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Original Article

Diagnostic value of serum tumor markers, multi-slice spiral CT combined with colonoscopy in high-grade colorectal intraepithelial neoplasia and early canceration

Dan Zhou[1], Xincheng Xie[1], Zhiqiang Li[2]

[1]*Department of Gastroenterology, Xixi Hospital of Hangzhou, Hangzhou, Zhejiang Province, China;* [2]*Department of Gastrointestinal Surgery, Yantai Municipal Laiyang Central Hospital, Laiyang, Shandong Province, China*

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Abstract: Objective: To investigate the diagnostic value of serum tumor markers, multi-slice spiral CT combined with colonoscopy biopsy in the diagnosis of high-grade colorectal intraepithelial neoplasia and early canceration. Methods: A prospective study was conducted in 145 patients with colorectal cancer, including 80 cases of colorectal cancer and 65 cases of high-grade intraepithelial neoplasia. Tumor markers (CA199, CA724, carcinoembryonic antigen), multi-slice spiral CT and colonoscopy biopsy were performed in all patients before the operation. Results: The values of CA199, CA724, carcinoembryonic antigen, CT and tumor size (cm) in the colorectal cancer group were higher than those in the high-grade intraepithelial neoplasia group ($P<0.05$). The area under the receiver operating characteristic (ROC) curve of serum tumor markers in the diagnosis of colorectal cancer was 0.750. The specificity was 0.721 and the sensitivity was 0.592. The area under the ROC curve of spiral CT in the diagnosis of colorectal cancer was 0.717. The specificity was 0.702 and the sensitivity was 0.731. The area under the ROC curve of colonoscopy in the diagnosis of colorectal cancer was 0.590. The specificity was 0.563 and the sensitivity was 0.608. The area under the ROC curve was 0.831 for the combined diagnosis of colorectal cancer. Tumor size was an independent risk factor for high-grade intraepithelial neoplasia ($P<0.05$). Conclusion: Serum tumor markers, multi-slice spiral CT combined with colonoscopy biopsy are valuable in the differential diagnosis of high-grade colorectal intraepithelial neoplasia and early canceration. Tumor size is an independent risk factor for high-grade intraepithelial neoplasia and canceration.

Keywords: Serum tumor markers, multi-slice spiral CT, colonoscopy biopsy, high-grade colorectal intraepithelial neoplasia, colorectal cancer, diagnostic value

Introduction

Colorectal cancer is the most common malignant disease of the digestive system. The latest global epidemiology shows that the incidence rate is 8%, ranking third in all cancers [1]. The number of newly diagnosed colorectal cancer in the United States in 2017 is 135,000 [2]. In China, the incidence of colorectal cancer has also increased, and 191,000 people have died of colorectal cancer [3]. Studies have shown that 1/3 patients with colorectal cancer have metastasis at the time of diagnosis, so early diagnosis is of great significance for the prognosis of colorectal cancer patients [4, 5].

Colorectal cancer intraepithelial neoplasia refers to the tumor lesions before the epithelial invasion, in which high-grade intraepithelial neoplasia is equivalent to severe dysplasia and carcinoma in situ [6]. It has been reported that the diagnosis of high-grade intraepithelial neoplasia by colonoscopy biopsy is quite different from the postoperative pathological results. About half of the patients were pathologically diagnosed as high-grade intraepithelial neoplasia by colonoscopy biopsy, but the postoperative pathology showed that patients have colorectal cancer with metastasis [7]. Therefore, early differential diagnosis of high-grade intraepithelial neoplasia and early colorectal cancer is of great significance.

Serum tumor markers can not only be used for the diagnosis of early lesions of tumor patients,

but also play an early warning role for changes in the body. However, clinical studies have found that there is still a phenomenon of low sensitivity when using a single indicator for diagnosis. Joint diagnosis can improve efficiency [8, 9]. CT examination is non-invasive and can clearly show the tumor size, shape, nature and the relationship between the tumor and surrounding tissues. Besides, distant metastasis can be well predicted by CT. But its disadvantages are that it is easy to miss the diagnosis of small lesions, and cannot accurately judge the nature of the mass [10]. The three detection methods have both advantages and disadvantages. At present, there is no study on the combination of the above three methods in the differential diagnosis of high-grade intraepithelial neoplasia and early colorectal cancer. The value of differential diagnosis between high grade intraepithelial neoplasia and early colorectal cancer is reported as follows.

