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STUDY OF THE EFFECT OF HUMAN PAPILLOMAVIRUS ON THE COURSE AND PROGNOSIS OF VULVAR CANCER

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Abstract. Human papillomavirus is a necessary cause for cervical cancer, and it has been associated with vulvar and vaginal cancer and vulvar and vaginal and anal intraepithelial neoplasia. We assessed the prevalence of HPV (and the types) to estimate the possible effect of a HPV vaccine on lower genital tract disease prevention.Along with an increase in the incidence of vulvar cancer, a corresponding increase in survival from vulvar cancer can be expected, provided that the proportion of cases associated with high-risk HPV increases
Keywords. Oncology, effect. Human, papilloma, virus, course, prognos, vulvar, cancer.

Introduction. Vulvar cancer is one of the rarest forms of gynecological malignant tumors and accounts for approximately 6% of all malignant neoplasms of the female genital organs, more common in older women. The incidence of RV is less than half a percent of the global incidence of malignant tumors. In 2018, 44,000 new cases of vulvar cancer were registered worldwide, while the number of deaths was about 15,000 cases [1,2,3].
It should be noted that there is more and more evidence of a moderately increasing incidence of vulvar cancer among young women in high-income countries associated with sexual behavior and, as a consequence, an increase in the number of infections with oncogenic HPV types. Along with an increase in the incidence of vulvar cancer, a corresponding increase in survival from vulvar cancer can be expected, provided that the proportion of cases associated with high-risk HPV increases [4,5,6,7].
Materials and methods. In order to achieve the goal set before this scientific work, we analyzed the results of examination and treatment of 186 patients with vulvar cancer who were treated at the RSNPMTSOIR, the P.A. Herzen Institute of Medical Research – a branch of the Federal State Budgetary Institution "NMIC of Radiology" of the Ministry of Health of Russia (Moscow, Russia), as well as the IstinyeUniversity clinic (Istanbul, Turkey) since 2011 by 2020
, the average age of patients was 61±11.7 years. The youngest patient was 38 years old, the oldest 83 years old.
Technically, a smear was used for PCR analysis, which was taken during the examination. In rare cases, the patient's blood was used.
HPV status and type were determined in all samples of 186 patients. 86 patients out of 186 had HPV, mainly type 16 and type 18. The HPV+ result was mainly found in younger patients than in the group of elderly patients.
The result of the PCR study indicated the number of genomic equivalents per 100 thousand cells: Lg < 3 — extremely low presence of HPV virus, Lg 3-5 — clinically significant amount of virus, Lg > 5 — high viral load (Table 1).

Table 1.
Viral (HPV) load in patients with vulvar cancer included in the study

№	*Clinical features*		*Lg<3 n=20*	*LG3-5 n=27*	*Lg>5 n=39*
1.	The stage of the tumor	pT_{1a}	4	2	3
		pT_{1b}	7	9	3
		pT_2	4	2	25
		pT_3	1	14	8
		pT_4	4	-	-
2	Metastases to the lymph nodes	Yes	13	21	27
		No	3	5	12
		No data available	4	1	-
3.	Distant metastases	M_0	20	25	25
		M_1	-	2	14
4.	Invasion of the stroma:	≤1mm	1	4	4
		≥1mm	19	22	32
		No data available	-	1	3
5.	Tumor gradation	1	7	8	3
		2	13	3	17
		3	-	16	19
6.	Lymphovascular invasion	Yes	-	3	14
		No	17	20	13
		No data available	3	4	2
7.	Vascular invasion	Yes	-	7	18
		No	16	15	17
		No data available	4	5	4
8.	FIGO Stage	Istage	-	3	13
		II stage	11	8	17
		III stage	5	5	3
		IV stage	4	11	6

86 patients (46.2%) were infected with HPV, of which 23.3% had an extremely small infection, 31.4% had a clinically significant lesion in the material, and 45.3% had a high viral load.

Results. As we can see from the data given in the table, the viral load does not depend on the stage of the disease, but such indicators as the presence of metastases in the lymph nodes, invasion of the stroma, tumor gradation, lymphovascular and vascular invasion had a natural connection with viral invasion. In the presence of metastases to the lymph nodes, HPV infection was detected in all 61 cases (100%), in the presence of distant metastases in 94.1%, with G3 – 87.5%, lymphovascular and vascular invasion 94.4 and 92.6%, respectively (p= 0.95).

