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Is HPV-negative cervical carcinoma a different type of cervical cancer?

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Abstract. – OBJECTIVE: Human papillomavirus (HPV), which is known to play a very important role in genital area (vulva, vagina, and cervix) cancers in women, is responsible for almost all cervical cancers. However, a significant proportion of cervical carcinomas (approximately 7%) is HPV-negative. Therefore, there are still two important questions to be answered: 1. Why is HPV Deoxyribonucleic acid (DNA) not found in all cervical carcinomas? 2. Are HPV-DNA-negative cervical cancers a specific subgroup of cervical cancers with different biological behavior (worse prognosis)? In this article, we aimed to evaluate the clinicopathological characteristics and survival of patients with confirmed HPV-negative tumors in order to answer these two questions.

PATIENTS AND METHODS: A total of 97 patients who underwent HPV-DNA testing and received a histological diagnosis of cervical cancer were included in the study. 14 HPV-DNA negative and 83 HPV-DNA positive cervical carcinoma patients were detected. Demographic profiles, clinicopathological characteristics, progression-free, and overall survival of all patients were analyzed.

RESULTS: Women with HPV-negative tumors were diagnosed at an older age range (p=0.05), and their demographic data other than age range were similar to HPV-positive tumors. P16 staining pattern was not observed in any of the HPV-negative tumors (p=0.001), and a positive P53 staining pattern was detected in 35.7% of the HPV-negative tumors. Although disease-free survival (PFS) (p=0.224) and overall survival (OS) (p=0.219) were worse in the HPV-negative patient group, this difference was not statistically significant.

CONCLUSIONS: HPV-negative cervical cancers do not have a poor prognosis unlike their counterparts in other anatomical regions where HPV-associated tumors are present.

Key Words:
Cervical cancer, Cervical cancer subtypes, HPV-negative cervical cancers, Human papillomavirus, Prognosis.

Introduction

Cervical cancer is the fourth most common cancer in women worldwide and can be prevented by detecting risky women through screening[1]. Every year, approximately half a million women, 80% of whom live in poor countries, are diagnosed with cervical cancer[1]. Human papillomaviruses (HPV), especially high-risk genotypes, have been identified as agents causing the development of this tumor. Cervical cancer is the best-documented cancer to be associated with HPV, and HPV positivity is present in almost all cervical cancers and premalignant cervical lesions[2,3]. However, despite the development of highly sensitive tests for the molecular detection of HPV in recent years, interestingly, a small proportion of cervical cancers are still negative for HPV[3-6]. Similarly, it has been reported[7-10] that tumors seen in the vulva-vagina and head-neck regions are associated with HPV at varying rates, while the remaining cases occur through HPV-independent mechanisms. HPV-associated carcinomas have been reported to have a better prognosis than HPV-independent tumors in anatomical locations other than the cervix (vulva-vagina-head-neck)[7-10]. However, whether HPV-negative carcinomas of the cervix are a subset of tumors with different epidemiological and biological behavior or represent only false-negative results of HPV detection techniques has not been precisely determined. There is also no clear evidence showing that these tumors have different clinical and prognostic characteristics. Therefore, further investigation is required regarding the demographic, clinical, prognostic, and pathological characteristics of this unusual HPV-negative cervical cancer group. The main purpose of this study is to contribute to the literature on the clinical, pathological, and prognostic characteris-

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tics of the unusual HPV-negative cervical cancer group.

Patients and Methods

Study Design

This study was approved by the ethics committee decision numbered 2023/240 of Selcuk University. Patients admitted to the Gynaecological Oncology Unit of Selcuk University Hospital, who underwent HPV-Deoxyribonucleic acid (DNA) test within 6 months before or simultaneously with the histological diagnosis and who were histologically diagnosed with cervical cancer were included in the study. Between 10/06/2011 and 10/12/2022, 158 women diagnosed with cervical cancer were identified retrospectively. The patients detected to have HPV results with the HPV viral DNA kit (QIAGEN, GmbH, Hilden, Germany) were included in the study. In addition, a gynecological pathologist confirmed all histological diagnoses after a careful review that included imaging data and immunostaining. 58 patients with no HPV-DNA test and 3 patients whose pathological diagnosis was not confirmed were excluded from the study. 97 patients who met the criteria were included in the study.