Materials and methods

General data

A prospective study was conducted on 145 patients with colorectal cancer who were treated in the oncology department of Xixi Hospital of Hangzhou from April 2017 to April 2020. Among them, 80 patients were diagnosed as colorectal cancer by postoperative pathology, including 49 males and 31 females aged from 34 to 75 years old, and 65 patients with high-grade intradermal neoplasia, including 37 males and 28 females aged from 33 to 74 years old. All of them signed informed consent and this study was approved by the Ethics Committee of Xixi Hospital of Hangzhou.

Inclusion and exclusion criteria

Inclusion criteria: (1) Diagnosed as colorectal cancer and high-grade intraepithelial neoplasia according to the diagnostic criteria of colorectal cancer issued by the health and Family Planning Commission of the people's Republic of China in 2015 [11]; (2) Aged between 18 and 75 years old; (3) Initially diagnosed of colorectal cancer or high-grade intraepithelial neoplasia; (4) Complete clinical data.

Exclusion criteria: (1) Patients receiving other chemotherapy currently; (2) Patients with severe cardiopulmonary diseases; (3) Patients with other primary malignant tumors; (4) Patients with abnormal coagulation or bone marrow function; (5) Patients with liver and kidney dysfunction; (6) Patients with incomplete clinical data.

Methods

Serum tumor marker detection: Before diagnosis, 5 mL venous blood was collected from patients who have fasted for 8 hours and stored in ethylenediaminetetraacetic acid sterile tube (Shanghai Hengyuan biological Co., Ltd., China). After being stored in the refrigerator at 4°C for 15 minutes, venous blood was centrifuged at a speed of 800×g and centrifugation time of 5 minutes to separate serum. The serum was added to a phosphate buffer solution containing 40 μL protease inhibitor (Shanghai Hengyuan biological Co., Ltd., China) and stored in a refrigerator at -80°C. The levels of CA (carbohydrate antigen) 199, CA724 and carcinoembryonic antigen (CEA) were determined by Roche electrochemiluminescence automatic immunoassay system (E170) (Roche company, Switzerland). CA199>40 U/mL, CA724>6 U/mL and CEA>5 ng/mL were positive. All operations were carried out in strict accordance with the instrument and reagent instructions.

CT detection: CT was 128 slice spiral CT optima ct540 of UE Company of the United States. Contrast agent of enhanced scanning was iohexol. Parameter setting: slice thickness: 5 mm, image window width: 200 Hu, window level: 40 Hu, scanning range: from diaphragm level to anal level.

Colonoscopy and biopsy: After admission, relevant examinations should be improved and the patient's condition should be evaluated. Anticoagulant drugs such as warfarin, clopidogrel and enteric-coated aspirin tablets should be prohibited within 3 days before the operation. After completing the above preparations, colonoscopy can be carried out. One day before the colonoscopy, patients should be instructed to take semi-liquid diet. On the same day of colonoscopy, patients should be prepared for intestinal tract before colonoscopy. Take compound polyethylene glycol electrolyte diluted with water at 6:00 am. and 11:00 am. respectively with a dilution ratio of 1,000:1. Take two bags at 6:00 am. Within 2 hours and take one package at 11:00 am. within 1 h. Fasting shall be

Table 1. Comparison of general data and baseline data

Project	Colorectal cancer group (n=80)	High-grade colorectal intraepithelial neoplasia group (n=65)	χ^2/t	P
Age (years)	58.8±10.3	57.9±9.8	0.535	0.594
Gender (male/female)	49/31	37/28	0.278	0.598
Position (colon/rectum)	10/70	12/53	0.990	0.320
Body index (kg/m^2)	20.03±2.04	20.49±2.01	1.359	0.176
Fecal occult blood	65/15	33/32	15.209	<0.001
Anemia	27/53	16/49	1.434	0.231
Stenosis of intestinal tract	33/47	18/47	2.891	0.089

