950
Positive	2 (7.7)	1 (7.1)	
Positive groin nodes	0.18±0.72	0.93±1.38	**0.047**
Concomitant preneoplastic lesion n, %			0.287
dVIN			
No	24 (92.3)	14 (100)	
Yes	2 (7.7)	-	
Lichen Sclerosis			
No	20 (76.9)	10 (71.4)	0.702
Yes	6 (23.1)	4 (28.6)	
Lichen simplex chronicus			
No	22 (84.6)	14 (100)	0.122
Yes	4 (15.4)	-	
FIGO 2021 stage n, %			
1	25 (83.3)	6 (37.5)	**0.003**
2	-	4 (25)	
3	4 (13.3)	6 (37.5)	
4	1 (3.3)	-	
Primary treatment n, %			
Surgery	26 (86.7)	14 (87.5)	0.936
CRT	4 (13.3)	2 (12.5)	
Surgery type, n (%)			
Radical vulvectomy+ILND	18 (69.2)	14 (100)	0.068
Simple vulvectomy	8 (30.8)	-	
Radiotherapy			
No	23(76.7)	3(18.8)	**<0.001**
Yes	7 (23.3)	13(81.2)	
Chemotherapy			
No	26 (86.7)	11 (68.8)	0.145
Yes	4 (13.3)	5 (31.2)	

LVSI; Lymphovascular space invasion, dVIN; Differentiated vulvar intraepithelial neoplasia, FIGO; International Federation of Gynecology and Obstetrics.

diagnosis were considerably higher in the recurrent group than in the non-recurrent group (p<0.05). LVSI and stage were found to be statistically significantly correlated with recurrence status (p<0.05). As the patient's FIGO stage increases, the likelihood of recurrence also increases. In the advanced-stage group (stage 3-4), the risk of recurrent disease was significantly higher compared to the group of patients with earlier-stage disease. It was observed that the group treated with RT developed significantly more recurrences compared to women who did not receive RT (p<0.05). However, tumor diameter, clinically measured mass size, depth of invasion, free surgical margin distance, involvement of the pathologic margin, associated preneoplastic lesions, surgery type and chemotherapy were not associated with a risk of recurrence. A backward stepwise logistic regression analysis, inclu- ding all parameters that could influence the risk of recurrence, was conducted, and the optimal model is presented in the table III.

Table III. Logistic Regression Model Established Based on Recurrence Risk

Characteristics	B	S.H.	Wald	sd	p	OR	95%C.I.
RT*	3.556	1.183	9.033	1	**0.003**	15.032	3.444-36.159
Neutrophil	0.001	0.001	4.445	1	**0.035**	1.0005	1.0001-1.0009
Constant	-0.174	0.923	0.036	1	**0.041**	0.840	

* Reference Category: Those who did not receive radiotherapy (RT) CCR=82.6% $\chi 2(5)=6.169$; p=0.520

It was determined that receiving RT is a significant parameter affecting the risk of recurrence (p<0.05). The risk of recurrence in those who received RT was found to be 15.032 times higher compared to those who did not receive RT (OR = 15.032). Furthermore, the neutrophil value was found to be a significant parameter influencing the recurrence probability (p<0.05). The chance of recurrence rises by 0.05% (OR = 1.0005) for every unit increase in the neutrophil value.

The overall recurrence rate was 34.7% (n=16). Six women recurred to the local region, seven to groin and three to distant site, after a mean interval of 40.9±4.95 months. Fourteen of these patients died of progressive disease while two of them are still alive. Recurrence was detected in six patients in each stages 1 and 3, and four in stage 2. A total of 13 patients developed local recurrence, three in vulva, three in clitoris, three in vagina and seven in groin; no skin bridge recurrence was observed. Two patients had distant metastasis in the lung and another patient had metastasis in the L5 vertebra. There was no correlation between the initial lesion site and localization of the recurrent disease. The recurrences were managed through various treatment modalities: three cases underwent excision alone, seven cases were treated with chemotherapy, three cases received RT following excision, and three cases were treated exclusively with RT .
Of the total number of participants 15 (32.6%) patients died and the average median overall survival (OS), 5-year OS rate and median 5-year OS was 172 months, 63.6% and 51.9 months, respectively (Figure 1 and 2).