In this study, we wanted to trace the degree of dependence of the anatomical location of the tumor with the presence of human papillomavirus, since, according to our assumptions, the entrance gate, with genital infection

with this virus, can play a significant role in the occurrence of a tumor. To do this, the presence or absence of the human papillomavirus in this patient and the anatomical localization of the vulvar tumor were analyzed in a comparative aspect. In addition to visual examination, the anamnesis of patients was carefully collected to clarify the location of the primary change in the patient's external genitalia (Table 2).

Table 2

Viral (VPH) load in patients with vulvar cancer included in the study depending on the anatomical localization of the tumor

№	*Localization of the tumor*	*HPV-*	*HPV+*
1.	Large labia n=91	58 (63,7%)	33 (36,3%)
2.	Labia minora n=13	3 (23,1%)	10 (76,9%)
3.	Back spike n=11	3 (73,7%)	3 (27,3%)
4.	Periurethral zone n=3	1 (33,3%)	2 (66,7%)
5.	Bartholin glands n=1	-	1 (100%)
6.	Clitorisn=25	7 (28%)	18 (72%)
7.	Several anatomical zones n=42	23 (54,8%)	19 (45,2%)
	Totaln=186	100 (53,8%)	86 (46,2%)

As a result of the study, a pattern of preferred tumor development in certain anatomical zones was found, depending on the presence of the HPV virus. In patients with lesions of the labia minora, clitoris, periurethral zone, the virus was detected in more than 66% of cases (p=0.95), with lesions of the posterior adhesions, labia majora and with lesions of several anatomical zones, infection was detected in less than 45% of cases. The greatest viral loads (Lg > 5) were found with lesions of the clitoris and labia minora (77.8% and 61.5%, respectively), and the smallest (Lg<3) lesions were found with cancer of the labia majora and with lesions of the posterior adhesions (17.6% and 27.3%), this was 48.5% and 100% patients infected with the virus of these anatomical zones.

Rough comparisons between vulvar neoplasms suggest that some types of HPV are associated with diseases, while other viral types of HPV cause non-tumor diseases of the genital organs. Case control studies completed to date have shown that the relative risk for women of HPV type 16.18, as well as HPV 6.11, is quite high, even after taking into account other known risk factors (e.g., sexual behavior, smoking).

In our study, among patients with vulvar cancer, the greatest number of viral lesions were observed in younger patients, whereas, in elderly patients, vulvar cancer was the result of degenerative – dystrophic changes in the vulva (Table 3).

Table 3

Distribution of patients with human papillomavirus depending on the age group of patients with vulvar cancer

№	***Age group and number of observations***	***HPV-***	***HPV+***
1.	Up to 40 years old n=11	2 (18,2%)	9 (81,8%)
2.	41 – 50 yearn=27	2 (7,4%)	25 (92,6%)

3.	51 – 60 yearn=55	13 (23,6%)	42 (76,4%)
4.	61 – 70 yearn=59	51 (86,4%)	8 (13,6%)
5.	71 – 80 yearn=24	22 (91,7%)	2 (8,3%)
6.	Over 80 years old n=10	10 (100%)	-
	Totaln=186	100 (53,8%)	86 (46,2%)

Of 86 patients with positive HPV, 76 (88.4%) patients were under the age of 60. At the same time, among patients with vulvar cancer under 40 years of age, about 82%, up to 50 to 93% of cases of infection with human papillomavirus. Among the patients in the age group up to 60 years, 32 patients infected with the human papillomavirus were under 55 years old. If this fact is taken into account, 76.7% of patients with HPV were under the age of 55.

The histological picture of the vulvar tumor varied from highly differentiated with abundant keratin to low-differentiated (hematoxylin, eosin staining, magnification 400). Among HBV positive patients, histological types of vulvar cancer did not differ from the general group of patients (Table 4).

Table 4

Distribution of patients with human papillomavirus depending on the histological structure of vulvar cancer included in the study

№	*Histological structure*	*Number of patients with HPV+*
1.	Carcinoma of the bartholin gland	1 (1,2%)
2.	Warty carcinoma	2 (2,3%)
3.	Squamous cell carcinoma	49 (56,9%)
4.	Squamous Intraepithelial neoplasia,	24 (27,9%)
5.	Grade 3	7 (8,1%)
6.	Adenocarcinoma	2 (2,3%)
7.	Paget's Disease	1 (1,2%)
8.	Adenoplanocellular carcinoma	-
	Total	86 (100%)

As in the general group, squamous cell carcinoma (56.9%) and intraepithelial neoplasia (27.9%) were most often diagnosed. The mechanism of tumor development in HPV is associated with the expression of proteins E7 and E6 that disrupt normal cell division, disrupting the function of blocking tumor cells p53, leads to the appearance of a tumor. Thus, the human papillomavirus initiates the neoplastic process, but does not affect the histotype of the tumor.