Table 2. Comparison of serum tumor indexes, spiral CT and enteroscopy indexes

Project	Colorectal cancer group (n=80)	High-grade colorectal intraepithelial neoplasia group (n=65)	t	P
CA199 (U/mL)	44.12±17.56	28.87±10.26	6.193	<0.001
CA724 (U/ml)	22.34±14.26	15.21±8.91	3.511	<0.001
CEA (ng/mL)	16.89±10.54	10.51±5.68	4.388	<0.001
CT value (Hu)	30.24±4.21	22.54±5.47	9.577	<0.001
Tumor size (cm)	3.89±1.46	2.68±1.62	4.725	<0.001

Note: CEA: carcinoembryonic antigen; CA: carbohydrate antigen.

started after 12:00 pm. until the stool of the patient excreted turn into clear water sample without residue. Colonoscopy can be carried out in the afternoon of the same day, and the lesion site shall be sampled during colonoscopy. Pathological biopsy was performed.

Statistical indexes

Statistics were analyzed by SPSS 17.0 statistical software. Continuous variables were tested by Kolmogorov test. Those who conform to normal distribution are represented by mean ± standard deviation ($\bar{x}$ ± sd). T test of independent samples is used for variables that conform to normal distribution and homogeneity of variance. Rank sum test is used for variables that do not conform to normal distribution and homogeneity of variance and represented by Z. The counting data were tested by chi square. ROC curve was drawn and area under ROC curve was calculated, including 95% confidence interval. P<0.05 was regarded as statistically significant.

Results

Comparison of general data and baseline data

There was no statistical difference in age, gender, lesion site, body mass index, anemia and intestinal stenosis (P>0.05). The incidence of occult blood in colorectal cancer group was higher than that in high-grade intraepithelial neoplasia group (P<0.05). See **Table 1**.

Comparison of serum tumor indexes, spiral CT and colonoscopy indexes

CA199, CA724, CEA, CT value and tumor size (cm) in colorectal cancer group were higher than those in high-grade intraepithelial neoplasia group (all P<0.05). See **Table 2**.

The value of serum tumor markers, spiral CT and colonoscopy in differentiating colorectal cancer from high-grade intraepithelial neoplasia

The accuracy of serum tumor markers, spiral CT and colonoscopy in the differential diagnosis of colorectal cancer and high-grade intraepithelial neoplasia were 71.72%, 73.10% and 56.55%, respectively. See **Table 3**.

ROC curve of serum tumor markers, spiral CT and colonoscopy in the diagnosis of colorectal cancer

The area under the ROC curve of serum tumor markers was 0.750. The specificity was 0.721 and the sensitivity was 0.592. The area under the ROC curve of spiral CT was 0.717. The specificity was 0.702 and the sensitivity was 0.731. The area under the ROC curve of colonoscopy was 0.590. The specificity was 0.563 and the sensitivity was 0.608. The area under ROC curve of combined diagnosis was 0.831. See **Figure 1**.

Table 3. The value of serum tumor markers, spiral CT and colonoscopy in differentiating colorectal cancer from high grade intraepithelial neoplasia

Pathological results	Three serum tumor markers		CT		Colonoscopy	
	+	-	+	-	+	-
Colorectal cancer (+)	54	26	56	24	40	40
Accuracy of high-grade colorectal intraepithelial neoplasia (-)	14	51	15	50	23	42
Accuracy	71.72%		73.10%		56.55%	

Note: Any index in the three serum tumor markers is positive, then serum tumor marker is positive. Accuracy calculation: accuracy = (actual number of positive cases + actual number of negative cases)/total number of two groups of samples.

