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Diagnostic Value of SMARCE1 and CRISP3 Combined with Tumor Markers in Cervical Cancer

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Abstract

Objective: To investigate the diagnostic value of SMARCE1, cysteine-rich secreted protein 3 (CRISP3) combined with tumor markers in the diagnosis of cervical cancer.

Methods: A total of 80 patients with cervical lesions who were diagnosed and treated in our hospital from January 2020 to March 2022 were selected and divided into control group (chronic cervicitis, n=30) and observation group (cervical cancer, n =50). Immunohistochemistry was used to detect the expression levels of SMARCE1 and CRISP3 in cervical tissue of the two groups of subjects, and the relationship between the expression of SMARCE1 and CRISP3 in cervical cancer tissue and the clinicopathological data of the patients was analyzed. In addition, the serum tumor marker levels of the two groups of subjects were detected, and the diagnostic value of SMARCE1 and CRISP3 combined with tumor markers in cervical cancer was analyzed.

Results: The positive expression rates of SMARCE1 and CRISP3 in the observation group were significantly higher than those in the control group (P<0.05). There was no significant difference in the positive expression of SMARCE1 and CRISP3 among cervical cancer patients with age, lymph node metastasis and TNM stage (P>0.05), and the lower the degree of tumor differentiation, the higher the positive expression rate of SMARCE1 and CRISP3 proteins (P<0.05). The serum levels of CEA, CA125 and CA153 in the observation group were significantly higher than those in the control group (P<0.05). The results of ROC curve analysis showed that the AUC values of SMARCE1, SMARCE1 + tumor markers, CRISP3, CRISP3 + tumor markers, SMARCE1, CRISP3 combined with tumor markers for the diagnosis of cervical cancer were 0.760, 0.851, 0.739, 0.810, and 0.944, respectively.

Conclusion: SMARCE1 and CRISP3 are expressed in patients with cervical cancer, and CEA, CA125, and CA153 are expressed at high levels in the serum of patients with cervical cancer. The combined detection of SMARCE1 and CRISP3 combined with tumor markers has high clinical diagnostic value for cervical cancer.

Keywords: SMARCE1; CRISP3; Tumor markers; Cervical cancer; Diagnostic value.

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Introduction

Cervical cancer is a common gynecological malignant tumor in clinical practice. As the second most common cancer among femal in the world, cervical cancer has become the second leading cause of death of malignant tumors in the female genital system and posing a serious threat to the safety and health of female in China [1]. Cervical cancer is a long-term process and it takes a long time (5 to 10 years) to develop from cervical of precancerous lesions to Cervical Intraepithelial Neoplasia (CIN). Therefore, early diagnosis and treatment of cervical cancer patients is of great significance to improve the prognosis of patients [2]. Patients with early cervical cancer have no conscious symptoms, and their cervical tissues are also lack of special changes with naked-eye, leading to missed diagnosis or misdiagnosis in clinical examination that affects early treatment of patients [3]. Therefore, it is very important to select reasonable and effective detection methods to improve the early diagnosis rate of cervical cancer. The studies found that the expression of SMARCE1 in cancer tissues of patients with gastric cancer, ovarian carcinoma and liver cancer are closely related to prognosis, and SMARCE1 is a critical gene to promote the invasion and metastasis of breast carcinoma cells [4-6]. Cysteine-Rich Secretory Protein 3 (CRISP3) is the third member of the cysteine-rich secretory protein family that has been confirmed to be low expressed in carcinoma of prostate, breast carcinoma and ovarian carcinoma, and the low expression of CRISP3 is related to the sur the stimulation reaction of malignant tumor cells or the body by tumors, the levels avival rate of breast carcinoma patients [7]. In addition, tumor markers refer to the special biochemical substances that exist in the body fluid, urine or blood of tumor patients and are generated byre higher than those of normal people, the changes can reflect the occurrence and development of tumors and play a role in early screening of cancer [8]. The study is to explore the diagnostic value of SMARCE1 and CRISP3 combined with tumor markers in cervical cancer, so as to provide reference for clinical diagnosis and treatment.

