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Clinical Value of Combined Detection of Tumor Markers and HPV DNA In the Diagnosis of Cervical Cancer and Precancerous Lesions

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Abstract

Objective: Clinical value of combined detection of tumor markers and HPV DNA in the diagnosis of cervical cancer and precancerous lesions. Methods: Select 64 cervical cancer patients admitted to our hospital from December 2017 to December 2018 as the cancer group, 35 patients with precancerous lesions as the precancerous lesion group, and 99 healthy people as the normal group, and compare the tumors of each group The level of markers, the positive rate of different detection methods in CIN Ⅰ (mild), CIN Ⅱ (moderate), CINⅢ (severe) cervical intraepithelial neoplasia and cervical cancer (CIS), comparison of the detection value of different methods, differences The accuracy, specificity, sensitivity, relationship between different ages and HPV infection in HSIL (high-grade squamous intraepithelial lesion) and LSIL (low-grade squamous intraepithelial lesion).Results: Each group has statistical significance among CA125, CYFRA21-1, SCCA, and CA15-3 (P<0.05). Through one-way analysis of variance: the precancerous lesion group and the cancer group have statistical significance compared with the normal group. (P<0.05), but there is no statistical difference between the precancerous lesion group and the cancer group (P>0.05); the positive rate of HPVDNA detection is higher than the positive rates of other tests, which is statistically significant (P<0.05), and Tumor marker detection combined with HPVDNA detection has a high positive rate and high sensitivity. The area under the ROC curve is 0.991, which has a high accuracy, which is higher than other single detections and is statistically significant (P<0.05); TCT combined with HPVDNA detection is in HSIL The accuracy, specificity, and sensitivity of LSIL are higher than that of TCT and HPV DNA testing alone, P<0.05; the HPV positive rate of patients aged 18-27 is higher than that of patients of other age groups, P<0.05. Conclusion: In the early diagnosis of cervical cancer, the accuracy, specificity and sensitivity of tumor markers, TCT combined with HPVDNA detection are relatively high, which can increase the detection rate and has a certain diagnostic value. The two combined detection and screening for cervical cancer and cancer the detection rate of pre-lesion is higher.

Keyword: Tumor markers; HPVDNA; Cervical cancer; Cervical precancerous lesions

Introduction

Cervical cancer is one of female malignant tumors. It has a very high incidence rate and has a serious impact on women's physical and mental health(Wu et al.,2016). In recent years, the incidence of cervical cancer in my country has been increasing year by year, and it accounts for 1/3 of the incidence of cervical cancer in the world. The cause of cervical cancer is that the patient is infected with high-risk human papillomavirus (HPV), and a long period of precancerous lesions is required before cervical cancer occurs. Precancerous lesions are reversible to a certain extent. If they can be detected in time during this period And receiving diagnosis and treatment can effectively prevent the occurrence of cervical cancer(Tao et al.,2017). Clinically, there are many methods to detect cervical cancer and precancerous lesions. The more widely used methods are thin-layer liquid-based cytology (TCT) detection and HPV-DNA detection

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(Lorincz et al.,2016). At present, the detection of tumor markers is clinically used as a new auxiliary method, and it is found that there is a certain connection between tumor markers and the occurrence of cervical cancer. Therefore, the examination of precancerous lesions is very important. The combination of tumor marker detection and HPVDNA detection can effectively improve the accuracy of lesion screening and increase the detection rate of precancerous lesions. During the diagnosis of cervical cancer and precancerous lesions, our hospital used tumor marker detection combined with HPVDNA to detect cervical cancer and precancerous lesions. It was found that tumor markers are closely related to the occurrence and development of cervical cancer. After tumor marker detection The accuracy, specificity, and sensitivity of combined HPVDNA detection are higher than that of TCT and HPV-DNA detection methods alone. The report is as follows.

1 Materials and Methods

1.1 General Materials

From December 2017 to December 2018, 35 patients with precancerous lesions diagnosed by medical examination in our hospital were selected as the precancerous lesion group, 64 patients with cervical cancer as the cancer group, and 99 patients with healthy physical examination during the same period as the normal group. Criteria: (1) The ages of both groups were ≥18 and <70 years; (2) Both groups were informed and agreed. Exclusion criteria: (1) patients with immune system diseases; (2) patients with multiple acute and chronic diseases; (3) patients with mental disorders. There were 64 patients with cervical cancer, aged 19-67 years old, with an average age of (44.5±3.2) years; 10 patients were 18-27 years old, 16 patients 28-38 years old, 20 patients 39-48 years old, 49-58 14 patients aged 59-68 years old; 35 patients with precancerous lesions, aged 20-66 years old, average age (43.3±3.8) years old, and histopathologically confirmed epithelial cell changes, including 19 cases of HSIL , Including 8 cases of CINⅡ (moderate), 11 cases of CINⅢ (severe) cervical intraepithelial neoplasia; 16 cases of LSIL, mainly 16 cases of CIN Ⅰ (mild). Normal group: 99 cases, aged 21-69 years, average age (44.1±4.2) years. The general data among the cancer group, precancerous lesion group, and normal group were comparable (P>0.05), and were reviewed by the hospital ethics committee.