Figure 1. Kaplan-Meier curve for overall survival (OS) in women with vulvar cancer.

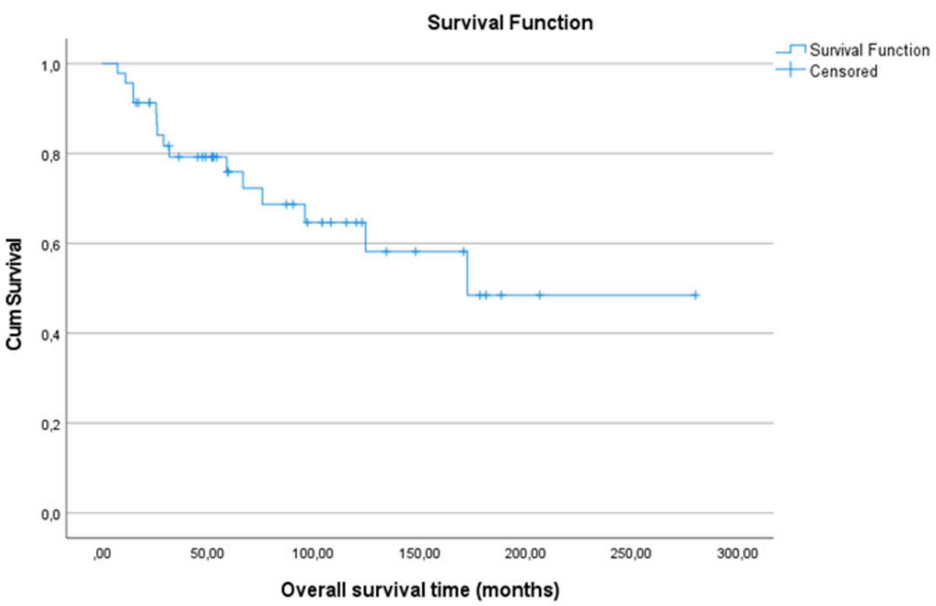
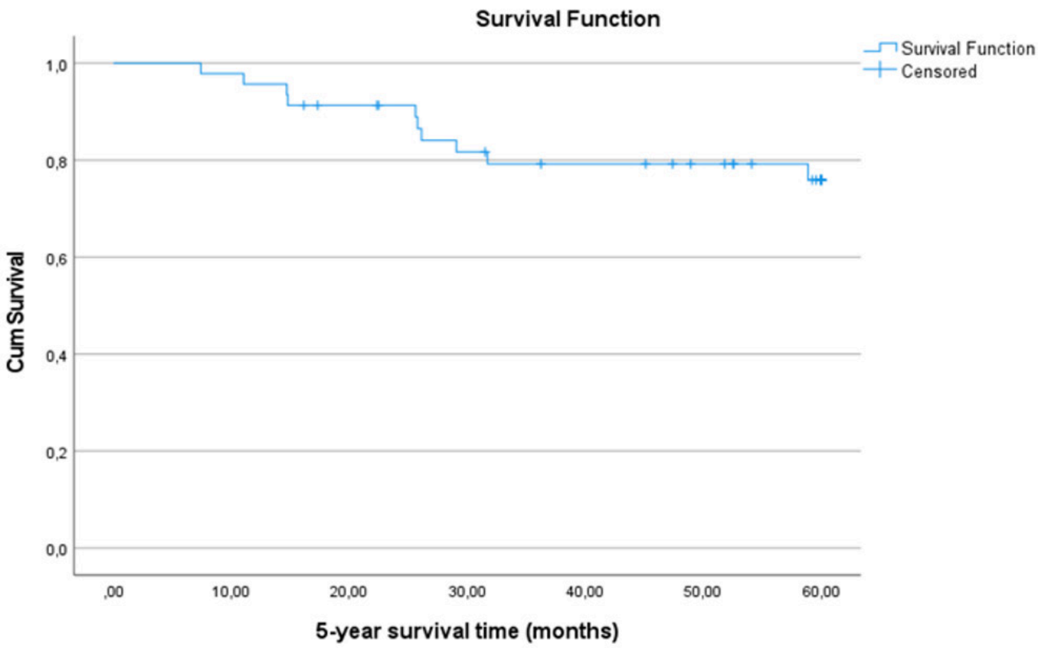
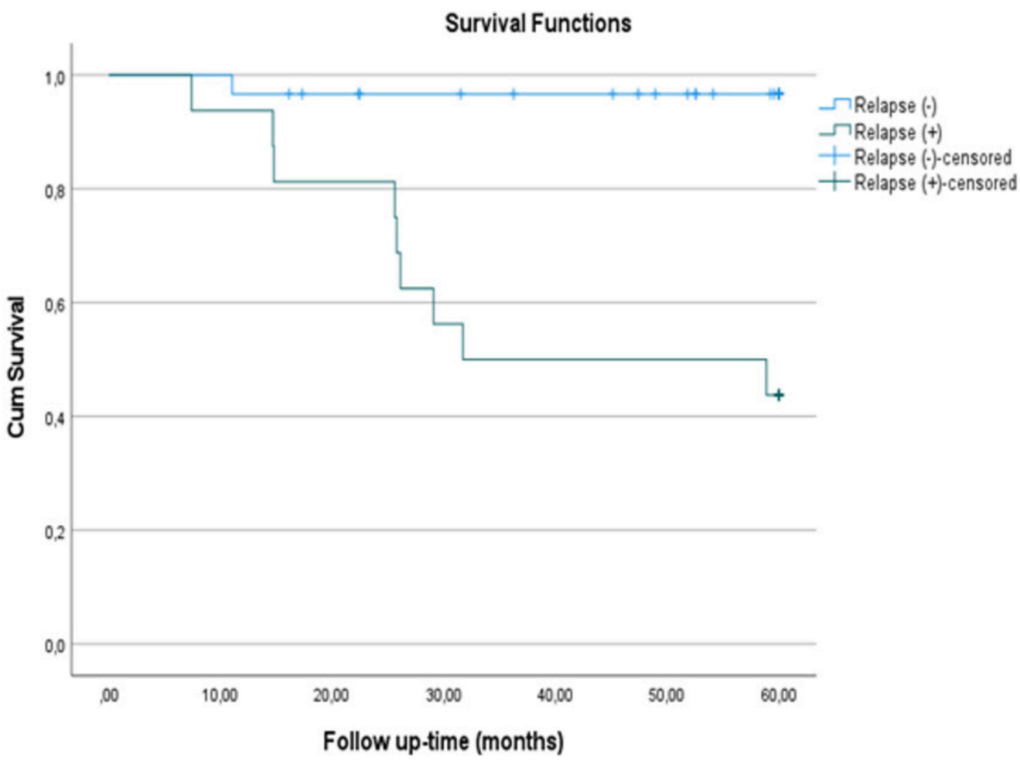


