APPLICATION STUDY OF CEA, CA199, CA125 AND CA153 COMBINED DETECTION IN DIFFERENTIAL DIAGNOSIS OF ESOPHAGEAL CANCER

Jun Lu[1#], Dan Chen[2,#], Xinsheng Han[3], Juan Qin[1], Jiayong Zhang[1], Jiaxiu Deng[1], Rongqiang Pan[1,*]
[1]Department of Oncology, Nanchong Central Hospital, The Second Clinical Institute of North Sichuan Medical College, Nanchong 637000, Sichuan Province, China - [2]Department of Medicine, Wufeng Community Health Service Center, Shunqing District, Nanchong 637000, Sichuan Province, China - [3]Department of Oral and Maxillofacial Surgery, Nanchong Central Hospital, The Second Clinical Institute of North Sichuan Medical College, Nanchong 637000, Sichuan Province, China
These authors contributed equally to this work as co-first author

ABSTRACT

Objective: *To investigate the application value of combined detection of carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199), carbohydrate antigen 125 (CA125) and carbohydrate antigen 153 (CA153) in differential diagnosis of esophageal cancer.*

Methods: *A total of 80 patients with esophageal cancer who were diagnosed and treated in our hospital from January 2021 to May 2022 were selected as the esophageal cancer group, 70 patients with benign esophageal tumors were selected as the esophageal benign tumor group, and 50 healthy people who underwent physical examination in our hospital were selected as healthy control group. The serum levels of CEA, CA199, CA125 and CA153 were compared among the three groups, and the positive rates of CEA, CA199, CA125 and CA153 in detecting esophageal cancer were analyzed. In addition, Spearman's method was used to analyze the relationship between indexes CEA, CA199, CA125, CA153 and esophageal cancer. The area under the receiver operating characteristic (ROC) curve (AUC) was used to analyze the application value of serum CEA, CA199, CA125 and CA153 alone and in combination in the diagnosis of esophageal cancer.*

Results: *The levels of serum CEA, CA199, CA125 and CA153 in esophageal benign tumor group were strikingly higher than those in the healthy control group ($p<0.05$). The levels of serum CEA, CA199, CA125 and CA153 in esophageal cancer group were significantly higher than those in the healthy control group and esophageal benign tumor group ($p<0.05$). The positive rates of CEA, CA199, CA125 and CA153 in detecting esophageal cancer were 72.50%, 70.00%, 72.50% and 73.75%, respectively. There was a positive correlation between CEA, CA199, CA125, CA153 and esophageal cancer ($r=0.394$, 0.432, 0.335, 0.457, all $p<0.05$). The AUC values of CEA, CA199, CA125 and CA153 alone and in combination in the diagnosis of esophageal cancer were 0.810, 0.739, 0.760, 0.851 and 0.944, respectively.*

Conclusions: *Our work suggests that CEA, CA199, CA125 and CA153 are highly expressed in patients with esophageal cancer, and their level changes are closely related to the occurrence and development of esophageal cancer. The combined detection of CEA, CA199, CA125 and CA153 has a higher clinical application value in the differential diagnosis of esophageal cancer.*

Keywords: *Esophageal cancer, carcinoembryonic antigen, carbohydrate antigen 199, carbohydrate antigen 125, carbohydrate antigen 153.*

DOI: 10.19193/0393-6384_2023_1_36

Received *March 15, 2021;* ***Accepted*** *October 20, 2022*

Introduction

Esophageal cancer is a malignant tumor occurring in the esophageal epithelial tissue, and is one of the common malignant tumors in the digestive tract, with a mortality rate only lower than that of gastric cancer(1). Esophageal cancer is relatively occult, the patients have no obvious special symptoms in the early stage, and the course of disease progresses rapidly. Most patients with esophageal cancer have developed to the middle and late stage when they go to hospital, but once the tumor progresses to the middle and late stage, the 5-year survival rate of patients is lower than 20%, which seriously affects the life safety and health of patients(2). Esophageal cancer develops from esophageal benign tumor, so effective differential diagnosis of esophageal cancer and esophageal

benign tumor, early diagnosis, regular monitoring, and targeted treatment of patients are of great clinical significance to improve the prognosis of patients[3]. In recent years, with the development of clinical laboratory technology, the use of serological indicators to detect and diagnose cancer patients has gradually become a research trend[4].