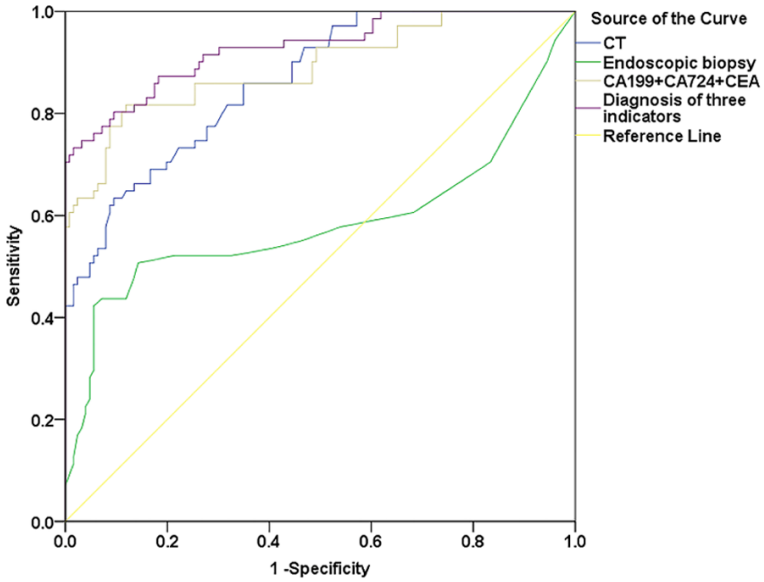

Figure 1. ROC curve of serum tumor markers, spiral CT and colonoscopy in the diagnosis of colorectal cancer. Sensitivity = actual positive cases/(actual positive cases + false negative cases) * 100%; specificity = actual negative cases/(actual negative cases + false positive cases) * 100%. ROC: receiver operating characteristic.

The analysis of the related factors of colorectal cancer patients diagnosed as high-grade intraepithelial neoplasia by colonoscopy biopsy

In this study, 80 patients were pathologically diagnosed as colorectal cancer. Among them, 40 patients were diagnosed as high-grade intraepithelial neoplasia by colonoscopy biopsy before operation and 40 cases were colorectal cancer. The coincidence rate between colonoscopy biopsy and pathological biopsy was only 50%. Forty cases of colorectal cancer confirmed by colonoscopy and pathological biopsy were taken as control group. Forty patients with high grade intraepithelial neoplasia but pathologically diagnosed as colorectal cancer by colonoscopy biopsy were selected as the observation group. The related factors causing the above results were further analyzed. There were differences in fecal occult blood and tumor size between the observation group and the control group ($P<0.05$). Multivariate analysis of variance showed that tumor size was an independent risk factor for patients diagnosed as high-grade intraepithelial neoplasia by colonoscopy but pathologically diagnosed as colorectal cancer ($P<0.05$). See **Tables 4**, **5** and **Figure 2**.

Discussion

Colorectal intraepithelial neoplasia can further develop into colorectal cancer. Early intervention and early diagnosis are of great significance for the prognosis of patients [12, 13]. Among them, high-grade intraepithelial neoplasia changes easily into progressive adenoma, which is more prone to canceration [14]. Previous studies have found that the occurrence of colorectal adenoma is related to gender, and the incidence in men is more than that in women. But there are studies that suggest the occurrence of colorectal adenoma was not related to age and gender [15-17]. In this study, we found that the incidence of colorectal cancer and high-grade intraepithelial neoplasia in men was higher than that in women, but there was no statistical difference. A large proportion of patients with high-grade intraepithelial neoplasia diagnosed by preoperative colonoscopy biopsy have undergone canceration, which cannot reflect the patient's real condition. Foreign

Table 4. Univariate analysis of those diagnosed as high-grade intraepithelial neoplasia in colorectal biopsy but pathologically regarded as colorectal cancer

Project	Control group (n=40)	Observational group (n=40)	χ^2/t	P
Age (year)	59.2±10.8	58.1±10.1	0.470	0.639
Gender (male/female)	24/16	25/15	0.053	0.818
Position (colon/rectum)	7/33	3/37	1.829	0.176
Body index (kg/m^2)	20.01±1.98	20.06±2.05	0.111	0.912
Fecal occult blood	37/3	28/12	6.646	0.010
Anemia	16/24	11/29	1.398	0.237
Stenosis of intestinal tract	18/22	15/25	0.464	0.496
CA199 (U/mL)	45.12±17.89	43.98±17.18	0.291	0.772
CA724 (U/mL)	22.69±14.26	22.15±14.14	0.170	0.865
CEA (ng/mL)	17.06±10.84	16.69±10.25	0.157	0.876
CT value (Hu)	30.87±4.39	30.23±4.16	0.669	0.505
Tumor size (cm)	4.14±1.51	3.46±1.48	2.043	0.045

Note: CEA: carcinoembryonic antigen; CA: carbohydrate antigen.