Materials and methods

General materials

80 patients with cervical diseases were diagnosed and treated in Tianjin Fifth Central Hospital from January 2020 to March 2022, and were divided into the control group (with chronic cervicitis, n=30) and the observation group (with cervical cancer, n=50) according to the pathological examination results. The observation group was 35~58 years old, with an average age of (47.63 ± 2.75) years. The control group was 35~57 years old, with an average age of (47.34 ± 3.12) years. There was no significant difference in age between the two groups (P>0.05). The study was reviewed and approved by the Ethics Committee of the Tianjin Fifth Central Hospital, and all subjects signed the informed consent form. Inclusive criteria: Ⅰ. Patients diagnosed as chronic cervicitis or cervical cancer by pathological examination [9]. Ⅱ. No previous pelvic radiation history. Ⅲ. Patients with complete clinical medical records. Exclusion criteria: Ⅰ. Patients have received drug and surgical treatment for cervical diseases. Ⅱ. Patients with other known tumors. Ⅲ. Patients with severe heart, liver and kidney dysfunction. Ⅳ. Patients with previous history of uterine surgery.

Methods

Instruments and reagents

Rabbit Anti-Human SMARCE1 and CRISP3 monoclonal antibodies were purchased from Abcam Corporation, USA, and the immunohistochemistry kits were purchased from ZSGB-BIO Co. Ltd., Beijing, China.

Detection method

SP (streptavidin-perosidase) immunohistochemical method was used to detect the immunoreactivity of SMARCE1 and CRISP3 proteins. Fix the cervical tissues sample with formalin solution (10%), embed them with paraffin, and cut the samples into 5μm thin slices after dehydrated. 3% hydrogen peroxide was used to block endogenous peroxidase for 30 minutes after EDTA antigen repair solution was used to repair under high pressure and Rabbit Anti-Human primary antibody of 1:500 concentration was added for overnight with 4^{O}C. After being taken out overnight, the room temperature was restored and being washed with phosphate buffer solution (PBS) and the Rabbit Anti-Human second antibody was added and incubated at 37^{O}C for 30 minutes, and the DAB chromogenic reagent kit was developed and thehematoxylin was stained and then sealed. The whole SP immunohistochemical process was strictly in accordance with the operating procedures of the instructions. During the test, PBS was used as the negative control instead of the primary antibody.

Result determination

Five visual fields were randomly selected from each section under high power microscope for observation, and the percentage of positive cells and the staining intensity of cells were judged. The positive signals of SMARCE1 and CRISP3 proteins were located in the cytoplasm, and the positive cells were brown yellow or brown granules. Ⅰ. According to the staining intensity of positive cells, it is judged that: colorless was 0 score, light yellow (weak positive) was 1 score, brown yellow (medium intensity) was 2 score, brown (strong positive) was 3 score. Ⅱ. According to the percentage of positive cells, positive cells accounted for 0% was 0 score, positive cells ≤ 10% was 1 score, positive cells accounted for 10%~50% was 2 score, positive cells accounted for 50%~75% was 3 score, positive cells accounted for>75% was 4 score. Ⅲ. Staining index =staining intensity+proportion of positive cells. negative expression was staining index was 0 score and positive expression was staining index was ≥ 3 [10].

Detection of tumor markers

Took 5 ml of fasting peripheral venous blood from all subjects in the morning, centrifuged for 10min at a rate of 3500 r/min, and placed in a refrigerator at -80°C temperature for testing. The level of serum CEA, CA125 and CA153 were measured by electrochemiluminescence immunoassay. The detection instrument was the automatic electrochemiluminescence immunoanalyzer of Roche, Germany. The Kits were purchased from Beijing Lidman Biochemical Co., Ltd., China and operated strictly according to the instructions.

