Diagnostic Value of CYFRA21-1, CA19-9 and SCCAg Detection in Esophageal Cancer

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Abstract: Objectives To investigate the value of serum cytokeratin 19 fragment (CYFRA21-1), carbohydrate anti-gen 19-9 (CA19-9) and squamous cell carcinoma antigen (SCCAg) in the diagnosis of esophageal cancer. Methods 100 cases of esophageal cancer (study group) and 50 healthy subjects (control group) were recruited in the study, the serum levels of CYFRA21-1, CA19-9 and SCCAg in these patients were detected. Subgroups analysis was performed in study group by clinical staging, and the diagnostic value of CYFRA21-1, CA19-9 and SCCAg in detecting esophageal cancer was analyzed by receiver operating characteristic curve (ROC). Results The serum levels of CYFRA21-1, CA19-9 and SCCAg in study group were significantly higher than those in control group, and those were significantly lower in patients with stage Ⅰ-Ⅱ disease than those with stage Ⅲ and Ⅳ disease, indicating statistically significant difference ($P<0.01$); the sensitivity of serum CYFRA21-1, CA19-9 and SCCAg in the diagnosis of esophageal cancer was 82.26%, and specificity was 91.33%, with positive predictive value being 86.14%, and negative predictive value being 89.57%, and AUC value was 0.864, the combined detection was superior to each measure utilized alone, the difference was significantly significant ($P<0.05$). Conclusion The combined detection of serum CYFRA21-1, CA19-9, and SCCAg can significantly improve the diagnostic sensitivity and specificity in detecting the esophageal cancer.

Key words: cytokeratin 19 fragment; carbohydrate antigen 19-9; squamous cell carcinoma antigen; esophageal cancer

0 Introduction

Esophageal cancer is a common malignant tumor of the digestive system, the median survival time of patients is less than 32 months, and the long-term prognosis is poor. Therefore, early diagnosis and intervention to improve the curative effect of esophageal cancer patients and improve the prognosis has an important role[1]. With the development of science and technology, the detection of serum tumor markers has become a common method of tumor detection, which can accurately reflect the proliferation of tumors and effectively judge the occurrence, development and prognosis of tumors. Cytokeratin 19 fragment CYFRA21-1, carbohydrate antigen 19-9 (car-bohydrate antigen 19-9, CA19-9) and squamous cell carcinoma antigen (SCCAG) are tumor markers in serum and are also fragments of cells secreted during the proliferation of tumor cells. According to some literatures, the combined detection of the 3 kinds of tumor markers can improve the sensitivity of early screening of esophageal carcinoma. This study detected the serum CYFRA21-1, CA19-9 and SCCAg levels of esophageal cancer patients and healthy volunteers in Chaoyang City Center hospital and analyzed their value in the diagnosis of esophageal carcinoma, which is reported as follows.

1 Objectives and Methods

1.1 Objectives

100 Patients with esophageal cancer (observation group) and 50 Healthy Volunteers (control group) were selected from Chaoyang City Hospital in January 2016-December. Inclusion criteria: ① Diagnostic criteria for esophageal carcinoma reference to the standard in the 8th edition of the "Foreign science" of the People's health press; ② esophageal carcinoma

patients were diagnosed by endoscopic biopsy, and ③ patients were not treated with radiotherapy and chemotherapy, and ④ patients in control group were from health volunteers in Physical Examination Center. ⑤ all subjects had informed consent to the study. Exclusion criteria: ① metastatic esophageal carcinoma, ② postoperative recurrent esophageal carcinoma, ③ patients with chemotherapy history, ④ without pathological examination confirmed. Among 100 patients in the observation group, there are 58 male cases, 42 female cases; age from 47 to 79, average age is (62.5 ± 13.5) years old; TNM Staging: There were 15 cases in period, 40 cases in Ⅱ period, 25 cases in Ⅲ period, and 20 cases in Ⅳ period; pathological typing: 32 cases of ulcerative type, 39 cases of poly-poidor fungating type, 18 cases of narrow contraction type, 11 cases of medullary type; differentiation degree: 27 cases of high differentiation, 34 cases of middle differentiation, 39 cases of low differentiation. Among 50 cases in the control group, there are 27 males and 23 female cases, age from 45~79 years old, average (61.3 ± 12.9) years old. There was no statistically significant difference in age and gender between the two groups ($p>0.05$), which were comparable. This study was approved by the Medical Ethics Committee of Chaoyang Town Center hospital.