Tumor markers refer to special biochemical substances in the body fluids, urine, or blood of tumor patients, which are produced by malignant tumor cells or the body in response to tumor stimulation and have a higher level than that of normal people. Changes in the level of tumor markers can reflect the occurrence and development of tumors and play a role in early cancer screening[5]. Carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199), carbohydrate antigen 125 (CA125) and carbohydrate antigen 153 (CA153) are all commonly used tumor markers in clinical practice, which have achieved good application effects in the diagnosis of gastric cancer, lung cancer, liver cancer and other malignant tumors[6]. This study explored the application value of CEA, CA199, CA125 and CA153 combined detection in the differential diagnosis of esophageal cancer, in order to provide reference for the selection of clinical diagnostic methods.

Methods

General information

A total of 80 patients with esophageal cancer who were diagnosed and treated in our hospital from January 2021 to May 2022 were selected as the esophageal cancer group, 70 patients with benign esophageal tumors were selected as the esophageal benign tumor group, and 50 healthy people who underwent physical examination in our hospital were selected as healthy control group.

There was no significant difference in the general data among the three groups (P>0.05), which were comparable, as shown in Table 1. The study was reviewed by the Ethics committee of our hospital and all study subjects signed informed consent.

Inclusion criteria:

• The patients' age was older than or equal to 18 years old and younger than or equal to 80 years old;

• According to clinical symptoms, signs, double contrast X-ray imaging of dilute barium in the esophagus and histopathological examination, the patients were confirmed as esophageal cancer or esophageal benign tumor[7];

• Patients who have not received related chemoradiotherapy;

• Patients with complete clinical medical records.

Exclusion criteria:

• Patients with mental disease;

• Patients complicated with other tumors;

• Patients with immune systemic diseases and blood systemic diseases;

• Patients with severe cardiac, hepatic and renal insufficiency.

Groups	Cases	Gender (cases)		Age (years old)
		Male	Female	
Esophageal cancer group	80	48	32	62.64±9.43
Esophageal benign tumor group	70	41	29	62.77±8.69
Healthy control group	50	30	20	63.63±9.75
χ^2/F		0.039		0.193
P		0.981		0.825

Table 1: Comparison of the general data among the three groups.

Method

5ml of fasting peripheral venous blood was collected from all subjects in the morning, and the serum was separated by centrifugation at a rate of 3500r/min for 10min.

The serum was placed in a refrigerator at -80°C for further experiments. The serum levels of CEA, CA199, CA125 and CA153 were measured by electrochemiluminescence immunoassay (Detecting instrument: automatic electrochemiluminescence immunoanalyzer, Roche, Germany). Kits were purchased from Beijing LiDeMan Biochemical Co., Ltd and operated in strict accordance with the instructions.

Statistical methods

SPSS20.0 was used for statistical analysis. χ^2 test was used for counting data analysis, and measurement data were expressed as mean ± standard deviation ($\bar{x}\pm s$). T-test was used for comparison between two groups, and ANOVA was used for comparison among multiple groups.

LSD test or Tamhane test was used for pairwise comparison among multiple groups. Correlation analysis was performed using the Spearman method. The area under the receiver operating characteristic (ROC) curve (AUC) was used to analyze the diagnostic value of each parameter. P<0.05 indicated the difference was statistically significant.

Results

Comparison of serum indexes among the three groups

The levels of serum CEA, CA199, CA125 and CA153 in esophageal benign tumor group were strikingly higher than those in the healthy control group ($p<0.05$).

The levels of serum CEA, CA199, CA125 and CA153 in esophageal cancer group were significantly higher than those in the healthy control group and esophageal benign tumor group ($p<0.05$). The results are shown in Table 2.

Groups	Cases	CEA (ng/mL)	CA153 (U/mL)	CA125 (U/mL)	CA199 (U/mL)
Esophageal cancer group	80	16.24±3.43^{ab}	29.37±5.73^{ab}	87.36±9.13^{ab}	77.08±22.24^{ab}
Esophageal benign tumor group	70	6.24±2.02^{a}	15.46±3.46^{a}	66.28±8.84^{b}	30.24±5.72^{a}
Healthy control group	50	2.85±0.90	6.84±2.12	41.34±6.76	8.50±2.13
F/χ^2		518.776	456.502	455.010	388.188
P		0.000	0.002	0.000	0.000

Table 2: Comparison of serum indexes among the three groups.

