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Research Article

CLINICAL FEATURES AND PROGNOSIS OF HR-HPV NEGATIVE CERVICAL CANCER

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ABSTRACT

As one of the most common gynecological malignancies, cervical carcinoma(CC) ranks the fourth among female malignancies in the world, with morbidity and mortality only second to breast cancer, colorectal cancer and lung cancer. The number of new cases of cervical cancer in China accounts for about 19% of the world's total every year, and it has a trend of getting younger in recent years. Currently, studies have confirmed that human papillomavirus (HPV), especially high risk human papillomavirus (HR-HPV) is the main factor leading to cervical cancer, and the infection rate of HR-HPV in cervical cancer tissue specimens is as high as 99%. However, HR-HPV is not the only factor causing cervical lesions, and a variety of non-HR-HPV infection factors also play an important role in the occurrence and development of cervical lesions. Studies have reported that 4% ∽52% of cervical cancer patients are negative in HR-HPV test, and more and more studies have shown that whether HR-HPV infection affects the treatment effect and prognosis of patients. However, HR-HPV negative cervical cancer is easy to be omitted in routine screening, so there are some difficulties in early clinical detection. At present, the etiology and pathogenesis of HR-HPV negative cervical cancer are still unclear. Compared with.

Keywords: HR-HPV negative, cervical cancer, clinical features

Clinical data and prognosis analysis of HPV negative cervical cancer

PREFACE

As one of the most common gynecological malignant tumors, cervical cancer ranks the fourth in the world in terms of morbidity and mortality. According to the latest global cancer statistics, in 2020, there will be 600,000 new cases and 340,000 deaths of female cervical cancer in the world, and 110,000 new cases and 60,000 deaths of cervical cancer in China, which seriously threatens women's life and health, and its incidence has a trend of continuous rejuvenation in recent years. Human papillomavirus, especially high-risk genotype HPV (13 species in total; 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68), has been identified as the pathogen of the tumor development. However, no matter what detection methods are used, there are still many cytological and histological research results that suggest the existence of HR-HPV negative cervical cancer. The negative rate of HR-HPV in cervical cancer patients is 4% to 52%, and there are different reports[1]. At present, more and more basic and clinical studies show that HR-HPV infection is an important factor affecting the prognosis of cervical cancer patients. With the increasing attention of HR-HPV negative cervical cancer, its related clinical research is also being carried out. The reasons for the negative results of HR-HPV cervical cancer detection are summarized as follows: ① False negative results caused by HR-HPV detection methods; ② At present, there are more than 200 HPV types detected, among which about 20 are related to tumors. At present, our commonly used detection methods can only detect 13 HR-HPV types, except that other types of infections other than these 13 lead to cervical cancer[2]. ③HR-HPV virus has been eliminated by the body's immune system, but cervical diseases have been induced before being eliminated; ④ Cervical lesions are caused by causes other than HPV infection. At present, the causes and pathogenesis of HR-HPV negative cervical cancer are still unclear. Related studies believe that smoking, delivery age, multiple births, immune mechanism defects, herpes simplex virus, EB virus, mycoplasma, gene methylation of cervical cells, p53 gene mutation and chromosome abnormality may all be related to the occurrence and development of cervical lesions, and the causes and pathogenesis of HR-HPV negative cervical cancer are still unclear. The research on the clinical characteristics and prognosis of HR-HPV negative cervical cancer is also being carried out continuously. Many domestic and foreign studies suggest that compared with HR-HPV positive cervical cancer, HR-HPV negative cervical cancer tends to be poorly differentiated, with deep myometrial infiltration, early lymphatic metastasis, poor sensitivity to radiotherapy and chemotherapy, poor clinical prognosis, and increased risk of postoperative recurrence and metastasis. At present, there is no obvious specific treatment scheme for HR-HPV negative cervical cancer in clinic. HR-HPV negative cervical cancer is easy to be missed in routine screening, so it is difficult to find it early in clinic, and there are few studies on its gene expression characteristics, pathogenic mechanism and prognostic risk factors. The purpose of this paper is to further clarify the specificity of HR-HPV negative cervical cancer in clinical characteristics and prognosis, improve the understanding of the disease, and reduce the overall incidence and mortality of cervical cancer[3].

MATERIALS AND METHODS

Research object:

From July 2018 to October 2021, 23 patients with HR-HPV negative cervical cancer were selected as the experimental group, and 69 patients with HR-HPV positive cervical cancer were randomly selected as the control group. The diagnosis age, menarche age, marriage age, last delivery age, pregnancy history, menopause, smoking history, drinking history, hypertension, diabetes, first symptom, clinical stage, cancer focus diameter, pathological type, degree of tissue differentiation, lymph node metastasis, lymphatic vessel invasion, LVSI), depth of muscular infiltration and The deadline for follow-up is October 2022. The clinical data and follow-up data were retrospectively analyzed to further explore the unique clinical characteristics and prognosis of HR-HPV negative cervical cancer. Before the collection of clinical data, patients or their families have informed consent, and this study has been approved by the Medical Ethics Committee[4].