1.2 Methods

1.2.1 Testing instruments and reagents

Tumor marker detection instrument uses automatic chemiluminescence instrument, model Maglumi2000, provided by Shenzhen New Industry Biomedical Company; thin-layer liquid-based cytology detection and analysis application liquid-based thin-layer cell preparation analysis system, model McT-Ⅱ Model, provided by Shaanxi Gaoyuan Company; HPV-DNA detection kit provided by Zhongshan Da'an Company; Application of the Biometra series qualitative PCR gene amplification instrument produced by German company; Application of the model DA24-provided by Shanghai Jinghong Company Type 2 electric heating constant temperature water bath; use the model K30B dry thermostat provided by Hangzhou Aosheng Company; use the biological safety cabinet provided by Guangzhou Daan Company as BioaerAG0410062; use the model provided by Changsha Xiangyi Company as TG16 Tabletop centrifuge of ws type(Guo et al.,2017).

1.2.2 Tumor marker detection method

Carbohydrate antigen-CA125 (CA125), keratin 19 fragment (CYFRA21-1), squamous cell carcinoma antigen (SCCA), carbohydrate antigen-CA15-3 (CA15-3) levels, which are tumor markers After admission, they were all water-free and fasted for 8 hours, and then 3ml of venous blood was collected and centrifuged to obtain the supernatant. When performing tumor marker detection, the instructions should be strictly followed (Xia et al.,2016).

1.2.3 Thin-layer liquid-based cytology

Use a clinical special sampling brush to collect suspicious lesions at the junction of cervical canal squamous-column, put the collected samples in the cell preservation solution and send them for testing in time, and detect the samples through the liquid-based thin-layer cell preparation analysis system When processing, apply the Pap staining method to stain the cells, then dry and seal them (Broglie et al.,2016).

1.2.4 HPV-DNA detection

Put a sterile cotton swab into the cervix to extract HPV-DNA, take out HPV-DNA with even force and rotate for 5 weeks, then put it in a sterile test tube for amplification, hybridization, membrane washing, color development, etc. Process, when performing this operation, strictly follow the instructions to ensure that the operation process is standardized (Tang et al.,2016).

1.2.5 Methods of cervical pathological biops

During pathological biopsy, colposcopy should be used for detection. Professional medical staff should perform the operation. Multi-point biopsy

should be performed on the more severely affected parts. If no abnormalities are found, the four places of 3, 6, 9, and 12 will be taken. It was fixed with formaldehyde and sent for inspection immediately (Qi,2016).

1.2.6 Criteria for judging the positive tumor markers

CA125>35.00IU/ml is positive, CYFRA21-1>2.08ng/ml is positive, SCCA>1.50ng/ml is positive, CA15-3>31.30IU/ml is positive. The criteria for abnormal pathological biopsy are: cervical cancer (CIS), CINⅢ (severe) cervical intraepithelial neoplasia, CINⅡ(moderate), CINⅠ(mild) (Basu et al.,2016).

1.2 Observation index

(1) Compare the levels of tumor markers in the two groups, mainly including CA125, CYFRA21-1, SCCA, and CA15-3. (2) Compare the positive rates of different detection methods in CINⅠ (mild), CINⅡ (moderate), CIN Ⅲ (severe) cervical intraepithelial neoplasia and cervical cancer (CIS)(Wei et al.,2016). (3) Compare the detection value of different methods. (4) Compare the accuracy, specificity and sensitivity of different detection methods in HSIL and LSIL. (5) The relationship between different ages and HPV infection.

1.4 Statistical method

SPSS24.0 statistical software was used for analysis, counting data was expressed as percentage (%), and chi-square test was used for statistical analysis between groups; measurement data was expressed as mean±standard deviation (x±s), and comparison among three groups was used One-way analysis of variance, P<0.05 indicated statistical significance; the ROC curve was used to calculate the area under the curve and statistically tested with the null hypothesis to calculate the sensitivity and specificity of the combined detection method for the diagnosis of cervical cancer.