Notes: Compared with the esophageal benign tumor group: $^{a}P<0.05$; Compared with the healthy control group: $^{b}P<0.05$.

Comparison of positive rate of CEA, CA199, CA125 and CA153 in detecting esophageal cancer

The positive rates of CEA, CA199, CA125 and CA153 in detecting esophageal cancer were 72.50%, 70.00%, 72.50% and 73.75%, respectively. The results were shown in Table 3.

Indexes	Number of esophageal cancer cases	Number of positivecases	Number of negative cases	Positive rate (%)
CEA	80	58	22	72.50
CA199	80	56	24	70.00
CA125	80	58	22	72.50
CA153	80	59	21	73.75

Table 3: Comparison of positive rate of CEA, CA199, CA125 and CA153 in detecting esophageal cancer.

Correlation analysis between tumor markers and esophageal cancer

There was a positive correlation between CEA, CA199, CA125, CA153 and esophageal cancer ($r=0.394$, 0.432, 0.335, 0.457, all $p<0.05$). The results were shown in Table 4.

Indexes	Number of esophageal cancer cases	Esophageal cancer	
		r	P
CEA	80	0.394	0.026
CA199	80	0.432	0.005
CA125	80	0.335	0.000
CA153	80	0.457	0.000

Table 4: Correlation analysis between tumor markers and esophageal cancer.

Diagnostic value of CEA, CA199, CA125 and CA153 alone and combined detection in esophageal cancer

The AUC values of CEA, CA199, CA125 and CA153 alone and in combination in the diagnosis of esophageal cancer were 0.810, 0.739, 0.760, 0.851 and 0.944, respectively. The results were shown in Table 5 and Figure 1.

Detection method	95%CI	AUC	Specificity (%)	Sensibility (%)
CEA	0.732-0.873	0.810	75.38	70.77
CA199	0.655-0.812	0.739	64.62	75.38
CA125	0.678-0.831	0.760	72.31	70.77
CA153	0.778-0.908	0.851	89.23	72.31
Combined detection	0.889-0.977	0.944	95.38	83.08

Table 5: Diagnostic value of CEA, CA199, CA125 and CA153 alone and combined detection in esophageal cancer.

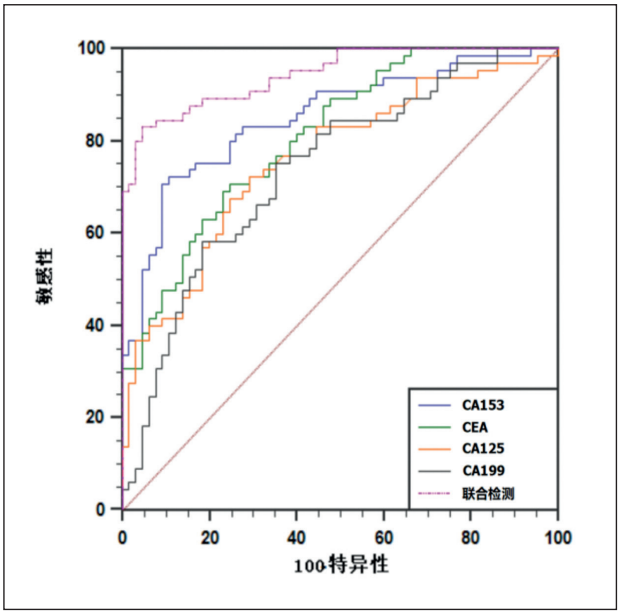

Figure 1: Diagnostic value of CEA, CA199, CA125 and CA153 alone and combined detection in esophageal cancer.

Discussion

Esophageal cancer is one of the common malignant tumors of the digestive system in clinical practice, and its incidence is increasing year by year in both the world and China[8]. Esophageal cancer patients in the early stage usually show retrosternal discomfort, burning sensation, acupuncture or pulling pain, food passes slowly and have a lingering feeling or a mild choking sensation, and other insignificant and atypical symptoms. Missed diagnosis and misdiagnosis of esophageal cancer often appeared clinically. Most patients have developed to the middle and late stage when they visit the clinic, and they have lost the best opportunity for surgical resection and treatment[9].