Inclusion and non-inclusion criteria:

Inclusion criteria: ① First diagnosis and no treatment. ② All cases were confirmed by pathology. ③ The clinical data are complete. ④ Those with high compliance can be followed up.

Not included in the criteria: patients with other primary malignant tumors and more serious medical diseases.

Treatment methods:

Patients with stage IA-IIA cervical cancer mainly choose laparoscopic radical hysterectomy plus chemotherapy/radiotherapy; Patients with stage IIB-III cervical cancer mainly choose chemotherapy plus radiotherapy.

Follow-up:

All the patients in this study were followed up by telephone, asking whether the patients with cervical cancer survived five years after their first diagnosis. The deadline for follow-up was October 2022[5].

Statistical treatment:

SPSS 26.0 software was used for statistical analysis, the measurement data was expressed by $\bar{X}$ s, independent sample T test was used, chi-square test was used for comparison of counting data, and rank sum test was used for grade data and those that did not conform to normal distribution. Univariate Logistic regression analysis was used to analyze the variables that may be related to the survival of cervical cancer, and the statistically significant variables were included in multivariate Logistic regression analysis. All statistical tests were bilateral tests, with $P<0.05$ as statistically significant[6].

RESULTS

Clinical analysis of HR-HPV negative cervical cancer:

In this study, 92 patients with cervical cancer were included, including 23 cases in HR-HPV negative

group and 69 cases in HR-HPV positive group. Both groups had no history of smoking and drinking. There was no significant difference between the two groups in diagnosis age, menarche age, marriage age, last delivery age, parity, menopause, hypertension, diabetes and first symptoms (P>0.05). The average age of onset was 48.92 9.23 years, the age of menarche was 14.62 1.72 years, the age of marriage was 22.62 2.41 years, the age of last delivery was 29.57 4.73 years, and the average parity was 2.36 0.99. The menopausal rate was 43.48%(HR-HPV negative group) and 56.52%(HR-HPV positive group), the probability of hypertension was 26.09%(HR-HPV negative group) and 13.04%(HR-HPV positive group), and the probability of diabetes was 0.00%(HR-HPV negative group) and 2.90, respectively[7].

In terms of initial symptoms, the two groups of cervical cancer patients mainly showed contact bleeding (34.78% and 46.38% respectively) and irregular vaginal bleeding (30.44% and 34.78% respectively). Secondary symptoms include vaginal discharge (21.74% and 5.80% respectively) and other symptoms, mainly including physical examination findings and vaginal/vulvar itching (13.04% and 13.04% respectively)[8].

To sum up, the samples of this study included HR-HPV negative and HR-HPV positive cervical cancer patients, and there was no significant statistical difference in many life characteristics and clinical manifestations between the two groups. The first symptoms are mainly bleeding-related symptoms. These results provide an important basis for further understanding the clinical characteristics of cervical cancer under different HPV infection conditions[9].

The average number of pregnancies in HR-HPV negative group (4.91 1.56) was higher than that in HR-HPV positive group (3.96 1.69), and the difference was statistically significant (P<0.05). The average number of abortions in HR-HPV negative group (2.70 1.61) was higher than that in HR-HPV positive group (1.61 1.49), and the difference was statistically significant (P<0.05). (See Table 3.1 for details)

General clinical data	HPV negative group (n=23)	HPV positive group (n=69)	$t/X^2/Z$	P
Age of diagnosis (years)	49.13±8.25	48.86±9.56	0.123	0.902
Age of menarche (years)	14.74±2.1	14.58±1.60	0.384	0.702
Marriage age (years)	22.48±2.43	22.67±2.42	-0.323	0.748
Last delivery age (years)	29.65±5.23	29.54±4.57	0.101	0.920
Maternity times (times)				
gravidity	4.9H1.56	3· 96±1.69	2.390	0.019
parity	2.39±1.11	2.35±0.95	0.181	0.856
Number of miscarriages	2.70±1.61	1.61±1.49	2.980	0.004
Whether menopause.			1.180	0.278
be	10 (43.48)	39 (56.52)		
no	13 (56.52)	30 (43.48)		
Is it complicated with hypertension?			2.151	0.143
be	6 (26.09)	9 (13.04)		
no	17 (73.91)	60 (86.96)		
Are you complicated with diabetes?			1.165	0.280
be	0 (0.00)	2 (2.90)		
no	23 (100.00)	67 (97.10)		
First symptom			4.458	0.216
contact bleeding	8 (34.78)	32 (46.38)		
Irregular vaginal bleeding	7 (30.44)	24 (34.78)		
Vaginal discharge	5 (21.74)	4 (5.80)		
other	3 (13.04)	9 (13.04)		

Table 3.1: Comparison of general clinical data of HR-HPV negative and HR-HPV positive cervical cancer (n,%)

Analysis of clinicopathological data of HR-HPV negative cervical cancer:

There was no significant difference in clinical stage, tumor diameter and LVSI muscle infiltration between HR-HPV negative group and positive group (P>0.05). The pathological types of patients in the two groups were mainly squamous cell carcinoma (60.87%, 89.85%) and adenocarcinoma (26.09%, 7.25%). Adenosquamous carcinoma and other types of cervical cancer accounted for a relatively low proportion (the two other types of cervical cancer were neuroendocrine carcinoma+endometrioid adenocarcinoma in the negative group and large cell carcinoma in the positive group), and the proportion of adenocarcinoma in the HR-HPV negative group was significantly higher than that in the HR-HPV positive group. The difference was statistically significant (P<0.05). The positive rate of O HR-HPV negative lymph nodes (39.13%) was

significantly higher than that of HR-HPV positive lymph nodes (14.49%), with statistical significance (P < 0.05). The degree of tissue differentiation of cervical cancer patients in both groups was mainly moderate differentiation (65.22%, 84.06%) and low differentiation (34.78%, 11.59%), and high differentiation (0.00%, 4.35%) was rare. The proportion of low differentiation in HR-HPV negative group was much higher than that in HR-HPV positive group, with statistical significance [10](P < 0 (See Table 3.2 for details)

Clinicopathological features	HPV negative group (n=23)	HPV positive group (n=69)	X^2/Z	P
FIGO clinical staging			2.215	0.137
IA-IIA period	14 (60.87)	53 (76.81)		
HB-III phase	9 (39.13)	16 (23.19)		
Cancer focus diameter			-0.463	0.643
<2	8(34.78)	27(39.13)		
> 2 and < 4	9(39.13)	27(39.13)		
>4	6(26.09)	15(21.74)		
Pathological types			10.320	0.016.
squamous carcinoma	14(60.87)	62(89.85)		
glandular cancer	6(26.09)	5(7.25)		
Adenosquamous	2(8.69)	1(1.45)		
other	1(435)	1(1.45)		
tissue differentiation			2646	0.008
poorly differentiated	8(34.78)	8(11.59)		
Moderate differentiation	15(65.22)	58(84.06)		
Highly differentiated	0(0.00)	3(4.35)		
Lymph node metastasis			6.390	0.011
be	9 (39.13)	10 (14.49)		
no	14 (60.87)	59 (85.51)		
LVSI			1.346	0.246
be	4 (17.39)	6 (8.70)		
no	19 (82.61)	63 (91.30)		
Muscle infiltration			0.060	0.807
Superficial muscle layer	10 (43.48)	28 (40.58)		
Deep muscularis	13 (56.52)	41 (59.42)		

Table 3.2: Comparison of Clinicopathological Data between HR-HPV Negative and HR-HPV Positive Cervical Cancer (n,%)

5-year survival rate of HR-HPV negative cervical cancer:

The 5-year survival rate of cervical cancer in HR-HPV negative group (52.17%) was lower than that in HR-HPV positive group (76.81%), and the difference was statistically significant (P<0.05). (See Table 3.3 for details)

Patients in the fifth year Survive or not	HPV negative group (n=23)	HPV positive group (n=69)		P
be	12 (52.17)	53 (76.81)	5.050	0.025
no	11 (47.83)	16 (23.19)		

Table 3.3: Comparison of 5-year survival rates between HR-HPV negative and HR-HPV positive cervical cancer (n,%)

Prognostic analysis of cervical cancer patients:

Single factor analysis:

The 5-year survival rate of 92 patients with cervical cancer was analyzed by univariate Logistic0 regression analysis. The results showed that the age of diagnosis, age of menarche, age of marriage, age of last delivery, parity and menopause had no significant relationship with the survival of patients (P>0.05). Negative or positive HR-HPV, pregnancy number, number of abortions, clinical stage, diameter of cancer focus, pathological type, degree of tissue differentiation, lymph node metastasis, LVSI and depth of myometrial infiltration are all risk factors affecting the prognosis of patients with cervical cancer (P<0.05) [11]. (See Table 3.4 for details)

influencing factor	B	SE	Wald	P value	OR value	95%CI	
						lower	upper limit
HR-HPV negative or …	1.111	0.506	4.826	0.028	3.036	1.127	8.179
Age of diagnosis	-.013	0.025	0.272	0.602	0.987	0.939	1.037
Age of menarche	0.041	0.133	0.093	0.761	1.041	0.802	1.352
marriageable age	-0.131	0.101	1.683	0.194	0.878	0.720	1.069
Last delivery age	-0.066	0.052	1.607	0.205	0.937	0.846	1.036
gravidity	0.310	0.141	4.858	0.028	1.363	1.035	1.795
parity	0.232	0，232	0.997	0.318	1.261	0.800	1.989
Number of	0.320	0.148	4.656	0.031	1.377	1.030	1.840
Whether menopause.	-0.561	0.469	1.430	0.232	0.570	0.227	1.431
clinical stages	2.494	0.549	20.643	0.000	12.112	4.13	35.524
Diameter of cancer	1.890	0.539	12.273	0.000	6.616	2.299	19.041
Pathological types	1.755	0.585	8.996	0.003	5.784	1.837	1&212
Degree of tissue	2.501	0.645	15.027	0.000	12.200	3.444	43.214
With or without	2.559	0.604	17.940	0.000	12.923	3.955	42.231
LVSI	1.427	0.693	4.507	0.034	4.357	1.120	16.957
Depth of myometrial	2.234	0.661	11.419	0.001	9.333	2.555	34.093

