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Management of Vulvar Cancer Our Clinical Experiences

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ABSTRACT

Background/Aim: Vulvar cancer is a rare malignancy. It frequently affects postmenopausal women. There is no specific screening for vulvar cancer. Treatment is often surgical. The risk of recurrence is high. Lymph node involvement is an important prognostic factor in vulvar cancer. The primary purpose of this study is to share our institutional experience in managing vulvar cancer patients.

Materials and Methods: This study is a retrospective study. The study was ultimately conducted with 39 participants. Descriptive analyzes are frequency, percentage, minimum/maximum values, mean, standard deviation, and median. Risk factors for relapse were evaluated by binary logistic regression analysis. Cox regression analyses analyzed analyzes of factors related to survival. Survival analyzes were calculated using the Kaplan-Meier method, and significant differences were determined by the Log Rank (Mantel-Cox) test. $P<0.05$ was considered statistically significant in the analyses.

Results: Half of the patients (n=19; 50.0%) had vulvar mass complaints. While lesions related to vulvar cancer were observed in 13 participants before cancer diagnosis, no lesions were observed in 25 participants (65.8%). Squamous cell carcinoma was detected in 31 (81.6%) participants. Eleven (28.2%) participants had a recurrence. According to the logistic regression analysis, it was determined that the risk factors included in the model did not have statistically significant effects. Cox regression analysis was performed to determine the effects of factors on overall survival. It was determined that the factors included in the models did not have a statistically significant effect.

Conclusion: Vulvar cancer is a type of cancer with limited prospective data. Therefore, it poses severe difficulties in treatment. Limited data on vulvar cancer necessitates the development of treatment paradigms. This means that we need to continue to study the disease.

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Introduction

Vulvar cancer is a rare malignancy. The most common subtype is squamous cell carcinoma [1]. It frequently affects postmenopausal women [2]. Its incidence is 2-3 per 100.000 annually [1,3]. Studies have shown that it constitutes approximately 5% of gynecological cancers seen in the USA [3]. There is no specific screening for vulvar cancer. Today, the method used to reduce its incidence is the treatment of predisposing lesions [4]. Vulvar cancer can be asymptomatic. However, in most cases, it presents with vulvar itching, pain, or ulcer [4,5]. Therefore, a biopsy should be taken from the suspected vulvar lesion [4,5]. Today, individualization of surgical treatment of vulvar cancer is preferred. Conservative operations that will provide a cure come to the fore in this regard [2]. Treatment is often surgical, especially in squamous cell carcinoma. Chemo radiotherapy may be an alternative for advanced tumors [6]. The risk of recurrence is high in vulvar cancer. Studies have reported that this risk is approximately 45% [7,8]. In vulvar cancers, the case population is usually elderly. Cases often have an additional disease. Therefore, the management of the recurrent disease is challenging. Local recurrence accounts for approximately half of all recurrences and is primarily treated surgically [7].

Lymph node involvement is an important prognostic factor in vulvar cancer. While the 5-year survival rate is over 80% in early-stage disease, it decreases to around 30% in the case of lymph node involvement [9]. Data on other prognostic factors remain unclear [10].The primary purpose of this study is to share our institutional experience in managing vulvar cancer patients.

Material and Method

Study Population

The study population consists of those diagnosed with vulvar cancer who received surgical treatment in the Gynecology and Obstetrics Clinic of the institution where the study was conducted.

Study Design

This study is a retrospective study. Forty-eight women who applied to a tertiary health care institution in Turkey between 2009 and 2021 and were diagnosed with vulvar cancer and operated on were included in the study. Those who were missing the data to be used in the study were excluded. The study was ultimately conducted with 39 participants. For information about the participants, the records in their files were used.

Data

The characteristics of the participants included in the statistical analysis; were age, date of diagnosis, stage of the disease, complaint, cancer-related lesions, and operation performed tumor histology, and location of the tumor.

Ethics

Ethical permissions for the study were obtained from the ethics committee of the institution where the researchers worked. There was no compulsion to participate in the research. Participation took place voluntarily. Participants were informed that their information would be used in the study, but their identities would remain confidential.

Statistical Analysis

Analysis of the data was done in SPSS 26 program. Descriptive analyzes are frequency, percentage, minimum/maximum values, mean, standard deviation, and median. Comparisons of two independent groups were made with the t-test. Risk factors for relapse were evaluated by binary logistic regression analysis. Cox regression analyses analyzed analyzes of factors related to survival. Survival analyzes were calculated using the Kaplan-Meier method, and significant differences were determined by the Log Rank (Mantel-Cox) test. $P<0.05$ was considered statistically significant in the analyses.