Statistical methods

The statistical analyses were performed using the Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, IL, USA), and the counting data were chi-square test or rank sum test for comparison. The measurement data were expressed by mean ± standard deviation ($\bar{x}$±s) with t-test for comparison. The area under the Receiver Operating Characteristic (ROC) curve (AUC) was used to analyze the diagnostic value of each parameter. The difference was statistically significant. $P \leq 0.05$ was considered statistically significant.

Table 1: Comparison of SMARCE1 and CRISP3 expression between the two groups, cases (%).

Group	Case	SMARCE1		CRISP3	
		Positive	Negative	Positive	Negative
Control group	30	14 (46.67)	16 (53.33)	11 (36.67)	19 (63.33)
Observation group	50	38 (76.00)	12 (24.00)	31 (62.00)	19 (38.00)
χ^2		7.092		4.825	
P		0.008		0.028	

Table 2: The relationship of the expression of SMARCE1 and CRISP3 in cervical cancer tissues and the clinicopathological characteristics of patients (Cases).

Group	Case	SMARCE1			CRISP3		
		Positive	χ^2	*P*	Positive	χ^2	*P*
Age			0.005	0.943		0.198	0.656
≥45	35	27			21		
<45	15	11			10		
Lymph node metastasis			1.576	0.209		2.972	0.085
Yes	18	16			14		
No	32	22			17		
Degree of tumor differentiation			6.255	0.0.012		4.089	0.043
Highly differentiated	20	11			9		
Medium and low differentiation	30	27			22		
TNM staging			1.882	0.170		2.266	0.132
Stage I	36	25			23		
Stage II and III	14	13			8		

Results

Comparison of SMARCE1 and CRISP3 expression

The positive expression rates of SMARCE1 and CRISP3 in the observation group were significantly higher than the control group ($P<0.05$). As shown in Table 1.

The relationship of the expression of SMARCE1 and CRISP3 in cervical cancer tissues and the clinicopathological characteristics of patients

There was no significant difference in the positive expression of SMARCE1 and CRISP3 among the age, lymph node metastasis and TNM stage of cervical cancer patients ($P>0.05$). The positive expression rates of SMARCE1 and CRISP3 were significantly different among different tumor differentiation degrees of cervical cancer patients ($P<0.05$) and the lower the tumor differentiation degree, the higher the positive expression rates of SMARCE1 and CRISP3 proteins ($P<0.05$). As shown in Table 2.

ROC curve of the clinical value of SMARCE1, CRISP3 combined with tumor markers in the diagnosis of cervical cancer

The ROC curve results shown that the AUC of SMARCE1, SMARCE1+tumor marker, CRISP3, CRISP3+tumor marker, SMARCE1, CRISP3 combined with tumor marker for diagnosis of cervical cancer were 0.760, 0.851, 0.739, 0.810 and 0.944 respectively. As shown in Table 4 and Figure 1.

Table 3: Comparison of serum tumor markers.

Group	Case	CEA (ng/mL)	CA153 (U/mL)	CA125 (U/mL)
Control group	30	6.24 ± 2.02	15.46 ± 3.46	66.28 ± 8.84
Observation group	50	2.85 ± 0.90	6.84 ± 2.12	41.34 ± 6.76
t		8.673	12.312	13.285
P		0.000	0.000	0.000

Table 4: ROC curve of clinical value of SMARCE1, CRISP3 combined with tumor markers in diagnosis of cervical cancer.

Screening method	95%CI	AUC	Specificity (%)	Sensitivity (%)
CRISP3	0.655-0.812	0.739	64.62	75.38
SMARCE1	0.678-0.831	0.760	72.31	70.77
CRISP3+ tumor markers	0.732-0.873	0.810	75.38	70.77
SMARCE1+ tumor markers	0.778-0.908	0.851	89.23	72.31
SMARCE1, CRISPS Combined tumor markers	0.889-0.977	0.944	95.38	83.08