1.2 Detection methods of serum tumor markers

All subjects were extracted 3ml of elbow vein blood on an empty stomach in the early morning, blood was centrifugalized for 10 min at a speed of 10 000 r/min to extract supernatant and keep them in - 20℃ refrigerator for inspection. Using the Swiss Roche Automatic Biochemical Analyzer E170 module to detect CYFRA21-1 and SCCAG levels, and the reagent box was purchased in Shanghai Enzyme-linked Biotechnology Co., Ltd.; using enzyme-linked immunosorbent assay test CA19-9 level, and the reagent Box was purchased in Shanghai West Tang Biological Technology Co., Ltd., and all operations are strictly in accordance with the instructions.

When a variety of indexes were combined in the test, the results were positive when any index was positive, and the results were negative when all the indicators were negative.

1.3 Statistical Method

Using SPSS 16.0 software to analyse data, and the measurement data were expressed by mean ± standard deviation ($\bar{x} \pm s$), the t test was used among groups; and the ROC curve was drawn, p<0.05 was statistically significant.

2 Results

2.1 Comparison of serum CYFRA21-1, CA19-9 and SCCAG levels in two groups of subjects

The serumCYFRA21-1, CA19-9 and SCCAG levels in the observation group were significantly higher than those in the control group, and the difference was statistically significant ($p<0.01$). (see table 1)

Table 1   Comparison of serum CYFRA21-1, CA19-9 and SCCAG levels in two groups of subjects($\bar{x} \pm s$)

Groups	CYFRA21-1（μg/L）	CA19-9（U/ml）	SCCAg（μg/L）
observation group（n=100）	4.29 ± 2.78	67.65 ± 38.14	2.01 ± 1.26
control group（n=50）	1.84 ± 0.72	26.84 ± 11.0	0.46 ± 0.33
t	6.120	7.402	8.54
P	<0.01	<0.01	<0.01

2.2 Comparison of serum CYFRA21-1, CA19-9 and SCCAG levels in different TNM stages

The serumCYFRA21- 1, CA19-9 and SCCAG levels were significantly lower in the Ⅰ~Ⅱ stage of the observation group than in the Ⅲ~Ⅳ period, and the difference was statistically significant ($p<0.01$). (see table 2)

Table 2   Comparison of serum CYFRA21-1, CA19- and SCCAG levels in patients with esophageal carcinoma at different TNM stages($\bar{x} \pm s$)

TNM stages	CYFRA21-1（μg/L）	CA19-9（U/ml）	SCCAg（μg/L）
Ⅰ~Ⅱ（n=55）	2.36 ± 1.44	48.52 ± 29.92	1.33 ± 0.96
Ⅲ~Ⅳ（n=45）	6.20 ± 2.57	93.74 ± 35.50	3.14 ± 1.21
t	9.425	6.913	8.342
P	<0.01	<0.01	<0.01

2.3 Comparison of the diagnostic value of serum CYFRA21-1, CA19-9 and SCCAG

The sensitivity ofCYFRA21-1, CA19-9 and SCCAG in the diagnosis of esophageal carcinoma was 82.26%, the specificity was 91.33%, the rate of missed diagnosis was 17.74%, the misdiagnosis rate was 8.67%, the positive predictive value was 86.14%, and the negative predictive value was 89.57%, the AUC is 0.864, which is higher than any one of the indicators alone, the difference is statistically significant ($p<0.05$). (see table 3, figure 1)

Table 3　Comparison of clinical value of serum CYFRA21-1, CA19-9, SCCAG alone and combined detection in diagnosis of esophageal carcinoma

Observation indicators	critical value	Sensitivity predictions AUC	Specificity value(%)	Positive (%)	prediction (%)	Negative (%)
CYFRA21-1	2.51 μg/L	62.84	83.39	72.21	78.95	0.721
CA19-9	9.61 U/ml	57.61	79.86	64.41	75.30	0.704
SCCAg	1.02 μg/L	52.28	73.39	59.88	69.12	0.693
CYFRA21-1+						
CA19-9+	-	82.26	91.33	86.14	89.57	0.864
SCCAg						

Note：compared with CYFRA21-1、CA19-9、SCCAg alone, all *P*<0.05.
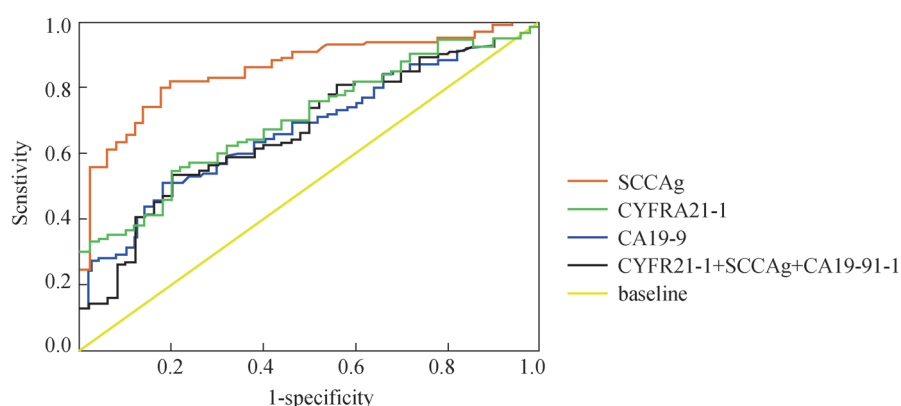