Results

The mean age of the participants was 69.26±10.72. It was determined that half of the patients (n=19; 50.0%) had vulvar mass complaints. While lesions related to vulvar cancer were observed in 13 participants before cancer diagnosis, no lesions were observed in 25 participants (65.8%). The most common operation is radical vulvectomy; 30 (78.9%) participants underwent radical vulvectomy. When the tumor was examined in histology, squamous cell carcinoma was detected in 31 (81.6%) participants. While the tumor was in the midline in ten (26.3%) participants, it was located in the left labium majus in nine (23.7%) participants. The most common stage of the disease is stage III, in which there are 19 (50.0%) participants (Table 1).

Table 1: Statistics of the Participants

		Number	Percentage
Diagnosis Date	2009 -2015	20	51.7
	2016 - 2021	18	48.3
Complaint	Vulvar Mass	19	50.0
	Vulvar itchingg	8	21.1
	Vulvar itching-mass	6	15.8
	Vulvar scar	4	10.5
	Hardness in the vagina	1	2.6
Associated Lesions	Positive	25	65.8
	Negative	13	34.2
Operation	Vulvectomy	2	5.3
	Simple vulvectomy	2	5.3
	Radical vulvectomy	30	78.9
	Hemi-vulvectomy	2	5.3
	Skinning vulvectomy	1	2.6
	Wertheim Operation	1	2.6
Tumor Histology	Squamous cell carcinoma	31	81.6
	Malignant melanoma	4	10.5
	Basal cell carcinoma	1	2.6
	Epithelioid sarcoma	1	2.6
	Hyperkeratosis	1	2.6
Tumor Location	Left labium majus	10	26.3
	Rightlabium majus	5	13.2
	Midline	12	31.5
	Clitoris	2	5.3
	Left vulva	1	2.6
	Right labium majus-mons pubis	1	2.6
	Left labium majus-clitoris	2	5.3
	Left labium majus and minus	1	2.6
	Left labium minus-clitoris	2	5.3
	Left labium majus-right labium majus	2	5.3
Phase	IA	7	18.4
	IB	7	18.4
	II	4	10.5
	IIIA	7	18.4
	IIIB	6	15.8
	IIIC	6	15.8
	IVA	1	2.6

A t-test was performed to determine whether there was a statistical difference in tumor size, right inguinofemoral lymph node count, and left inguinofemoral lymph node count in patients with and without recurrence. It was determined that there was no statistically significant difference between the groups (Table 2).

Table 2: Comparison of Groups in Terms of Recurrence

	Recurring Mean ± SD	Non-Reccuring Mean ± SD	p
Tumor Size (cm)	5.07±3.77	3.28±1.53	0.155
Sağ Ingüinofemoral Lenf Nodu Sayisi	8.81±4.87	8.51±4.38	0.854
Sol Ingüinofemoral Lenf Nodu Sayisi	8.00±4.17	7.77±3.83	0.875

It was determined that 11 (28.2%) of the study participants had a recurrence. According to the findings of the logistic regression analysis performed to determine the effects of risk factors for relapse, it was determined that the risk factors included in the model did not have statistically significant effects (Table 3).

Table 3: Analysis of risk factors for relapse. Binary logistic regression analysis

	p	OR	95% CI
Sentinel Lymph Node Biopsy	0.948	1.093	0.076 – 15.650
Tumor Size (cm)	0.107	1.517	0.915 – 2.516
Lymphovascular Space Invasion	0.501	0.308	0.010 – 9.482
Perineural Invasion	0.628	0.577	0.063 - 5.329
Right Inguinofemoral Lymph Node Count	0.701	1.071	0.754 – 1.521
Left Inguinofemoral Lymph Node Count	0.444	0.851	0.563 - 1.287
Urethra Involvement	0.079	18.626	0.716 – 484.587
Vaginal Involvement	0.336	0.224	0.011-4.733
Infective Complication	0.892	1.227	0.064 - 23.550
Chemotherapy	0.576	0.495	0.042 - 5.817
Radiotherapy	0.204	5.337	0.404 - 70.517

According to the results of univariate Cox regression analysis performed to determine the effects of factors related to overall survival, it was determined that the factors included in the models did not have statistically significant effects (Table 4).