Demographic profiles and clinicopathological characteristics (age, smoking habit, clinical presentations, histological type, International Federation of Gynecology and Obstetrics (FIGO) stage and nodal status), treatment modalities, complications, adjuvant treatments, recurrences, progression-free survival (PFS), and overall survival (OS) of all patients were analyzed. PFS was defined as the time from the date of diagnosis to the date of first recurrence or last follow-up, and OS as the time from the date of diagnosis to the date of death or last follow-up.

Statistical Analysis

Statistical analysis was performed with the statistical package for the SPSS v. 21 (IBM Corp., Armonk, NY, USA). Data were presented as number of observations (n, %), mean ± standard deviation, and range. The results of homogeneity (Levene's test) and normality (Shapiro-Wilk test) were used to decide the statistical methods for comparing the study groups. Among normally distributed groups with homogeneous variances, dependent groups were compared using the Student's *t*-test. According to the test results, parametric test assumptions were not available for some variables. Therefore, the independent groups were compared using the Mann-Whitney U test. Categorical data were analyzed using Fisher's exact test and the Chi-square test. In cases in which the expected counts for inclusion were not met in less than 20% of the cells, the "Monte Carlo Simulation Method" was used, and the values were determined. Cox regression analysis was used to reveal the model of the relationship between independent and dependent variables in the study. In addition, survival times were estimated according to the Kaplan-Meier estimator. While comparing the survival times of the groups, evaluation was made with the Log-Rank test. $p<0.05$ and $p<0.01$ values were accepted for the significance level of the tests.

Results

Of the 97 patients included, 14 (14.4%) were negative for HPV-DNA. Table I shows the comparison between demographic, clinicopathological characteristics, and survival of patients with HPV-negative and HPV-positive cervical cancer. Patients with HPV-negative cervical cancer were older ($p=0.05$), and clinical presentation with vaginal bleeding was more common in this group ($p=0.753$). Squamous cell carcinoma (SCC) type histology was observed more frequently in both HPV-negative and HPV-positive patients (11/14, 78/83 *vs.* 78.6%, 94%; $p=0.085$). All adenocarcinomas were of mucinous type, and a total of 89 (91.8%) SCCs in both groups had non-keratinized pathology. There was no difference between HPV-negative and positive patients in terms of FIGO stage and retroperitoneal lymph node metastasis ($p=0.905$, $p=0.220$, respectively).

When SCCs were analyzed separately, it was seen that the clinical symptoms of patients with HPV-negative tumors (n = 14) and women with HPV-positive neoplasms (n = 83) did not differ (Table I).

The median follow-up was 74 months (95% confidence interval 56.6-92.0 months). Figure 1 shows disease-free survival (Figure 1a) and overall survival (Figure 1b) by HPV status of patients included in the study. Disease-free survival was significantly worse in patients with HPV-negative cervical cancer than in patients with HPV-positive cervical cancer [74.3±9 months (95% confidence interval: 56.6-92.0), 88.4±8.6 months (95% confidence interval: 71.5-105.3), $p=0.224$, respectively]. Similarly, overall survival was worse

Table I. Clinical and histological characteristics of the patients.

		HPV-positive (n=83)	(%)	HPV-negative (n=14)	(%)	p
Age. year		58.1±12.3 (55.4-60.8)		65.2±15.2 (56.4-74.0)		0.057
Gravida		4 (0-13)		4 (1-9)		0.266
Parity		3 (0-10)		4 (1-8)		0.099
Comorbid diseases						0.059
	DM	2	2.4	0	0	
	HT	3	3.6	1	7.1	
	Other	22	26.5	7	50.0	
	None	56	67.5	6	42.9	
Diagnosis						0.860
	Cervical biopsy	68	81.9	13	92.9	
	Konizasyon	15	18.1	1	7.1	
Histology						0.085
	SCC	78	94.0	11	78.6	
	Other	5	6.0	3	21.4	
Smoking						0.627
	Yes	6	7.2	1	7.1	
	No	77	92.8	13	92.9	
RLND						0.220
	Yes	59	71.1	8	57.1	
	No	24	28.9	6	42.9	
Stage						0.905
	1	4	4.8	1	7.1	
	2	30	36.1	5	35.7	
	3	37	44.6	5	35.7	
	4	12	14.5	3	21.4	
Tumor size						0.134
	≤ 4 cm					
	35	42.2	8	57.1		
	> 4 cm	48	57.8	6	42.9	
Clinical presentation						0.753
	Vaginal bleeding	60	72.3	12	85.7	
	Groin pain	16	19.3	2	14.3	
	Urinary incontinence	1	1.2	0	0	
	None	6	7.2	0	0	
p16						0.001
	Positive	82	98.8	0	0	
	Negative	1	1.2	14	100.0	
p53					0.209	
	Positive	59	71.1	5	35.7	
	Negative	24	28.9	9	64.3	
Radiotherapy						0.230
	Pelvic	74	89.2	14	100	
	Pelvic+paraaortic	9	10.8	0	0	
Additional operation						0.795
	No	55	67.9	7	58.3	
	Urinary	12	14.8	4	33.3	
	GIT	8	9.9	1	8.3	
	Urinary+GIT	6	7.4	0	0	
Recurrence						0.295
	Yes	16	19.3	2	15.4	
	No	67	80.7	11	84.6	
DFS. month		88.4±8.6 (71.5-105.3)		74.3±9.0 (56.6-92.0)		0.224
OS. month		89.4±8.1 (73.4-105.3)		84.8±10.1 (65.0-104.7)		0.219