Table 3.4: Univariate Logistic Regression Analysis of Prognosis of Cervical Cancer Patients

Multifactor analysis:

According to the results of univariate analysis, the statistically significant variables were included in multivariate Logistic regression analysis. The results showed that clinical stage, pathological type, tissue differentiation degree and myometrial infiltration depth were independent risk factors affecting the prognosis of cervical cancer patients (P<0.05). When its influencing factors remain unchanged, the death risk of patients with advanced cervical cancer (stage IIB-III) is 8.905 times higher than that of patients with early stage (stage IA-IIA); The death risk of patients with non-squamous cell carcinoma is 6.166 times higher than that of patients with squamous cell carcinoma. The death risk of poorly differentiated cervical cancer is 10.251 times higher than that of moderately well differentiated patients. The death risk of patients with deep myometrial infiltration is 6.159 times that of patients with shallow myometrial infiltration[12]. (See Table 3.5 for details)

influencing factor	B	SE	Wald	P value	OR value	95%CI	
						lower	upper limit
clinical stages	2.187	0.680	10.336	0.001	8.905	2.348	33.771
Pathological types	1.819	0.844	4.643	0，031	6.166	1.179	32.253
Degree of tissue	2.327	0.879	7.016	0.008	10.251	1.832	57.372
Depth of	1.818	0.783	5.391	0.020	6.159	1.328	28.569

Table 3.5: Multivariate Logistic Regression Analysis of Prognosis of Cervical Cancer Patients

DISCUSSION

Relationship between HR-HPV infection and cervical cancer:

Cervical cancer, as one of the common gynecological malignant tumors, originated from the precancerous stage of cervical cancer, and experienced a long and gradual development process, which was influenced by a variety of factors. Among them, human papillomavirus (HPV) infection is recognized as the main cause of cervical cancer, and its importance lies in its high detection rate in cervical cancer tissues, even reaching 99%. This understanding can be traced back to 1974, when Professor Harald zur Hausen, a German virologist at that time, first proposed that HPV might play an important role in the development of cervical cancer. Since then, the research on HPV virus has gradually started[13].

There are many kinds of HPV viruses, but 13 of them are called high-risk HPV(HR-HPV), which are closely related to the incidence of cervical cancer, including HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68[14]. These HR-HPV continue to infect cervical tissue cells and integrate their double-stranded DNA into host cells, interfering with the normal function of tumor suppressor genes, thus causing abnormal proliferation of cervical cells. HPV virus is epitheliophilic, it replicates and proliferates at the junction of cervical squamous column and the surface of cervical mucosa, and its encoded E6 and E7 proteins are closely related to the occurrence of cervical precancerous lesions. The expression levels of E6 and E7 proteins in cervical high-grade squamous intraepithelial lesions were higher than those in normal cervical tissues. Especially E6 protein, which can make cells escape immune monitoring, change the mechanism of cell aging and apoptosis, and lead to abnormal cell proliferation.

In a word, high-risk HPV plays a key role in the development of cervical cancer. Its infection caused a series of pathological changes, including changes in gene activity and abnormal cell proliferation and apoptosis. The importance of HPV virus makes it an important way to explore the pathogenesis of cervical cancer. Through further research, we hope to further understand the relationship between HPV infection and cervical cancer, so as to provide more accurate and effective strategies for prevention, diagnosis and treatment[15].

Relationship between HR-HPV Negative and Cervical Cancer:

First of all, the false negative results of HR-HPV detection may be due to technical errors. For example, when using HC-II method to detect HPV infection in patients with cervical cancer, the false negative rate is high, but when using highly sensitive PCR technology to detect again, the false negative rate decreases. In addition, the secretion and blood on the cervical surface are not completely removed before sampling, which may also affect the accuracy of the test results[16].

Secondly, there are many subtypes of HPV virus, and the association with cervical cancer is mainly concentrated in about 20 subtypes, of which 13 high-risk types are closely related to cervical cancer. However, the commonly used detection methods can only detect these 13 high-risk types, and can't rule out cervical cancer caused by other subtypes of infection[17].

Thirdly, research shows that 80% of women have been infected with HR-HPV in their lifetime, but most of the infections are transient and then cleared by the body's immune mechanism. When the HR-HPV virus is cleared by the body, the cell atypia and cervical cancer induced by the virus may persist, resulting in a negative HR-HPV test result[18].

Finally, cervical lesions may be caused by many causes, not just HPV infection. Smoking, delivery age, multiple deliveries, deficiency of immune mechanism, virus infection (such as herpes simplex virus and EB virus), mycoplasma infection, gene methylation of cervical cells, P53 gene mutation, chromosome abnormality and other factors may all be related to the occurrence of cervical lesions[19].

To sum up, there are many reasons for the negative results of HR-HPV test in patients with cervical cancer, including technical errors, failure to detect other subtypes of infection, and cervical cancer after immune clearance. The occurrence of cervical lesions may be affected by many factors, not just HPV infection. Future research should further explore these mechanisms in order to better understand the complexity of cervical cancer and provide basis for more accurate prevention and treatment.