Table 5. Multivariate analysis of those diagnosed as high-grade intraepithelial neoplasia in colorectal biopsy but pathologically regarded as colorectal cancer

Project	β	SE	Wald vale	OR (95%CI)	P
Age (year)	0.302	0.785	0.162	0.754 (0.168-3.426)	0.703
Gender (male/female)	0.013	0.036	0.146	1.013 (0.963-1.079)	0.723
Position (colon/rectum)	-0.598	1.169	0.238	0.598 (0.067-5.469)	0.641
Body index (kg/m^2)	0.368	0.845	0.174	0.746 (0.173-3.574)	0.689
Fecal occult blood	1.398	0.864	2.568	3.789 (0.754-19.264)	0.126
Anemia	0.697	1.128	0.384	2.036 (0.269-18.169)	0.567
Stenosis of intestinal tract	0.493	0.841	0.356	1.698 (0.369-8.046)	0.862
CA199 (U/mL)	0.198	1.126	0.038	1.215 (0.154-10.739)	0.873
CA724 (U/mL)	0.193	1.135	0.041	1.256 (0.169-9.685)	0.812
CEA (ng/mL)	0.182	1.119	0.029	1.195 (0.136-10.687)	0.887
CT value (Hu)	0.312	0.803	0.174	0.769 (0.174-3.454)	0.712
Tumor size (cm)	2.016	0.769	6.987	7.598 (1.723-32.699)	0.008

Note: OR: odds ratio; CI: confidence interval.

studies have found that the pathological results of high-grade intraepithelial neoplasia by colonoscopy biopsy are significantly different from those after surgery [7]. Domestic studies also found that among patients whose pathology of colonoscopy biopsy was high-grade intraepithelial neoplasia, 75% of patients had postoperative pathology of colorectal cancer [18]. In this study, 50% of the patients with high-grade intraepithelial neoplasia by colonoscopy biopsy were diagnosed as colorectal cancer, which indicated that the misdiagnosis rate of high-grade intraepithelial neoplasia and colorectal cancer by colonoscopy alone was high, which was consistent with the above results. In this study, we also found that the tumor size of patients with colorectal cancer under colonoscopy was higher than that of patients with high-grade intraepithelial neoplasia. It is related to the invasion of surrounding tissue into muscle layer and metastasis.

Therefore, this study further used serum tumor indicators and CT for joint diagnosis. Serum tumor indicators CA199, CA724 and CEA are auxiliary indicators for the diagnosis of digestive tract tumors. Some studies have found that the use of serum tumor markers in the differential diagnosis of colorectal cancer, colorectal benign lesions and healthy people has a certain value, and the joint diagnosis effect is better [9, 19]. In this study, we found that the levels of CA199, CA724 and CEA in colorectal cancer group were higher than those in high-grade intraepithelial neoplasia group. As an important auxiliary means for the diagnosis of colorectal cancer patients, CT can also be used in patients who cannot have colonoscopy. And the operation is simple and repeatable, so its application range is wider [20, 21]. In this study, it was found that the CT value level in the lesions of patients with colorectal cancer was higher than that in patients with high-grade intraepithelial neoplasia, which may be due to the invasion of tumor cells to surrounding tis-