2 Results

2.1 Comparison of tumor marker levels between groups

Each group is statistically significant among CA125, CYFRA21-1, SCCA, and CA15-3 (P<0.05). The one-way analysis of variance shows that the precancerous lesion group and the cancer group are compared with each other in the normal group. Significance (P<0.05), but there was no statistical difference between the precancerous lesion group and the cancer group (P>0.05).

Table 1. **Comparison of tumor marker levels in cancer group, precancerous lesion group and normal group (x±s)**

Group	CA125(IU/ml)	CYFRA21-(ng/ml)	SCCA(ng/ml)	CA15-3(IU/ml)
Cancer group (64)	46.3±4.6	5.2±1.7	4.2±1.1	49.2±4.7
Precancerous lesion group (35)	38.1±4.0[a]	2.3±0.8[a]	1.3±0.2[a]	34.3±3.8[a]
Normal group (99)	21.55±3.92	1.16±0.31	0.69±0.15	18.21±3.53
F	19.173	15.702	12.605	21.817
P	＜0.05	＜0.05	＜0.05	＜0.05

Note: "a": P＜0.05 compared with the normal group

2.2 Comparison of the positive rates of different detection methods in CINⅠ, CINⅡ, CINⅢ, CIS

The positive rate of HPVDNA detection was higher than the positive rates of other tests, P<0.05, and the positive rate of tumor marker detection combined with HPVDNA detection was higher than the positive rates of other single tests, P<0.05, as follows Table 2.

Table 2. **Comparison of positive rates of different detection methods in CINⅠ, CINⅡ, CINⅢ, CIS (cases, %)**

Detection method	CINⅠ(16)	CINⅡ、CINⅢ(19)	CIS(64)	Total(n=99)
TCT	5(31.3)[ab]	13(68.4)[ab]	53(82.8)[ab]	71(71.7)[ab]
HPVDNA	10(62.5)[b]	16(84.2)[b]	57(89.1)[b]	83(83.8)[b]
CA125	3(18.8)[ab]	3(15.8)[ab]	54(84.4)[ab]	60(60.6)[ab]
CYFRA21-1	2(12.5)[ab]	2(10.5)[ab]	52(81.3)[ab]	56(56.6)[ab]
SCCA	3(18.8)[ab]	2(10.5)[ab]	50(78.1)[ab]	55(55.6)[ab]
CA15-3	4(25.0)[ab]	4(21.1)[ab]	51(79.7)[ab]	59(59.6)[ab]
Joint detection	14(87.5)	18(94.7)	62(96.9)	94(94.9)

Note: "a": Comparison between various indicators and HPVDNA: P<0.05; "b" Comparison between various indicators and combined testing: P<0.05.

2.3 Comparison of the detection value of different methods

The sensitivity of tumor marker detection combined with HPVDNA detection is higher than that of other individual detections, P<0.05, as follow Table 3.

Table 3. **Comparison of detection value of different methods (examples, %)**

Detection method	Area under ROC curve	Standard deviation	Sensitivity	Positive predictive value	Negative predictive value
TCT	0.746[a]	0.025[a]	71(71.7)[a]	69.73	41.56
HPVDNA	0.861[a]	0.077[a]	83(83.8)[a]	82.44	59.47
CA125	0.737[a]	0.639[a]	60(60.6)[a]	51.24	30.84
CYFRA21-1	0.768[a]	0.068[a]	56(56.6)[a]	51.36	31.41
SCCA	0.767[a]	0.069[a]	55(55.6)[a]	55.42	41.72
CA15-3	0.737[a]	0.039[a]	59(59.6)[a]	52.47	32.63
Joint detection	0.991	0.028	94(94.9)	89.62	67.42

Note: Compared with the detection of tumor markers combined with HPVDNA detection aP＜0.05.

2.4 Comparison of accuracy, specificity and sensitivity of different detection methods in HSIL and LSI

The accuracy, specificity and sensitivity of TCT combined with HPVDNA detection in HSIL and LSIL is higher than that of TCT and HPVDNA detection alone, P<0.05, the accuracy, specificity and sensitivity of single TCT and HPVDNA detection in HSIL and LSIL No significant difference, P>0.05, as follow Table 4.

Table 4. **Comparison of accuracy, specificity and sensitivity of different detection methods in HSIL and LSIL (example, %)**

Detection Indicator	TCT	HPVDNA	Joint detection	*P*
HSIL				
Accuracy	79.4%	76.5%	92.7%	＜0.05
Specificity	71.7%	75.3%	91.1%	＜0.05
Sensitivity	72.2%	76.4%	92.7%	＜0.05
LSIL				
Accuracy	80.1%	74.5%	94.2%	＜0.05
Specificity	78.3%	76.7%	93.5%	＜0.05
Sensitivity	75.5%	79.3%	91.1%	＜0.05

2.5 The relationship between different ages and HPV infection

The positive rate of HPV in patients aged 18-27 was higher than that of patients in other age groups, P<0.05, as follow Table 5.