Figure 1　ROC curve of serum CYFRA21-1, CA19-9, SCCAG alone and combined detection in diagnosis of esophageal carcinoma

3 Discussion

As a digestive tract disease, esophageal cancer's early clinical symptoms are more insidious. When the sense of food choking and dysphagia shows, it is already in the late stage of disease, so, the treatment is more difficult, and it can seriously threaten the patient's life safety[4-5]. The diagnosis of esophageal cancer is an important problem for clinicians, and also a key part of the diagnosis and treatment of the disease. Tumor markers are mainly synthesized by the gene expression of tumor cells, which is a kind of material which is produced by the organism to the tumor tissue reaction, which reflects the occurrence and differentiation of tumor cells, and can guide the diagnosis, classification and prognosis of tumor. [7-8]

Serum tumor markers are commonly used non-invasive examination methods with the advantages of simple operation, small trauma, economic benefits and repeated detection, and it has been expressed before the changes of tissues and organs of esophageal carcinoma, so it is paid attention by clinicians.

As an acidic protein, cytokeratin 19 fragment CYFRA21-1 is an important molecular structure of epithelial cytoskeleton[10]. In normal physiological condition, the expression of CYFRA21-1 in peripheral blood was lower; and after cell carcinogenesis, activated protease accelerated the degradation of keratinocytes and produced a lot of CYFRA21-1 and released into blood circulation[11-12]. A19-9 is a kind of high molecular weight glycoprotein and belongs to the glycoprotein super family members, and it exists in the serum mainly in the form of salivary mucin, and content in the healthy esophageal tissue is less. The factor can enter into the blood circulation with cancer cell apoptosis and membrane fragmentation, so that serum CA19-9 level is increased[13-14]. As a glycoprotein, SCCAG is a specific antigen of esophageal squamous cell, whose level changes are correlated with the activity of esophageal carcinoma cells. The serum CYFRA21-1, CA19-9 and SCCAG levels in the observation group were significantly higher than those in the control group (*p*<0.01), indicating that CYFRA21-1, CA19-9 and SCCAG were involved in the pathogenesis of esophageal cancer. In the abnormal proliferation and differentiation of tumor cells, the metabolites of the membrane fragments and the cytoskeleton of the cells release these factors and enter the blood circulation. In clinic, by detecting CYFRA21-1, CA19-9 and SCCAG levels regularly, the pathogenesis of esophageal cancer

can be predicted, providing important reference information for the diagnosis and identification of esophageal carcinoma. In this study, according to the clinical staging of the observation group of patients with subgroup analysis, serum CYFRA21-1, CA19-9 and SCCAG levels of stage patients at Ⅲ~Ⅳ stage of the observation group are significantly higher than the Ⅰ~Ⅱ period, and the difference is statistically significant ($p<0.01$), prompting CYFRA21-1, CA19-9 and SCCAG levels increased with the increase of esophageal carcinoma stage and the progression of disease, and the change could make a more reasonable treatment plan for clinic. In order to further clarify the value of CYFRA21-1, CA19-9 and SCCAG detection in the diagnosis of esophageal carcinoma, the study use the ROC curve to analyse the serum CYFRA21-1, CA19-9 and SCCAG of the subjects, and the sensitivity is 82.26%, the specificity is 91.33%, the missed diagnosis rate is 17.74%, the AUC value is 0.864. The effect of the combined detection of the three is better than any one index alone, which makes up the shortcoming that the single index detection sensitivity is not strong, and has important significance in the diagnosis and prognosis of esophageal cancer. The diagnosis of esophageal cancer is often analyzed by single tumor markers, and the innovation of this study is not only to compare and analyze the serum CYFRA21-1, CA19-9 and SCCAG levels of the patients with esophageal cancer and the control group, but also to compare the serum tumor marker levels in different TNM stages, and also analyze the sensitivity and specificity of the combined detection and diagnosis of single index. From different respects and angles, it was proved that CYFRA21-1, CA19-9 and SCCAG were valuable in the early diagnosis of esophageal carcinoma, which provided a new method for the detection of tumor markers. But this study has a limited sample size, so, the conclusion lacks objectivity and needs to be confirmed by further large number of samples and multicenter research.

To sum up, serumCYFRA21-1, CA19-9 and SC-CAG levels are closely related to the pathological types and clinical stages of esophageal carcinoma, and the combination of three can improve the sensitivity and specificity of esophageal cancer diagnosis, and it is worthy of clinical application.

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