We also conducted a correlation study of the relationship between the human papillomavirus and the genetic profile of vulvar cancer. Staining of ligand 1 of apoptosis (PD-L1) of squamous cell carcinoma of the vulva, with a negative result for human papillomavirus, showed a higher incidence of this ligand, whereas with positive HPV, the occurrence of PD-L1 was significantly low (Table 5).

Table 5

Studied gene mutation for a comprehensive analysis of the genetic profile of the vulva tumor

№				
1.	*PIK3CA*	*32,6*	*14,7*	*0,005*
	PIK3CA T545K	*13,9*	*3,1*	*0,0005*
	KMT2D	*16,3*	*7,9*	*0,05*
	PTEN	*11,9*	*1,5*	*<0,0001*

	STK11	*11,8*	*1,5*	*<0,0001*
	FBXW7	*10,1*	*3,6*	*0,02*
	SOX2amp	*4,4*	*1,3*	*0,0218*
	PIK3R1	*3,1*	*0,8*	*0,18*
	AKT1	*2,1*	*0,8*	*0,61*
	MTOR	*2,1*	*0,9*	*0,59*
2.	*EP300*	*14,1*	*1,4*	*<0,0001*
	BAP1	*5,2*	*0,9*	*0,02*
	PBRM1	*5,4*	*1,5*	*0,07*
	KDM6A	*6,6*	*2,7*	*0,01*
	KMT2C	*6,6*	*3,4*	*0,40*
	ARID1A	*3,1*	*2,9*	*0,07*
3.	*RB1*	*5,5*	*1,3*	*0,09*
4.	*CDK12 inactivating*	*5,5*	*1,6*	*0,07*
	AR	*4,6*	*0,3*	*0,002*
5.	*FGFR3*	*4,7*	*0,1*	*0,003*
6.	*CR*	*4,2*	*0,3*	*0,09*
7.	*PD-L1*	*7,8*	*3,5*	*0,03*
8.	*MSI-H/dMMR*	*21,3*	*3,7*	*0,0001*
9.	*VEGF*	*27,3*	*41,1*	*0,005*
10.	*HER1/EGFR*	*11,2*	*18,2*	*0,0013*
11	*P53*	*15,9*	*39,7*	*0,0021*

Although the median TVM for HPV+ in squamous cell vulvar cancer was generally higher than the HPV result (7.8 vs. 3.7; p=0.03), a complicating factor was a higher percentage of HPV-squamous cell vulvar cancer sequenced from the primary tumor.

STK11 with HPV+ was significantly higher than HPV-test results.

When comparing the mutation frequency between groups with positive and negative HPV for squamous cell vulvar cancer (PRV), a difference in mutations between HPV+ and HPV tumors was observed. Most CCND1-amplified RIGHTS demonstrated amplification of other genes, such as, in 11q13, including FGF3, FGF4 and FGF19. The main specific point mutation with a significant difference between HPV+ and HPV- tumors, which was saturated with the activating mutation PIK3CAE545K.

Conclusions. Thus, this study showed that the presence or absence of human papillomavirus dramatically affects tumor differentiation. With a positive test for human papillomavirus, mutations in the PI3K/mTOR pathway increased, on the contrary, with a negative test, GA was more often detected in TP53, TERTp, CDKN2A, CCND1, FAT1, NOTCH1, EGFR.

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papillomavirus. Among the patients in the age group up to 60 years, 32 patients infected with the human papillomavirus were under 55 years old. If this fact is taken into account, 76.7% of patients with HPV were under the age of 55. As in the general group, squamous cell carcinoma (56.9%) and intraepithelial neoplasia (27.9%) were most often diagnosed. Although the median TVM for HPV+ in squamous cell vulvar cancer was generally higher than the HPV result (7.8 vs. 3.7; p=0.03), a complicating factor was a higher percentage of HPV-squamous cell vulvar cancer sequenced from the primary tumor. STK11 with HPV+ was significantly higher than HPV-test results.[5]. When comparing the mutation frequency between groups with positive and negative HPV for squamous cell vulvar cancer (PRV), a difference in mutations between HPV+ and HPV tumors was observed. Most CCND1-amplified PRVs have demonstrated amplification of other genes, such as, in 11q13, including FGF3, FGF4 and FGF19. The main specific point mutation with a significant difference between HPV+ and HPV-tumors, which was saturated with the activating mutation PIK3CAE545K.

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