Esophageal benign tumors mainly include hemangioma, esophageal papilloma, lipoma, fibrolipoma, esophageal leiomyoma, etc. Patients with esophageal benign tumors mainly show symptoms such as retrosternal discomfort, food passes slowly and have a lingering feeling, which are similar to patients with esophageal cancer. Therefore, the effective differential diagnosis of patients with esophageal cancer and esophageal benign tumor lesions, early diagnosis, regular monitoring, and targeted treatment are conducive to improving the prognosis of patients[10]. Ultrasound, endoscopy, imaging examination, serum examination and pathological tissue biopsy are currently commonly used in clinical diagnosis of esophageal cancer, but X-ray, CT and other imaging tests are radiative, endoscopy and pathological tissue biopsy have great trauma to the patient's body, so these tests have certain limitations in clinical screening[11]. In recent years, with the development of clinical laboratory technology, the use of serological indicators to detect and diagnose cancer patients has gradually become a research trend[12].

Tumor markers refer to the proteins, peptides, or other biological substances produced during occurrence and development of tumors, as well as the infiltration and metastasis of tumor cells, synthesized and secreted or shed into body fluids or tissues by tumor cells themselves or the body in response to tumor cells. Tumor markers are extremely low in normal healthy people, but they are expressed at significantly high levels in tumor tissues. Therefore, the determination of their presence or content can be used to diagnose the generation of malignant tumors, analyze the disease condition, monitor metastasis and judge the prognosis of patients[13]. CEA is an acidic glycoprotein that is expressed on the surface of tissue cell membrane and is isolated from embryonic colon mucosal tissue and colon adenocarcinoma, which is widely used in the differential diagnosis of malignant tumors[14]. Scholars have found that the serum CEA level of patients with esophageal cancer is notably higher than that of non-tumor patients, and the serum CEA level of patients with esophageal cancer after surgical resection of lesions is obviously lower than that before surgery[15].

The results of this study showed that the level of serum CEA in esophageal benign tumor group was significantly higher than that in healthy control group and serum CEA level in esophageal cancer group was conspicuously higher than that in healthy control group and esophageal benign tumor group. CEA was positively correlated with esophageal cancer. It is suggested that CEA is highly expressed in patients with esophageal cancer, and its level changes are closely related to the occurrence and development of esophageal cancer, which can be used for clinical differential diagnosis of esophageal cancer and esophageal benign tumor patients. As an adhesion molecule, CEA has an immunosuppressive effect, which can help the immune escape of esophageal cancer tumor cells, thereby promoting tumor cell proliferation and metastasis[16].

CA125 is a mucin-like glycoprotein with high relative molecular weight, which can promote cell metastasis and infiltration by affecting cell mutual recognition and adhesion[17]. CA125 is expressed in normal epithelial cells of the trachea and airway, bronchial glands and pleural mesothelial cells, but it cannot enter the blood circulation, so its expression is low in the serum of normal healthy people[18]. The results of this study proved that the level of serum CA125 in the esophageal benign tumor group was significantly higher than that in the healthy control group, and serum CA125 level in esophageal cancer group was markedly higher than that in healthy control group and esophageal benign tumor group. CA125 was positively correlated with esophageal cancer. It is suggested that CA125 is highly expressed in patients with esophageal cancer, and its level change is closely related to the occurrence and development of esophageal cancer, which can be used for clinical differential diagnosis of esophageal cancer and esophageal benign tumor patients. Studies have found that the greater the absolute number of cancer cells and the larger the lesion, the higher the serum CA125 level in patients with esophageal cancer[19]. CA153 is a polymorphic epithelial mucin secreted

by glands and found in many adenocarcinomas. It has been demonstrated that when tumor cells metastasize, the increase rate of CA153 can reach about 70%, which has good diagnostic value for the development degree and prognosis of the disease[20]. The results of this study found that serum CA153 levels in esophageal benign tumor group were remarkably higher than that in healthy control group, and serum CA153 levels in esophageal cancer group were enormously higher than that in healthy control group and esophageal benign tumor group. CA153 was positively correlated with esophageal cancer.