Figure 2. Kaplan-Meier curve for five-year overall survival (OS) in women with vulvar cancer.



The progression-free survival rate at 5 years was 71.7%. Upon analysis of the overall survival duration stratified by recurrence status, it was observed that the mean survival time for patients with recurrence was 40.9 months, whereas for those without recurrence, the mean survival time was 58.4 months. Statistical analysis revealed a significant difference in mean survival times between the two groups, with patients experiencing recurrence demonstrating a notably shorter survival duration compared to those without recurrence ($p<0.05$). Comparison of overall survival according to recurrence status is shown in Figure 3.

Figure 3. Comparison of overall survival with Kaplan-Meier curves according to recurrence status.



DISCUSSION

In this study, 46 patients suffering from vulvar squamous cell carcinoma were analyzed for prognostic factors and recurrence patterns. The results demonstrate that palpable lymphadenopathy (LAP), leukocyte and neutrophil values in the initial serum analysis, SII, LVSI, metastasis to groin lymph nodes, FIGO stage, and receiving RT were statistically significant predictors for vulvar recurrence. On multivariate analysis, only neutrophil value and receiving RT were identified as significant independent predictors for recurrence.

Prior reports evaluating the prognostic factors associated with vulvar cancer recurrence have shown conflicting results. Some retrospective studies have identified tumor size, depth of invasion, tumor-free margin distance, BMI, and age as significant prognostic factors; however, these factors were not found to be predictive of recurrence in other studies (1, 9-12, 16-18). According to the study conducted by Tan et al., adjuvant RT and chemotherapy have been demonstrated to be statistically significant factors influencing prognosis (5). However, our findings partially align with this study, as chemotherapy was not identified as a significant prognostic factor in the univariate analysis.

The clinicopathological factors influencing the recurrence of vulvar cancer remain incompletely understood, with several critical issues requiring further clarification. These include the optimal number of lymph nodes to be surgically removed, the clinical significance of isolated tumor cells and micrometastases in sentinel lymph nodes, the role of adjuvant therapy, and the minimum tumor-free surgical margin required to prevent recurrence. Additionally, the impact of these factors on OS and DFS has yet to be fully elucidated. It has been suggested that, following complete tumor resection, the significance of free surgical margins may be relatively limited (19). Furthermore, it is hypothesized that many cases classified as recurrences may, in fact, represent second primary tumors arising from the surrounding abnormal tissue, particularly in patients with premalignant vulvar disease. This hypothesis is further supported by the findings of our study, as well as by other studies in the literature, which collectively demonstrate that the majority of local recurrences occur at sites distinct from the primary tumor location (20).

Although our study population is relatively small, we observed that recurrences consistently occurred at sites distinct from the primary tumor and were independent of lymph node status. This finding suggests that recurrence may be influenced by a multifactorial etiology, highlighting the potential involvement of diverse contributing factors. Genomic alterations or disruptions in molecular signaling pathways may contribute to the pathogenesis of vulvar cancer relapse; however, this association is not as well-defined as it is in endometrial cancer (21). Currently, our understanding of the patterns and mechanisms underlying recurrence in vulvar cancer remains limited and insufficiently characterized.

There is continuing debate regarding the ideal tumor-free margin to lower the risk of local recurrences. In general, it is recommended to resect a 1-2 cm margin of grossly normal tissue to achieve a pathologic tumor-free distance of at least 8 mm in formalin-fixed specimens, as this is considered essential for reducing the risk of local recurrence (9). A retrospective study demonstrated that a surgical margin of >8 mm is associated with a 50% reduction in local recurrence rates (22). Furthermore, another study reported a 58% recurrence rate among patients with close surgical margins (<8 mm) (23). Additionally, some authors have observed a significantly higher risk of recurrence in cases where the surgical margin was ≤5 mm (24). Woelber and Nooij et al. demonstrated that the recurrence rate did not significantly differ between lesions with surgical margins of less than 8 mm and those with margins of at least 8 mm (25, 26). In another study, surgical margins of ≤2 mm were associated with a significantly higher risk of recurrence compared to margins >2 mm. However, a contrasting review has reported findings that contradict this observation, suggesting variability in the evidence regarding the impact of surgical margin width on recurrence risk (27, 28). ESGO (European Society of Gynaecological Oncology) recommends that a pathological minimal margin of greater than 2–3 mm is considered adequate (7). In the conducted study, no statistically significant difference was observed in the free surgical margin distances between the patient groups with and without recurrence. Therefore, this parameter was not identified as a significant prognostic factor in the analyses performed.

The most significant individual predictor in our analysis was the administration RT. Specifically, patients who received adjuvant RT were found to have a 15-fold greater probability of developing recurrence. Neutrophil value was another significant factor; however, its effect was not as pronounced as that of RT. Although RT is an effective treatment modality for preventing local recurrence, it has been demonstrated that patients who received RT had lower survival rates compared to those who did not. This observation may be attributed to several factors, including the diagnosis of RT-treated patients at more advanced stages, closer surgical margins than recommended, larger tumor diameters, a higher number of metastatic lymph nodes, the presence of lymphovascular or perineural invasion, and a greater depth of tumor invasion (1).