Table 5. **The relationship between different ages and HPV infection**

Age	Number of cases	HPV positive number	HPV negative number	HPV positive rate
18-27	10	6(60.0)	4(40.0)	60.0%
28-38	16	5(31.3)	12(68.7)	31.3%
39-48	20	5(25.0)	15(75.0)	30.0%
49-58	14	3(21.4)	11(78.6)	21.4%
59-68	4	1(25.0)	3(75.0)	25.0%

3 Discussion

Cervical cancer is one of the common gynecological malignancies in clinic, and it is one of the main cancers that cause women's death (Li et al.,2017). In my country, the age of onset of cervical cancer tends to be younger, which is often related to HPV infection. The small sample size survey found that the positive detection rate of HPV among cervical cancer patients between 18-27 years old is higher, about 60.0%; It is very important to have a reasonable early diagnosis method. The current diagnosis methods for cervical cancer mainly include TCT detection, HPVDNA detection, colposcopy detection, tumor markers, etc. (Chatzistamatiou et al.,2016; Liu et al.,2016; Xu et

al.,2017). However, the detection rate of a single test method is very low in clinical practice. This study mainly explored the clinical value of tumor marker detection combined with HPVDNA detection in the diagnosis of cervical cancer and precancerous lesions. Through this study, it was found that the serum levels of CA125, CYFRA21-1, SCCA, and CA15-3 tumor markers in the cervical cancer group and precancerous lesion group were higher than those in the normal group, and there was statistical significance between the groups (P<0.05). The comparison between the cancer group and the precancerous lesion group was not statistically significant (P>0.05); it indicated that the levels of CA125, CYFRA21-1, SCCA, and CA15-3 tumor markers in patients with cervical cancer or precancerous lesions were higher than those in healthy people. The study found that the positive rate of tumor markers combined with HPVDNA detection increased significantly. A total of 94 (94.9%) cases were detected, including CIN Ⅰ: 14 (87.5%) cases, CIN Ⅱ and CIN Ⅲ: 18 (94.7%) cases, CIS: 62 (96.9%); the specificity and sensitivity are verified by the area under the ROC curve: the combined detection area under the curve is about 0.991 with high accuracy, and the area under the ROC curve for the serum detection of tumor markers is between 0.7-0.9 It represents a certain degree of accuracy, so the combined detection of tumor markers with HPVDNA can further increase the detection rate.

According to the diagnosis and treatment guidelines for cervical precancerous lesions in CAP/ASCCP, cervical diseases are divided into low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL) with two-level orders; LSIL has certain self-limiting properties About 60%-85% of patients can subside, and about 13% of LSIL will progress to HSIL; 5% of HSIL patients may further develop into cervical cancer; current interventions for HSIL increase the risk of postoperative miscarriage and premature delivery(Lma et al.,2016; Nasierowska et al.,2016). Therefore, the early diagnosis of cervical squamous intraepithelial lesions is of great significance. Most patients with cervical cancer are related to HPV infection. HPV DNA testing alone can effectively screen patients with high-risk precancerous lesions, but its specificity is low (LSIL: 75.3%, HSIL: 76.7%), which will cause certain errors in the inspection results. However, the specificity and sensitivity of TCT detection alone are relatively high, and the field of view of cell smears is relatively clear. However, if the materials are not properly collected, the rate of misdiagnosis and missed diagnosis will increase. In this study, TCT combined with HPVDNA was used to detect patients with precancerous lesions. Through combined detection, it was found that the accuracy, specificity and sensitivity of HSIL and LSIL were higher than those of TCT and HPVDNA detection alone. There was statistical significance between the groups (P<0.05) However, the accuracy, specificity, and sensitivity of TCT and HPVDNA detection in HSIL and LSIL are not statistically different (P>0.05); therefore, the combined detection of the two can effectively increase the detection rate of precancerous lesions, which is a clinical treatment The method provides a certain basis and clues, and early intervention and treatment will ultimately help reduce the risk of precancerous lesions developing into cervical cancer.

In summary, in the early diagnosis of cervical cancer, the accuracy, specificity and sensitivity of tumor markers, TCT combined with HPVDNA detection are relatively high, which can increase the detection rate and has certain diagnostic value. The two combined detection and screening of the cervix the detection rate of cancer and precancerous lesions is higher.

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