Although many studies have mentioned that the history of female pregnancy is closely related to the incidence of HR-HPV negative cervical cancer, there are few research data in this regard. The results of this study showed that there was no statistical difference in the last delivery age and parity between HR-HPV negative group and positive group ($P>0.05$). The average pregnancy times and the average delivery times in HR-HPV negative group were higher than those in high-risk HR-HPV positive group ($P<0.05$), suggesting that the increase of pregnancy times and abortion times may be the risk factors for the occurrence of HR-HPV negative cervical cancer. Relevant literature suggests that HR-HPV negative cervical cancer patients are affected by multiple births and early delivery age. Zhang Xingliang et al.' s research shows that the related factors of cervical cancer in China are: the number of pregnancies ≥3, the number of deliveries ≥3, the number of abortions ≥3, the age of first pregnancy ≤21, the age of first sexual intercourse ≤20 and so on. It can lead to the decline of immune function due to the increase of pregnancy and abortion times, which can provide an immune microenvironment for cervical cancer, and can also cause different degrees of cervical damage due to the increase of abortion times, which can provide a foundation for cervical cancer. At present,

the specific pathogenesis of this kind of etiology needs further in-depth research and confirmation[20].

HRHPV Clinical characteristics of HPV negative cervical cancer:

Among 92 patients, the rate of patients in the middle and late stage (stage IIB-III) in HR-HPV negative group (39.13%) was higher than that in the positive group (23.19%), but there was no significant difference in clinical stages between the two groups. A pathological analysis of 785 cases of cervical cancer showed that there was no significant difference in the composition ratio of different clinical stages between high-risk HPV negative and positive patients, which was consistent with the results of this study. However, some research results show that the diagnosis rate of HPV-negative tumors in FIGO is higher than that of HPV-positive tumors (91%; 57%; P<0.01); The results of various studies on the influence of HR-HPV negative on cervical cancer staging are different, and more large sample data are needed for further verification.

The first symptoms of cervical cancer patients in the two groups mainly include contact bleeding and irregular vaginal bleeding, but the data of different studies are different. In this study, there was no significant difference in the proportion of contact bleeding and irregular vaginal bleeding between HR-HPV negative group and positive group (P>0.05). However, compared with the research results of Huang Shan et al, the proportion of contact bleeding and irregular vaginal bleeding in the negative group was smaller than that in the positive group (3/9: 41/84, 1/9: 33/84, x2 = 12.889, P = 0.006).

In addition, a study on the clinical data of 174 young women with cervical cancer showed that the main clinical symptom of cervical cancer was contact vaginal bleeding, followed by irregular vaginal bleeding and abnormal leucorrhea. Among these patients, 25.9% were misdiagnosed as cervicitis. Therefore, for women with symptoms such as contact vaginal bleeding, irregular vaginal bleeding, abnormal vaginal discharge and abnormal leucorrhea, we should actively seek medical treatment to eliminate malignant tumor diseases. Early detection, early diagnosis and early treatment are of great significance for reducing the mortality rate of female malignant tumors.

To sum up, the clinical symptoms of cervical cancer are different in different studies, but contact vaginal bleeding and irregular vaginal bleeding are usually considered as the more common first symptoms. In clinical practice, medical staff should be highly alert to the appearance of these symptoms and conduct comprehensive examination in time to ensure early diagnosis and treatment, thus reducing the risk of malignant tumors of patients.

This study found that there was no significant difference between HR-HPV negative group and positive group in tumor focus diameter, LVSI and myometrial infiltration depth. Zou Lianying and others' research results confirmed that HPV negative or not had no effect on tumor diameter, but their research also suggested that HPV negative cervical cancer is more prone to deep infiltration, which is inconsistent with the results of this study. The reason may be that with the improvement of people's health awareness and the increasing popularity of cervical cancer screening, cervical invasive cancer can be found, diagnosed and treated earlier, and the progress of cervical cancer can be blocked earlier, resulting in no significant difference in myometrial infiltration between the two groups of cervical cancer patients. At present, there is

no other report on LVSI of HR-HPV negative cervical cancer.

The accumulated data of many studies show that HR-HPV negative cervical cancer has obvious differences in several key aspects compared with HR-HPV positive cervical cancer, which provides valuable clues for understanding its disease characteristics and prognosis.

Specifically, the study found that HR-HPV negative cervical cancer is more prone to lymph node metastasis, and its tissue differentiation is poor, with a higher proportion of low differentiation. The results of Nicolas et al showed that the lymph node metastasis rate of HPV negative cervical cancer was significantly higher than that of HPV positive cervical cancer (67%:36%,F<0.01), which was consistent with the results of this study. In addition, the data of this study showed that the proportion of adenocarcinoma in HR-HPV negative group was significantly higher than that in HR-HPV positive group (P<0.05), among which squamous cell carcinoma accounted for 60.9% and adenocarcinoma accounted for 26.1% in negative group, while squamous cell carcinoma accounted for 89.9% and adenocarcinoma accounted for 7.3% in positive group. This is consistent with the results of some other studies, which further confirms the high proportion of adenocarcinoma in HR-HPV negative cervical cancer.