It is hinted that CA153 is highly expressed in patients with esophageal cancer, and its level change is closely related to the occurrence and development of esophageal cancer, which can be used for clinical differential diagnosis of esophageal cancer and esophageal benign tumor patients. CA199 is a oligosaccharide tumor-associated antigen synthesized and secreted by human stomach, colon and other epithelial cells as well as pancreatic and bile duct cells. The content of CA199 is very low in the serum of normal healthy people, and it is mainly present in the tissues of patients with gastrointestinal cancer or pancreatic cancer[21]. The results of this study showed that the level of serum CA199 in the esophageal benign tumor group was significantly higher than that in the healthy control group and serum CA199 level in esophageal cancer group was obviously higher than that in healthy control group and esophageal benign tumor group. CA199 is positively correlated with esophageal cancer. It is implicated that CA199 is highly expressed in patients with esophageal cancer, and its level change is closely related to the occurrence and development of esophageal cancer, which can be used for clinical differential diagnosis of esophageal cancer and esophageal benign tumor patients.

According to previous research findings, the mechanism of increased CA199 level may be related to the release of some markers in esophageal cancer cells into the blood due to the severe degeneration and necrosis of tissue cells in tumor lesions, which plays a certain role in the tumorigenesis of esophageal cancer[22]. In this work, we showed that the AUC values of CEA, CA199, CA125 and CA153 alone and in combination in the diagnosis of esophageal cancer were 0.810, 0.739, 0.760, 0.851 and 0.944, respectively, which suggested that the combined detection of CEA, CA199, CA125 and CA153 has high clinical application value in the differential diagnosis of esophageal cancer.

In conclusion, CEA, CA199, CA125 and CA153 are highly expressed in patients with esophageal cancer, and their level changes are closely related to the occurrence and development of esophageal cancer. The combined detection of CEA, CA199, CA125 and CA153 has a higher clinical application value in the differential diagnosis of esophageal cancer.

References

1) Chen Y, Huang X, Chen L, et al. Characterization of the Immune Infiltration Landscape and Identification of Prognostic Biomarkers for Esophageal Cancer. Mol Biotechnol. 2022 Jul 3.
2) Gao Y, Kang M, Niu L, et al. The effects of radiotherapy after thoracic and laparoscopic surgery on patients with esophageal cancer and on their prognoses. Am J Transl Res. 2021 Jun 15; 13(6): 6446-6456.
3) Guo D, Zheng K. Effect of Prophylactic Radiotherapy on Patients with Stage II-III Esophageal Cancer after Esophageal Cancer Radical Operation and Influencing Factors in Its Recurrence. J Oncol. 2021 Aug 20; 2021: 7462012.
4) Ju M, Ge X, Di X, et al. Diagnostic, Prognostic, and Recurrence Monitoring Value of Plasma CYFRA21-1 and NSE Levels in Patients With Esophageal Squamous Cell Carcinoma. Front Oncol. 2022 Jan 21; 11: 789312.
5) Liu Y, Lu L, Cheng X, et al. The Index of Esophageal Cancer Related Ischemic Stroke: A Retrospective Patient Control Study. Neuropsychiatr Dis Treat. 2022 Mar 2; 18: 477-485.
6) van der Kaaij RT, Voncken FEM, van Dieren JM, et al. Elevated Pretreatment CEA and CA19-9 Levels are Related to Early Treatment Failure in Esophageal Adenocarcinoma. Am J Clin Oncol. 2019 Apr; 42(4): 345-350.
7) Hao J, Liu W, Zhao C, et al. The diagnostic significance of 64-slice spiral CT combined with serological CA19-9, Bcl-2, CYFRA21-1 detection in thoracic esophageal carcinoma. Transl Cancer Res. 2021 Dec; 10(12): 5383-5389.
8) Furukawa K, Niihara M, Kawata T, et al. Adenocarcinosarcoma at the esophagogastric junction with long esophageal invasion: a case report. Surg Case Rep. 2020 Jan 20; 6(1): 26.
9) Yang Y, Huang X, Zhou L, et al. Clinical use of tumor biomarkers in prediction for prognosis and chemotherapeutic effect in esophageal squamous cell carcinoma. BMC Cancer. 2019 May 31; 19(1): 526.
10) Yajima S, Suzuki T, Oshima Y, et al. New Assay System Elecsys Anti-p53 to Detect Serum Anti-p53 Antibodies in Esophageal Cancer Patients and Colorectal Cancer Patients: Multi-institutional Study. Ann Surg Oncol. 2021 Jul; 28(7): 4007-4015.