DM: diabetes mellitus. HT: hypertension. SCC: squamous cell carcinoma. RLND: retroperitoneal lymph node dissection. cm: centimeter. GIT: gastrointestinal tract. DFS: disease-free survival. OS: overall survival. $p<0.05$ and $p<0.01$ values were accepted for the significance level of the tests.

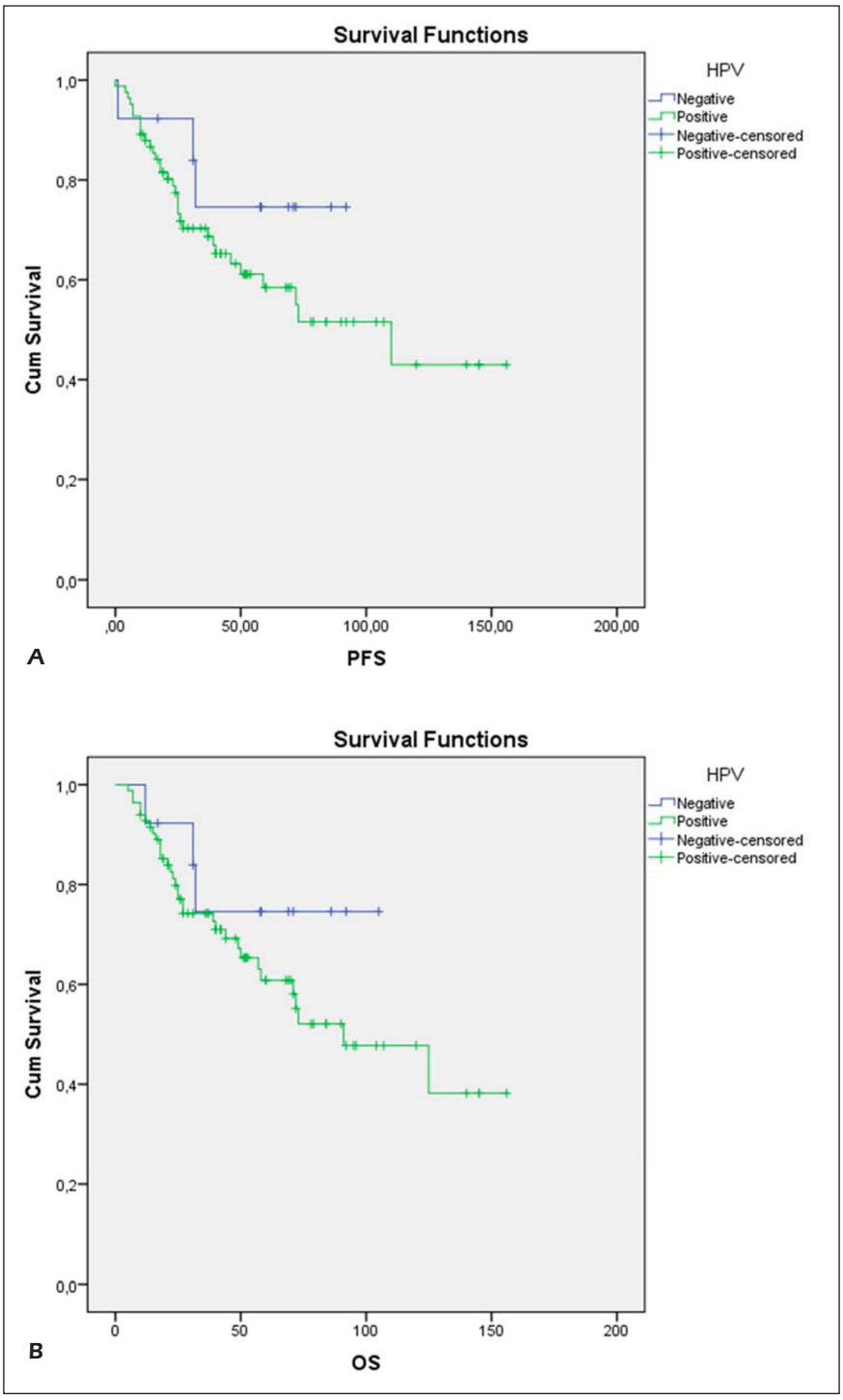

Figure 1. **A**, Disease-free survival by HPV status of patients. **B**, Overall survival by HPV status of patients.

in patients with HPV-negative cervical cancer [84.8±10.1 months (95% confidence interval: 65.0-104.7), 89.4±8.1 months (95% confidence interval 73.4-105.3), p=0.219, respectively].

Although disease-free survival and overall survival were worse in patients with HPV-negative cervical cancer, this difference was not statistically significant.

None of the 14 patients with HPV-negative cervical cancer showed p16 staining, while 5/14 (35.7%) patients showed p53 staining. p16 and p53 staining patterns were 82/83 (98.8%) and 59/83

(71.1%) for HPV-positive patients, respectively (p=0.001 for p53, p=0.209 for P53). No clinical or histological differences were found between HPV-negative/p53-positive tumors and HPV-negative/p53-negative tumors. No clinical or histological differences were found between HPV-positive/p16-positive tumors and HPV-positive/p16-negative tumors. No clinical or histological differences were found between HPV-positive/p53-positive tumors and HPV-positive/p53-negative tumors.

SCC histology, p16 negativity, p53 negativity, advanced FIGO stage, and lymph node metastases were not associated with disease-free survival and overall survival in univariate and multivariate analyses. In univariate analysis, only SCC was associated with histology relapse (p=0.014), but this relationship was not observed in multivariate analysis (p=0.291). The results of univariate and multivariate analyses for disease-free progression and mortality are shown in Tables II and III.

Discussion