Table 4: Univariate cox regression analysis to determine factors related to overall survival

	p	OR	95% CI
Sentinel Lymph Node Biopsy	0.320	1.729	0.587 - 5.086
Tumor Size (cm)	0.143	1.108	0.966 - 1.270
Lymphovascular Space Invasion	0.643	0.776	0.265 - 2.272
Perineural Invasion	0.722	1.167	0.498 - 2.736
Right Inguinofemoral Lymph Node Count	0.109	0.921	0.832 - 1.019
Left Inguinofemoral Lymph Node Count	0.197	0.935	0.844 - 1.036
Urethra Involvement	0.368	1.529	0.607 - 3.856
Vaginal Involvement	0.092	2.233	0.877 - 5.685
Infective Complication	0.147	2.925	0.686 - 12.471
Chemotherapy	0.119	1.915	0.847 - 4.334
Radiotherapy	0.207	1.769	0.730 - 4.287

Tumor size according to univariate Cox regression analysis findings to determine the effects of disease-specific survival factors [OR=1.164(1.008-1.344); p=0.038] is an effective factor for survival. It was determined that other factors included in the models did not have statistically significant effects (Table 5).

Table 5: Univariate cox regression analysis to identify disease-specific survival factors

	p	OR	95% CI
Sentinel Lymph Node Biopsy	0.398	1.593	0.541 - 4.687
Tumor Size (cm)	**0.038**	**1.164**	**1.008 - 1.344**
Lymphovascular Space Invasion	0.888	0.926	0.316 - 2.714
Perineural Invasion	0.744	1.153	0.492 - 2.701
Right Inguinofemoral Lymph Node Count	0.157	0.927	0.834 - 1.030
Left Inguinofemoral Lymph Node Count	0.265	0.944	0.853 - 1.045
Urethra Involvement	0.386	1.506	0.597 - 3.800
Vaginal Involvement	0.112	2.140	0.838 - 5.467
Infective Complication	0.237	0.417	0.098 - 1.777
Chemotherapy	0.132	1.867	0.828 - 4.210
Radiotherapy	0.231	1.715	0.710 - 4.143

According to the Kaplan Meier analysis findings performed to determine whether there is a difference in survival in factors related to disease-specific survival and overall survival, there was a statistically significant difference in disease-specific survival according to the status of receiving radiotherapy. It was found to be 39.5 (Figure 1). It was determined that there was no statistically significant difference in disease-specific survival and other factors related to overall survival.

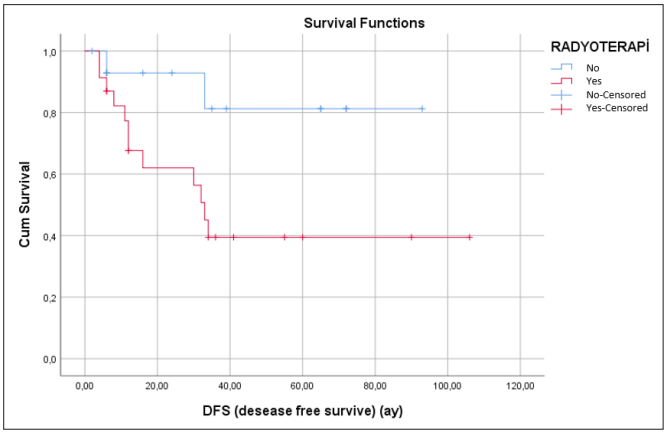

Figure 1: Disease-specific survival plot by radiotherapy status (Kaplan-Meier Analysis)

Discussion

This study investigated prognostic and risk factors for recurrence and survival in vulvar cancer. Overall survival and disease-specific survival were calculated using the Kaplan-Meier method, and multivariate analyses analyzed prognostic factors. According to Cox regression analysis findings, tumor size was determined to be an effective factor regarding survival. The Kaplan-Meier analysis determined that disease-specific survival differed statistically significantly according to radiotherapy status. The disease-specific survival rate is over 80% in those who do not receive radiotherapy. Our study's results revealed limited risk factors and prognostic factors associated with recurrence and survival in vulvar cancer, a rare malignancy.