Other studies have also mentioned the negative HR-HPV in some rare types of cervical cancer. For example, the research of An et al. found that HR-HPV was negative in some rare pathological types (such as clear cell adenocarcinoma, middle kidney adenocarcinoma, endometrioid adenocarcinoma and cervical micrometastasis adenocarcinoma, etc.). In addition, Pirog et al. pointed out that HR-HPV test was positive in most cases of mucinous adenocarcinoma and adenosquamous carcinoma, but negative in some non-mucinous adenocarcinoma.

These findings emphasize the special characteristics of HR-HPV negative cervical cancer. However, although many studies have shown the poor prognosis of HR-HPV negative cervical cancer, there is still a lack of specific treatment programs in clinic. Therefore, future research should further explore the molecular mechanism, pathological characteristics and individualized treatment strategies of HR-HPV negative cervical cancer, so as to provide more accurate guidance for the diagnosis and treatment of such patients and improve their prognosis.

Prognosis and influencing factors of patients with cervical cancer:

The prognosis of cervical cancer is the result of multiple risk factors, and the results of various studies are different. At present, it is considered that HR-HPV infection, FIGO clinical stage, onset age, pregnancy times, lymph node metastasis in LVSL, maximum diameter of cancer focus, histological differentiation, pathological tissue type, myometrial infiltration depth, parauterine infiltration, positive surgical margin and different treatment methods can all be risk factors affecting the prognosis of cervical cancer.

HR-HPV infection, as the main influencing factor of inducing cervical cancer, has been concerned by researchers, and more and more studies show that HR-HPV infection has an important impact on the treatment effect and prognosis of patients. Riou et al. confirmed that compared with HPV positive cervical

cancer patients, the total recurrence risk of HPV negative cervical cancer patients increased by 2-6 times (P<0.05), and the risk of distant metastasis increased by 2 times (P<0.01). The results of Nicolas et al. showed that the median disease-free survival time of patients with HR-HPV negative cervical cancer was 59.8 months, which was much lower than that of patients with HR-HPV positive, which was 132.2 months (P<0.01). The median total survival time of 77.0 months was significantly lower than that of patients with HR-HPV positive tumor, which was 153.8 months (P = 0.01).

The research results of Rodrfguez-Carunchio and others reveal that there are significant differences between HPV-negative cervical cancer and HPV-positive cervical cancer in clinical data and prognosis. It is pointed out that the disease-free survival, DFS) of HPV-negative cervical cancer patients is significantly shorter than that of HPV-positive cervical cancer patients, which shows that the median survival time in DFS is shorter [51.9 months (95%CI 12.2-91.7 months): 109.9 months (95%CI 98.2-121.5 months), P In addition, the overall survival, OS) of HPV-negative cervical cancer patients was also low, although the difference did not reach statistical significance [67.7 months (95%CI 20.0-106.9 months): 108.9 months (95%CI 97.7-120.0 months), P=0.225].

The data obtained in this study further strengthened the understanding of the prognosis difference of HPV-negative cervical cancer. It was found that the 5-year survival rate of patients with cervical cancer in HR-HPV negative group (52.17%) was significantly lower than that in HR-HPV positive group (76.81%), and the difference was statistically significant (X2=5.050, P=0.025). This is consistent with previous research results, suggesting that the poor prognosis of HPV negative group may be related to many factors, including high proportion of adenocarcinoma, poor tissue differentiation, high lymph node metastasis rate and insensitivity to radiotherapy and chemotherapy.

In addition, some studies have found that the proportion of adenocarcinoma in HPV-negative cervical cancer patients is relatively high, and adenocarcinoma is characterized by its easy infiltration into cervical tissue and invasion of blood vessels and lymphatic spaces, leading to early metastasis and increased positive rate of pelvic lymph nodes. At the same time, adenocarcinoma is insensitive to radiation and its prognosis is relatively poor, which may be a key reason for the poor prognosis of HPV-negative cervical cancer.

Other studies have also proposed possible factors for the difference in prognosis between HPV negative and HPV positive groups. On the one hand, the differentiation of HPV-negative cervical cancer cells is poor, and the expression concentration of apoptosis-inducing factor A decreases, thus the apoptosis rate of cancer cells decreases and the proliferation rate increases. On the other hand, the DNA in cancer cells of HPV-negative cervical cancer patients is not integrated with HR-HPV virus gene, which makes cancer cells escape the immune surveillance of tregT lymphocytes.

Although many studies consistently suggest that the prognosis of HPV-negative cervical cancer is poor, there is no specific treatment for HPV-negative cervical cancer in clinic. However, with the in-depth research on HPV-negative cervical cancer, evidence-based medical evidence will help to better understand its clinical characteristics, pathogenesis and individualized treatment programs. This provides a new idea for the

diagnosis and treatment of HPV-negative cervical cancer patients and is expected to improve the prognosis of patients.