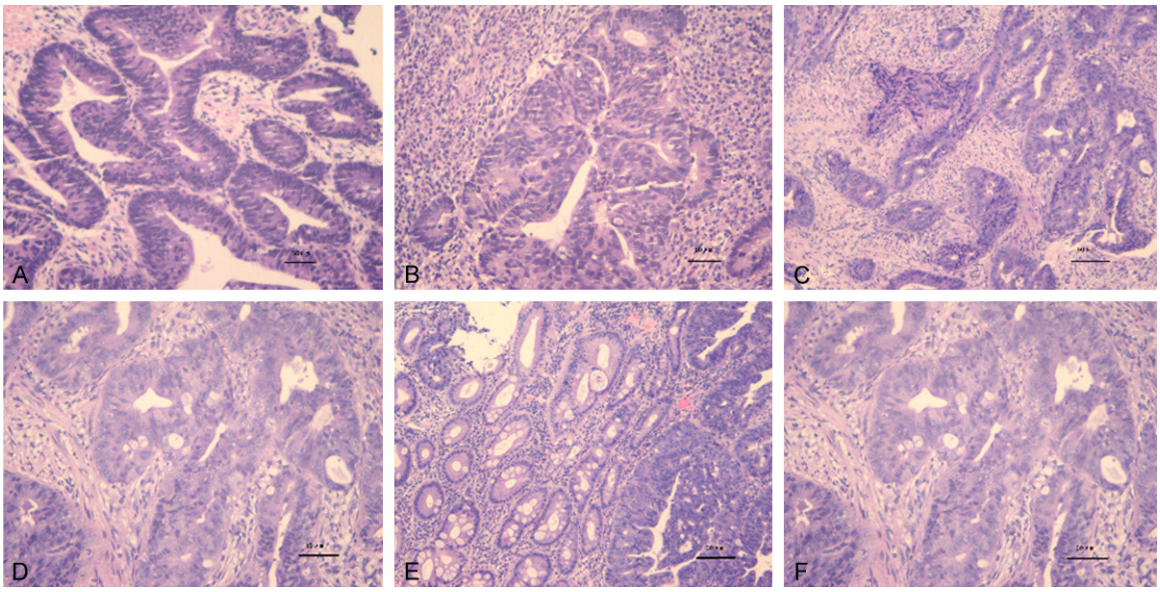

Figure 2. Pathological pictures of colonoscopy biopsy. (A-C) is high-grade intraepithelial neoplasia in colorectal biopsy but postoperative pathology is colorectal cancer; (D-F) is colorectal cancer diagnosed by colonoscopy biopsy, which is consistent with postoperative pathological results. The scale of the picture is 50 μm and the magnification is 200 times.

sues in patients with colorectal cancer. CT can clearly show the location of lesions and surrounding tissues, muscle infiltration and metastasis. At present, there is no study on the combined use of the three in the differential diagnosis of high-grade intraepithelial neoplasia and colorectal cancer. In this study, we used the combined three methods to diagnose colorectal cancer, and found that the area under the ROC curve of the three combined diagnosis of colorectal cancer was 0.831. The diagnostic value of combined three is higher.

At present, there are few studies on the related factors leading to the diagnosis of colorectal cancer by postoperative pathology while the diagnosis of high-grade intraepithelial neoplasia by colonoscopy biopsy. Some studies think that high-grade intraepithelial neoplasia by merely colonoscopy is a high-risk factor for canceration [22]. Some studies have analyzed patients with high-grade intraepithelial neoplasia by colonoscopy biopsy, and found that tumor size and high-grade epithelial neoplasia are closely related to tumor size. There is a correlation between intraepithelial neoplasia and canceration. If the tumor size >3 cm and patients are diagnosed as high-grade intraepithelial neoplasia by colonoscopy, the incidence of canceration may be larger [18]. In this study, we also found that tumor size is an independent risk factor for high-grade intraepithelial neoplasia and canceration.

The sample size of this study is small and it is a single center study, which can be further developed into a multi-center study with large samples.

To sum up, serum tumor markers, multi-slice spiral CT combined with colonoscopy biopsy have certain value in differential diagnosis of high-grade intraepithelial neoplasia and early canceration of colon. And the tumor size is an independent risk factor affecting high-grade intraepithelial neoplasia and canceration.

Disclosure of conflict of interest

None.

Address correspondence to: Zhiqiang Li, Department of Gastrointestinal Surgery, Yantai Municipal Laiyang Central Hospital, No. 111 Changshan Road, Laiyang 265200, Shandong Province, China. Tel: +86-0535-7232211; E-mail: lizhiqianggs08@163.com

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