The minimal impact of neutrophil values on recurrence or the inability to identify the SII as an independent factor may be attributed to the fact that the majority of our patients (n=31) were diagnosed at stage 1 and low tumor load. Preoperatively free circulating tumor cells were linked to elevated inflammatory indices, potentially indicating advanced illness and a higher likelihood of metastasis (29, 30). In a study conducted by Bartl et al., the SII measured before treatment was independently associated with poorer survival outcomes, separate from other prognostic factors (31). Previous studies have also demonstrated that the pretreatment neutrophil-to-lymphocyte ratio (NLR) is directly associated with the nodal involvement status in vulvar squamous cell carcinoma (32). The exact role of inflammatory indices in vulvar cancer has not yet been fully understood. However, given that inflammatory processes are thought to play a role in the development of vulvar cancer, a potential relationship between these indices and the disease is likely to exist.

The limitations of our study stem from its retrospective design, single-institutional scope, and relatively small population size. Consequently, the results of our study may not fully capture the precise clinicopathological prognostic factors and recurrence characteristics of this rare disease. However, conducting a prospective study for such a rare condition presents significant challenges. One of the limitations of the study is that the pathology slides archived were not reviewed. Considering the changes in the definition of invasion depth in the recently updated FIGO staging system, the stages of some patients, and consequently their survival outcomes might have been revised, if the slides had been re-reviewed by the pathologists. Furthermore, we were unable to assess the impact of prognostic factors, including sentinel lymph node status, tumor grade, and HPV status of the tumor, as data on these variables were unavailable. The sentinel lymph node biopsy is now a standard procedure in the treatment of patients with early-stage vulvar cancer which significantly reduces morbidity and improves quality of life. Since, the patients included in our study were diagnosed long before the concept of sentinel lymph node emerged, we were unfortunately unable to examine the impact of this factor. It is important to note that HPV status is a relevant prognostic factor, as HPV-positive vulvar cancers are generally associated with more favorable outcomes compared to HPV-negative cases. Had we been able to incorporate the HPV status of the tumors into the logistic regression analysis, more definitive results could have been obtained. The primary etiological factor in the development of vulvar cancer in HPV-negative patients may be the premalignant potential of chronic dermatoses, such as lichen sclerosus. However, in our study, the presence of concomitant lichen sclerosus with vulvar cancer did not emerge as a significant prognostic factor in univariate analysis. One advantage of the study was that uniform surgical procedures were performed by a limited number of specialized surgeons at our university hospital, which serves as a referral center for vulvar cancer.

CONCLUSION

Palpable lymphadenopathy, leukocyte and neutrophil values in the initial serum analysis, SII, LVSI, metastasis to groin lymph nodes, FIGO stage, and receiving RT were identified as statistically significant predictors for vulvar cancer recurrence. However, on logistic regression analysis, only neutrophil value and the administration of RT were found to be significant independent predictors for recurrence.

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Ethics Committee Approval

This research complies with all the relevant national regulations, institutional policies and is in accordance the tenets of the Helsinki Declaration, and has been approved by the Akdeniz University Medical Faculty Ethical Committee (approval number: KAEK-854).

Informed Consent

All the participants’ rights were protected and written informed consents were obtained before the procedures according to the Helsinki Declaration.

Conflicts of Interest

The authors have no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

Author contributions

S.S developed the theory and performed the computations, S.S designed the study, T.Ş. encouraged S.S. to investigate and supervised the findings of this work. H.A.T. and S.S. collected data, verified the analytical methods, S.D. reviewed the literature, S.S. wrote the manuscript, T.Ş. conducted a peer review, S.S provided resources, tools and equipment,T.Ş. took responsibility for biological materials and patients All authors discussed the results and contributed to the final manuscript.

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