A foreign study conducted multivariate Cox analysis on the progression and mortality of cervical cancer, and found that HR-HPV negative status and advanced FIGO were related to the progression and mortality of cervical cancer. However, some studies show that, although in univariate analysis, negative HR-HPV, negative pl6 immunostaining, FIGO staging and lymph node metastasis are associated with low disease-free survival rate and increased cervical cancer-related mortality, in multivariate analysis, only FIGO staging and lymph node metastasis are still associated with poor disease-free survival rate and overall survival rate. A study of 174 young women with cervical cancer found that clinical stage, tumor diameter, specimen margin, cervical myometrial infiltration depth, lymphatic involvement and pelvic lymph node metastasis were related to pre-and post-treatment in univariate analysis, and further multivariate analysis showed that clinical stage, cervical myometrial infiltration depth and lymphatic involvement were independent risk factors affecting young women with cervical cancer. Related research shows that lymph node metastasis is an independent risk factor for patients' survival, and the rate of lymph node metastasis increases with the increase of clinical stages. The 5-year survival rate of patients with pelvic lymph node metastasis is about 38%-62% > when pelvic lymph nodes are involved, the total 5-year survival rate decreases by about 50%. Lu et al. think that the survival rate of patients with cervical cancer decreases with the increase of the number of lymph nodes involved, and the size of local tumors will also affect the survival rate of patients. Univariate analysis by Liu Dan et al. confirmed that the clinical stage of the tumor, the diameter of the cancer focus, the recurrence of the disease, the type of pathological tissue and the infiltration of cervical stroma were the risk factors for the prognosis of early cervical cancer (P< 0.05). Yuan Fengling and others found that among young patients with cervical cancer, the proportion of low and medium differentiated squamous cell carcinoma was 78.2%; The positive rate of lymph node metastasis was 27.7%; The research data showed that some pathological high-risk factors were closely related to the prognosis of patients with cervical cancer. The median survival time of patients with LVSI positive cervical cancer was 51 months, while that of patients with LVSI negative cervical cancer was 58 months. The median survival time of patients with LVSI negative cervical cancer was significantly higher than that of patients with positive cervical cancer, with statistical significance (P<0.05). The median survival time of cervical cancer patients with shallow cervical interstitial infiltration (< 1/2) was 59 months, which was significantly higher than that of cervical cancer patients with deep cervical interstitial infiltration (≥1/2) (P<0.05). Among the patients with early cervical cancer, the median survival time of squamous cell carcinoma patients was significantly longer than that of non-squamous cell carcinoma patients, with statistical significance (P<0.05). COX multivariate retrospective analysis showed that pathological types and lymph node metastasis were closely related to the prognosis of young patients with cervical cancer (P<0.05). There are also related literature reports on the influence of age on the prognosis of cervical cancer, especially for cervical cancer above stage II, the younger the patient is, the worse the prognosis is (P<0.01). The proportion of adenocarcinoma in young cervical cancer patients is high, and most of them are

endogenous, which is easy to infiltrate into the deep muscle layer of cervical tissue, invade the vascular lymphatic space, and can metastasize earlier. Adenocarcinoma is not sensitive to radiation.Radiotherapy is one of the important treatments for cervical cancer, which may also be an important reason for the poor prognosis of young people. Univariate analysis of the survival rate of 92 patients with cervical cancer showed that the negative or positive HR-HPV, pregnancy number, number of abortions, clinical stage, tumor diameter, pathological type, degree of tissue differentiation, lymph node metastasis and LVSL myometrial infiltration were all risk factors affecting the prognosis of patients with cervical cancer ($P<0.05$). Multivariate analysis showed that clinical stage, pathological type, degree of tissue differentiation and depth of myometrial infiltration were independent risk factors affecting the prognosis of patients with cervical cancer ($P<0.05$). In this study, lymph node metastasis is excluded from the independent risk factors affecting the prognosis of cervical cancer patients, which may be related to the high correlation between lymph node metastasis and clinical staging. Whether HR-HPV is negative or positive is closely related to the pathological type, histological differentiation and lymph node metastasis of cervical cancer patients, which may be the reason why HR-HPV is negative or not in this study is also excluded from the independent risk factors affecting the prognosis of cervical cancer patients.

Shortcomings of this study:

The data sample of this study is small, which may affect the accuracy of the results to some extent. This study failed to discuss the treatment scheme for patients with cervical cancer, and the follow-up data after treatment were few, which failed to analyze the sensitivity difference of radiotherapy and chemotherapy for cervical cancer between the two groups.

Up to now, there have been a lot of studies and discussions on HR-HP positive cervical lesions, but there are few studies on the pathogenic factors, clinical characteristics and individualized treatment of HR-HPV negative cervical lesions. It is hoped that with the development of related research on HR-HPV negative cervical cancer, more evidence-based medical evidence can be obtained to provide new ideas for individualized diagnosis and treatment of HR-HPV negative cervical cancer in order to reduce the mortality rate of cervical cancer.

CONCLUSION

The increase of pregnancy times and abortion times may be the risk factors for inducing HR-HPV negative cervical cancer.

Compared with HR-HPV positive group, the proportion of adenocarcinoma in HR-HPV negative cervical cancer is higher, the tissue differentiation is poor, and lymph nodes are more prone to metastasis.

Compared with HR-HPV positive group, HR-HPV negative cervical cancer patients have higher mortality and poorer prognosis.

Clinical stage, pathological type, degree of tissue differentiation and depth of myometrial infiltration are independent risk factors affecting the prognosis of patients with cervical cancer.