11) Yuan X, Zhang AZ, Ren YL, et al. Cytokine-induced killer cells/dendritic cells and cytokine-induced killer cells immunotherapy for the treatment of esophageal cancer: A meta-analysis. Medicine (Baltimore). 2021 Apr 2; 100(13): e24519.
12) Kaya Z, Karan BM, Almalı N. CDKN1A (p21 gene) polymorphisms correlates with age in esophageal cancer. Mol Biol Rep. 2022 Jan; 49(1): 249-258.
13) Suzuki T, Yajima S, Okamura A, et al. Prognostic impact of carcinoembryonic antigen in 1822 surgically treated esophageal squamous cell carcinoma: multi-institutional study of the Japan Esophageal Society. Dis Esophagus. 2022 Jun 4: doac029.
14) Turner MA, Amirfakhri S, Nishino H, et al. A Patient-Derived Orthotopic Xenograft Model of Gastroesophageal-Junction Adenocarcinoma Translated to the Clinic by Tumor-Targeting Fluorescent Antibodies to Carcinoembryonic-Antigen-Related Cell-Adhesion Molecules. In Vivo. 2021 Jul-Aug; 35(4): 1959-1963.
15) Zheng Q, Zhang L, Tu M, et al. Development of a panel of autoantibody against NSG1 with CEA, CYFRA21-1, and SCC-Ag for the diagnosis of esophageal squamous cell carcinoma. Clin Chim Acta. 2021 Sep; 520: 126-132.
16) Qian W, Huang P, Liang X, et al. High expression of carcinoembryonic antigen-associated cell adhesion molecule 1 is associated with microangiogenesis in esophageal squamous cell carcinoma. Transl Cancer Res. 2020 Aug; 9(8): 4762-4769.
17) Acharya A, Markar SR, Matar M, et al. Use of Tumor Markers in Gastrointestinal Cancers: Surgeon Perceptions and Cost-Benefit Trade-Off Analysis. Ann Surg Oncol. 2017 May; 24(5): 1165-1173.
18) Luo T, Chen W, Wang L, et al. CA125 is a potential biomarker to predict surgically incurable gastric and cardia cancer: A retrospective study. Medicine (Baltimore). 2016 Dec; 95(51): e5297.
19) Edula RG, Muthukuru S, Moroianu S, et al. CA-125 Significance in Cirrhosis and Correlation with Disease Severity and Portal Hypertension: A Retrospective Study. J Clin Transl Hepatol. 2018 Sep 28; 6(3): 241-246.
20) Oktaviyanti IK, Ali DS, Awadh SA, et al. Recent advances on applications of immunosensing systems based on nanomaterials for CA15-3 breast cancer biomarker detection. Anal Bioanal Chem. 2022 May 31.
21) Shen Y, Ding Y, Ma Q, Zhao L, Guo X, Shao Y, Niu C, He Y, Zhang F, Zheng D, Wei W, Liu F. Identification of Novel Circulating miRNA Biomarkers for the Diagnosis of Esophageal Squamous Cell Carcinoma and Squamous Dysplasia. Cancer Epidemiol Biomarkers Prev. 2019 Jul; 28(7): 1212-1220. DOI: 10.1158/1055-9965.EPI-18-1199. Epub 2019 Apr 15. PMID: 30988139.
22) Lee T, Teng TZJ, Shelat VG. Carbohydrate antigen 19-9 - tumor marker: Past, present, and future. World J Gastrointest Surg. 2020 Dec 27; 12(12): 468-490.

Acknowledgement:
Rongqiang Pan, Nanchong Municipal School Science and Technology Strategic Cooperation Project (No.: 19SXHZ0451).

Corresponding Author:
Rongqiang Pan
No. 97, Renmin South Road, Shunqing District, Nanchong City, Sichuan Province, China
Email: 1073392992@qq.com
(China)