Various studies[11-13] have reported that HPV-negative tumors often have poor prognostic factors and may be a more aggressive subtype of cervical cancers. In this context, in a recent meta-analysis[14] including data from 2,838 patients with cervical cancer, HPV-positive cervical cancers have been reported to have a better prognosis. Moreover, HPV-negative carcinomas have been shown[7-9] to have a worse prognosis compared to HPV-positive tumors in neoplasms of other anatomical regions (head-neck and vaginal) where HPV-associated carcinomas are present. However, whether HPV-negative carcinomas of the cervix are a subset of tumors with different epidemiological and biological behavior has not been precisely determined. There is also no clear evidence showing that these tumors have different clinical and prognostic features. Therefore, in this study, we aimed to compare the demographic, clinicopathological, and prognostic characteristics of HPV-negative patients with unusual cervical cancer with those of HPV-positive patients. The most striking findings of our study were that women with HPV-negative tumors were diagnosed at an older age range (p=0.05) and did not show a p16 staining pattern (p=0.001). Although disease-free survival (p=0.224) and overall survival were worse in the HPV-negative patient

Table II. Univariate and multivariate Cox models for relaps.

	Univariant relaps			Multivariant relaps		
	HR	95% CI	p	HR	95% CI	p
SCC histology	0.2	0.154-0.541	0.014	0.291	0.121-0.330	0.291
p16 negativity	-	0.061-0.739	0.599			
p53 negativity	-	0.112-0.606	0.285			
Advanced FIGO stage	-	0.063-0.450	0.427			
Lymph node positivity	-	0.052-0.569	0.077			

HR: hazard ratio. CI: confidence interval. SCC: squamous cell carcinoma. FIGO: International Federation of Gynecology and Obstetrics. p<0.05 and p<0.01 values were accepted for the significance level of the tests.

Table III. Univariate and multivariate Cox models for relaps.