REFERENCES

1. Bray F, Ferlay J, Soeijomataram I, et al. Global cancer statistics 201& GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [J]. CA Cancer J Clin, 2018, 68(6): 394-424.
2. Wu C, Li M, Meng H, et al. Analysis of status and countermeasures of cancer incidence and mortality in China [J]. Sci China Life Sci, 2019, 62(5): 640-647.
3. Liu P, Lin L, Kong Y, et al. Comparison of survival outcomes between radio-chemotherapy and radical hysterectomy with postoperative standard therapy in patients with stage IB1 to IIA2 cervical cancer: long-term oncological outcome analysis in 37 Chinese hospitals [J]· BMC Cancer, 2020, 20(1): 189.
4. Nicolas I, Saco A, Bamadas E, et al. Prognostic implications of genotyping and pl6 immunostaining in HPV-positive tumors of the uterine cervix [J], Mod Pathol, 2020, 33(1): 128-137.
5. No J H, Sung M W, Hah J H, et al. Prevalence and prognostic value of human papillomavirus genotypes in tonsillar squamous cell carcinoma: a Korean multicenter study [J], Cancer, 2015, 121(4): 535-544.
6. Barreto C L, Martins D B, de Lima Filho J L, et al. Detection of human Papillomavirus in biopsies of patients with cervical cancer, and its association with prognosis [J]. Arch Gynecol Obstet, 2013, 288(3): 643-648.
7. Rodriguez-Carunchio L, Soveral I, Steenbergen R D, et al. HPV-negative carcinoma of the uterine cervix: a distinct type of cervical cancer with poor prognosis [J]. BJOQ 2015, 122(1): 119-127.
8. Igidbashian S, Schettino M T, Boveri S, et al. Tissue genotyping of 37 in situ and invasive cervical cancer with a concomitant negative HC2 HPV DNA test [J]. J Low Genit Tract Dis, 2014, 18(1):87-91.
9. Oei A L, van Leeuwen C M, ten Cate R, et al. Hyperthermia Selectively Targets Human Papillomavirus in Cervical Tumors via p53-Dependent Apoptosis [J]. Cancer Res, 2015, 75(23):5120-5129.
10. Jun S Y, Park E S, Kim J, et al. Comparison of the Cobas 4800 HPV and HPV 9G DNA Chip Tests for Detection of High-Risk Human Papillomavirus in Cervical Specimens of Women with Consecutive Positive HPV Tests But Negative Pap Smears [J]. PLoS One, 2015, 10(10): e0140336.
11. Yu S5 Kwon M J, Lee E H, et al. Comparison of clinical performances among Roche Cobas HPY RFMP HPV Papillolyper and Hybrid Capture 2 assays for detection of high-risk types of human papillomavirus [J]. J Med Virol, 2015, 87(9): 1587-1593.
12. Park Y, Lee E, Choi J, et al. Comparison of the Abbott RealTime High-Risk Human Papillomavirus (HPV), Roche Cobas HPY and Hybrid Capture 2 assays to direct sequencing and genotyping of HPV DNA [J]. J Clin Microbiol, 2012, 50(7): 2359-2365.
13. Kim J, Jun S Y. Analytic performance of PANArray HPV and HPV 9G DNA chip tests for genotyping of high-risk human papillomavirus in cervical ThinPrep PreservCyt samples [J]. PLoS One, 2019? 14(10): e0224483.
14. Li N, Franceschi S, Howell-Jones R, et al· Human papillomavirus type distribution in 30,848 invasive cervical cancers worldwide: Wriation by geographical region, histological type and year of publication [J]

· Int J Cancer, 2011,128(4): 927-935.

15. Ozturk M, Umudum H, Alanbay I, et al. Risk of HSIL (CIN 2-3) on colposcopic biopsy is minimal in postmenopausal women with LSIL on cytology and a negative HRHPV test [J]. Diagn Cytopathol, 2016, 44(12): 969-974.
16. zur Hausen H, Meinhof W, Scheiber W, et al· Attempts to detect virus-secific DNA in human tumors. I. Nucleic acid hybridizations with complementary RNA of human wart virus [J]. Int J Cancer, 1974,13(5): 650-656.
17. Segura S E, Ramos-Rivera G Hakima Ls et al. Low-grade squamous intraepithelial lesion, cannot rule out high-grade lesion: Diagnosis, histological outcomes and human papillomavirus results [J]. Cytopathology, 2019,30(1): 99-104.
18. Ryu K J, Lee S, Min K J5 et al. Management of atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesions of the uterine cervix with human papilloma virus infection among young women aged less than 25 years [J]· Diagn Cytopathol, 2016, 44(12): 959-963.
19. Zhang H, Varma K R, Han M, et al. Immediate histopathologic follow-up of cervista and aptima high-risk HPV assays in women with LSIL cytology [J]. Cancer Cytopathol, 2018, 126(8): 525-532.
20. Miller R A, Waters L Ls Mody D R, et al. Squamous cell carcinoma of the cervix: a cytology-histology-hximan papillomavirus correlation in clinical practice [J]. Arch Pathol Lab Med, 2015, 139(6): 776-781.