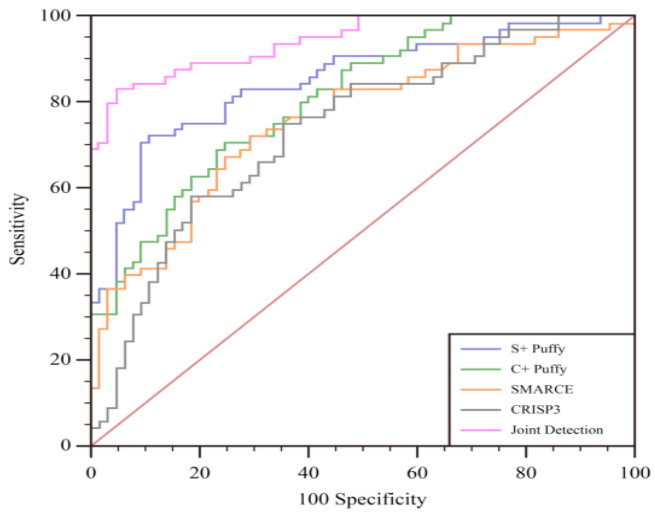

Figure 1: ROC curve of the clinical value of SMARCE1, CRISP3 combined with tumor markers in the diagnosis of cervical cancer.

Discussion

In recent years, with the change of people's life and eating habits, the incidence of cervical cancer has been increasing year by year [11]. The main clinical picture of patients with cervical cancer are thin liquid discharge like water, earthy smell of leucorrhea, irregular vaginal bleeding, anemia, algopareunia and other clinical symptoms which have a serious impact on the patient's reproductive function and life safety and health] [12]. Cervical cancer is also known as Invasive Carcinoma of Cervix. Cervical intraepithelial neoplasia is the early stage of cervical cancer, also known as Precancerous Lesion Phase [13]. According to clinical studies, patients with cervical cancer have a long Precancerous Lesion State, and it takes about 5-10 years to develop from cervical intraepithelial neoplasia to cervical cancer [14]. Therefore, early detection and diagnosis of cervical intraepithelial neoplasia and cervical cancer, and active treatment of precancerous lesions can effectively reduce the incidence and mortality of cervical cancer and improve the quality of life of patients with cervical lesions. In clinical screening and diagnosis of cervical cancer with vinegar white test combined with iodine test, colposcopy, HPV screening, cervical smear cytology, cervical and cervical tube biopsy, cervical conization screening [15]. The emergence of various screening technologies has improved the detection rate of clinical cervical cancer, but the screening costs of various screening methods are different, and the sensitivity and specificity are different. In recent years, with the development of clinical testing technology, the detection and diagnosis of cancer patients using molecular marker detection has gradually become a perspective study trend.

It was found that human SWI/SNF chromatin-remodeling complex consists of 9~12 subunits, and SMARCE1 was one of the subunits of human SWI/SNF chromatin remodeling complex [16]. The human SWI/SNF chromatin-remodeling complex contains one of the ATPases of the SMARCA4 or SMARCA4 and three major core subunits and other complex specific variant subunits. The subunits together played biological roles in regulating cell cycle progress, differentiation, DNA repair, activation, genomic instability, and programmed cell death [17]. Zhang Li, et al. [18] found that SMARCEI was a specific and sensitive marker of clear cell meningioma, and SMARCEI mutation could lead to the occurrence of clear cell meningioma. SMARCEI mutation causes the loss of SMARCEI function, leading to the loss of inhibition of SWI/SNF complex on tumor and participating in the occurrence and development of tumor [19]. The results of the study shown that the positive expression rates of SMARCE1 and CRISP3 in the observation group were significantly higher than the control group. It was indicated that SMARCEI was expressed in cervical cancer patients and the abnormal expression of SMARCEI maid participate in the occurrence and development of cervical cancer. The results of the study also found that the positive expression rate of SMARCE1 was statistically significant in different tumor differentiation degrees of cervical cancer patients, and the lower the tumor differentiation degree, the higher the positive expression rate of SMARCE1 and CRISP3 proteins. It was indicated that the abnormal expression of SMARCEI may have an impact on the pathological changes of cervical cancer and may play a key role in promoting the carcinogenesis and development of cervical cancer.