Nodal involvement is the most important prognostic factor in patients with vulvar cancer [11,12]. Five-year survival is approximately 80% in those without lymph node involvement, while it is approximately 35% in those with involvement [13]. According to the results of one study, the five-year overall and disease-specific survival was 76.8% and 81.1% in those without lymph node involvement. In the same study, these values were 51.7% and 61.8% in patients with positive lymph node involvement [14]. The addition of adjuvant radiation and/or chemotherapy to the treatment in patients with positive lymph node involvement produced a significant difference in overall and disease-specific survival. The data obtained in our study do not support these findings; this may be due to the difference in the number of participants between studies.

In a study by Imoto et al., age and surgical margin less than 5 mm were determined to be prognostic factors for overall survival. Positive inguinal LN metastases and a surgical margin less than 5 mm have been defined as prognostic factors for disease-specific survival [15]. In another study conducted, patients treated for squamous cell carcinoma were examined. In light of the data obtained, it was determined that the tumor's location, the surgery performed, surgical margins, histopathological features, and recurrence status did not differ in terms of the prognosis of the disease [16]. Another study designed similarly to these studies determined that stage and lymph node involvement affected overall survival, and extracapsular metastasis and nodal involvement affected both overall and disease-free survival [17]. In our study, it was determined that the factors included in the models did not have a statistically significant effect on overall survival, according to the results of the analysis on survival with the Cox regression method. However, univariate Cox regression analysis findings to determine the effects of disease-specific survival factors showed that tumor size is an effective factor in survival. This finding obtained in our study was confirmed by a similar study. In the study mentioned above, positive inguinal nodes were defined as a prognostic factor for both overall survival and disease-specific survival, and tumor size as a prognostic factor for overall survival [18].

The diversity of data on prognostic factors in studies on vulvar cancer draws attention. The general acceptance on the subject is that lymph node involvement is an important prognostic factor [10]. However, it is known that data on prognostic factors still need to be clarified [9]. Studies conducted point to different prognostic factors. This supports the view that more detailed studies are needed.

It has been reported in the literature that the most critical risk factor for recurrence is lymph node metastasis [19]. In our study, risk factors were examined in terms of recurrence with binary logistic regression analysis. Lymph node metastasis, considered the most critical risk factor, was not found statistically significant in terms of recurrence in our study. The recurrence frequency detected in our study was 28.2%. In general, the results obtained from the studies in the literature are close to those obtained in our study. It is observed that these results are generally between 25% and 30% [8,20]. However, there are also studies reporting a lower recurrence rate, which was reported as 22.3% in one of them [21].

It has also been noted that the recurrence of vulvar cancer recurrence is increased in the relatively elderly population or when aggressive treatment is avoided. In this case, the treatment of cancer is also more difficult. Five-year survival was calculated as 50-90% in patients with relapse and 25-50% in patients who did not [7,22]. In another study, five-year overall and disease-specific survival in relapsed and non-relapsed subjects were 80% and 53%, and 98% and 62%, respectively. These data necessitate lifelong follow-up of the vulvar cancer patient population.

In our study, tumor size and right and left inguinofemoral lymph node counts were compared in terms of recurrence frequency. It was observed that the listed variables did not have statistically significant effects on recurrence. The results of a similar study differed in terms of tumor size. Accordingly, the data on the participants with and without recurrence were compared with the independent t-test, and it was found that tumor size affected the recurrence at a statistically significant level [20]. It was evaluated that the difference between the two studies was due to the difference in the number of participants. The number of participants in the study examined is higher than in our study.

The data obtained in our study show that receiving radiotherapy harms survival. This finding is inconsistent with general acceptance. According to the latest findings from some studies, the presence of human papillomavirus and p16 immunostaining is an important prognostic factor that can provide sensitivity to radiotherapy [23,24]. Our study evaluated that the data obtained on the adverse effects of radiotherapy on survival may be related to human papillomavirus and p16 immunostaining. However, in our study, these were not investigated.

Vulvar cancer is a type of cancer with limited prospective data. Therefore, it poses severe difficulties in treatment. Limited data on vulvar cancer necessitates the development of treatment paradigms. This means that we need to continue to study the disease. Although methods to reduce morbidity, such as sentinel lymph nodes, have entered our agenda, surgical treatment is still the primary treatment method. Although it has been shown that patients with positive lymph node involvement benefit from adjuvant therapy, the results of our study indicate that this may need to be re-examined. In addition, the survival effect of radiotherapy with human papillomavirus and p16 immunostaining needs to be investigated in larger cohorts.

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