	DFS cox regression analysis			OS cox regression analysis		
	HR	95% CI	p	HR	95% CI	p
SCC histology	1.179	0.229-6.067	0.844	1.403	0.269-7.319	0.688
p16 negativity	3.707	0.457-30.061	0.220	4.584	0.541-38.858	0.163
p53 negativity	1.068	0.412-2.770	0.892	1.173	0.443-3.108	0.748
Advanced FIGO stage	2.228	0.484-10.248	0.303	3.092	0.646-14.798	0.158
Lymph node positivity	2.428	1.017-5.797	0.046	2.616	1.074-6.373	0.034

HR: hazard ratio. CI: confidence interval. SCC: squamous cell carcinoma. FIGO: International Federation of Gynecology and Obstetrics. DFS: disease-free survival. OS: overall survival. p<0.05 and p<0.01 values were accepted for the significance level of the tests.

group, this difference was not statistically significant (p=0.219).

In this study, HPV-negative tumors represented a small percentage (14.4%) of cervical cancer, which is consistent with the literature[5,15]. Although it is generally accepted that HPV is a necessary cause of cervical cancer, HPV-negative cervical cancers are reported[3,16-18] at a rate ranging from 4% to 52% in the literature. The low sensitivity of HPV testing methods may be the reason for the high prevalence of HPV-negative tumors observed in studies[16]. Histological misclassification can also be counted among the possible causes of false HPV-negative results in cervical cancer[19]. In this study, an HPV viral DNA kit (QIAGEN, GmbH, Hilden, Germany) was used. In addition, a gynecological pathologist confirmed all histological diagnoses after a careful review that included imaging data and immunostaining. However, the design of our study does not allow us to conclude whether HPV-negative cervical cancers represent HPV clearance or whether they are truly HPV-independent tumors, which is one of the most important limitations of this study.

Many studies[3,6,10,17] have shown that HPV-negative cervical cancers mostly have adenocarcinoma histology. Contrary to previously published series, adenocarcinomas were observed less frequently, and SCCs were observed more frequently in our study (21.4% *vs.* 78.6%, respectively).

It was shown that there is a strong and widespread overexpression of p16 in most HPV-positive cervical cancers. In addition, p16 positivity was also found in a significant proportion (57%) of HPV-negative cervical cancers[7,8,10]. In our series, p16 staining was positive in 98.8% of HPV-positive cervical cancer patients, while p16 staining was not detected in any of the HPV-negative patients.

FIGO stage and lymph node involvement are considered the most important prognostic parameters for cervical cancer[20,21]. Remarkably, in this series, HPV-negative cervical carcinomas showed the same clinical and prognostic characteristics when compared with HPV-positive cervical carcinomas. In our series, no difference was found between HPV-negative and HPV-positive patients in terms of FIGO stage and lymph node involvement.

Strengths and Limitations

The main strength of our study is that it included a large number of cervical cancer cases, and the HPV status was evaluated using the highly sensitive Hybrid Capture 2 technology (HC2). The main limitation of our study is that it included a small number of HPV-negative cervical cancer patients. Therefore, multicenter studies with more patients are needed to evaluate the prognostic factors of this subset of cervical cancers. The second limitation is that the study is retrospective and limited to data in the registry, so misclassification bias is possible. In addition, the data of patients have been reviewed for over 10 years to obtain a large sample size, and treatment patterns/practices may have changed during this time.

Conclusions

Although our results show that a low percentage of cervical cancer occurs in an HPV-independent manner, HPV-negative cervical cancers seem not to have a poor prognosis unlike their counterparts in other anatomical regions where HPV-associated tumors are present.

Data Availability

The data supporting this study is available through the corresponding author upon reasonable request

Funding

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Conflict of interest

All authors declare that they have no conflict of interest.

Ethics Approval

This study was approved by the Ethics Committee decision numbered 2023/240 of Selcuk University, and was conducted in accordance with the ethical standards of the Helsinki Declaration.

Informed Consent

Informed consent was obtained from all participants in the study before treatment.

Authors' Contributions

Mehmet Kulhan: protocol/project development, data collection, data analysis, manuscript writing/editing. Ahmet Bilgi: data collection, data analysis, manuscript writing/editing. Fazil Avci: data collection, data analysis, manuscript writing/editing. Cetin Celik: protocol/project development, data collection, data analysis, manuscript writing/editing. Mustafa Gazi Ucar, Nur Gozde Kulhan: data analysis, manuscript writing/editing. All authors read and approved the final version of the manuscript.

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