Human CRISP3 is located on human chromosome 6 and is the third member of the cysteine rich secretory protein family and is widely distributed in human tissues. It is detected in human body fluid secretion including sweat, plasma, prostate, pancreas and salivary glands [20]. The study found that CRISP3 is low expressed in colon, thymus, ovary and epididymis tissues, but its specific function has not been clearly studied [21]. CRISP3 is also low expressed in various tumor tissues that Henriksen R, et al [22]. found that CRISP3 is low expressed in malignant ovarian epithelial cells. Volpert M, et al. [23] found that CRISP3 can be used as a prognostic marker of prostate cancer. The higher the expression level of CRISP3 in prostate tissue, the higher the risk of recurrence of prostate cancer patients. WANG Y, et al. [24] found that the detection of CRISP3 level may be a new method to predict breast cancer. The low expression of CRISP3 in breast cancer patients is related to the overall survival rate and disease-free survival rate. The results of the study shown that the positive expression rate of CRISP3 in the observation group was significantly higher than the control group. It is indicated that CRISP3 is expressed in patients with cervical cancer and the abnormal expression of CRISP3 may participate in the occurrence and development of cervical cancer. The results of the study also shown that the positive expression rate of CRISP3 was statistically significant in different tumor differentiation degrees of cervical cancer patients, and the lower the tumor differentiation degree, the higher the positive expression rate of SMARCE1 and CRISP3 proteins. The abnormal expression of CRISP3 may have an impact on the pathological changes of cervical cancer, and may play a key role in promoting the carcinogenesis and development of cervical cancer.

Tumor markers refer to proteins, peptides or other biological substances are produced by the body in the process of tumor occurrence, development, invasion and metastasis of tumor cells which are synthesized, secreted or shed into body fluids or tissues by the tumor cells or the body in response to tumor cells [25]. The content of tumor markers in normal healthy people is extremely low, but it is obviously expressed at a high level in tumor tissues. Therefore, the determination of tumor markers presence or content could be used to diagnose the generation of malignant tumors, analyze the patient's condition, monitor metastasis, and judge the prognosis of patients [26]. CEA is an acid glycoprotein isolated from embryonic colon mucosa and colon adenocarci-

noma which is expressed on the surface of tissue cell membrane and is widely used in the differential diagnosis of malignant tumors [27]. CA125 is a mucin-like glycoprotein with high molecular weight which can promote cell metastasis and infiltration by influencing mutual recognition and adhesion among cells [28]. CA153 is a polymorphic epithelial mucin secreted by glands and exists in many kinds of adenocarcinoma. Studies have found that the increase rate of CA153 can reach about 70% when tumor cells metastasize so that it has good diagnostic value for the development and prognosis of the disease [29]. The results of the study shown that the level of the serum CEA, CA125, CA153 in the observation group were significantly higher than the control group. It is indicated that CEA, CA125 and CA153 are highly expressed in cervical cancer patients, and the changes are related to the occurrence and development of cervical cancer.

In addition, the study results also found that the ROC curve analysis showed that the AUC values of SMARCE1, SMARCE1+tumor markers, CRISP3, CRISP3+tumor markers, SMARCE1 and CRISP3 combined tumor markers in the diagnosis of cervical cancer were 0.760, 0.851, 0.739, 0.810, 0.944, respectively. It is indicated that the combined detection of SMARCE1 and CRISP3 combined tumor markers has high clinical diagnostic value for cervical cancer. The study has the following deficiencies including only a small sample, single center study, and does not clarify how SMARCE1 and CRISP3 participate in the occurrence and development of cervical cancer. Large sample, multi-center studies are still needed in the future, and more in-depth biological research is needed to further clarify the relevant pathways.

Conclusion

To sum up, SMARCE1 and CRISP3 are expressed in cervical cancer patients, CEA, CA125 and CA153 are highly expressed in the serum of cervical cancer patients, and the combined detection of SMARCE1, CRISP3 and tumor markers has high clinical diagnostic value for cervical cancer.

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