

Original Article

Efficiency of the combination of ^{18}F -FDG PET/CT, CEA, and CA199 in detection of colorectal cancer and monitoring postoperative tumor metastasis

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Abstract: Objective: The aim of this study was to evaluate the efficiency of the combination of ^{18}F -FDG PET/CT, carcinoembryonic antigen (CEA), and carbohydrate antigen (CA) 199 in detection of colorectal cancer (CRC) and its application in monitoring postoperative tumor metastasis. Methods: From January 2012 to November 2016, 319 patients, admitted to The Weifang Traditional Chinese Hospital and confirmed as having CRC by biopsy, were recruited for this retrospective analysis. They received ^{18}F -FDG PET/CT examination, CEA, and CA199 tests. Additionally, 200 volunteers were also enrolled. During the PET/CT examination, maximum standard uptake value (SUV) of lesions was calculated according to the region of interest of lesion site and $\text{SUV} \geq 2.5$ was adjudicated as the presence of malignant tumor. Serum $\text{CEA} > 3.4 \text{ ng/mL}$ and $\text{CA199} > 27 \text{ U/mL}$ were adjudicated as positive CRC results. In the combined detection by ^{18}F -FDG PET/CT, CEA, and CA199, SUV equal to or greater than 2.5 and positivity of CEA and CA199 were defined as presence of a malignant tumor. The diagnostic efficiency of combining ^{18}F -FDG PET-CT, CEA, and CA199 in detecting CRC and its value in monitoring tumor metastasis were analyzed. Results: The results of SUV, CEA, and CA199 in CRC patients were remarkably higher than those in normal volunteers (all $P < 0.001$). SUV, CEA, and CA199 were highly expressed in patients. Accuracy of the three-modality combination in detection of CRC was 92.23%, sensitivity was 96.87%, and specificity was 87.00%, which were superior to those of the single modality ($P < 0.05$). Moreover, the three-modality combination had high sensitivity and specificity for monitoring postoperative metastasis of tumors. Conclusion: Combination of ^{18}F -FDG PET-CT, CEA, and CA199 in the diagnosis of CRC has higher accuracy, sensitivity, and specificity, and it was effective in monitoring postoperative metastasis of CRC in patients. Thus, it is worthy of extensive clinical use.

Keywords: ^{18}F -FDG PET/CT, CEA, CA199, three-modality combination, colorectal cancer

Introduction

Colorectal cancer (CRC) is a malignant tumor arising from the mucosal epithelium of the large intestine. It is one of the most frequent malignancies involving the digestive tract [1]. CRC occurs, predominantly, in the elderly population [2]. Moreover, Sung et al. reported that, in recent years, CRC patients have shown a younger trend [3]. According to statistical results of Liu et al., there were more than 1.2 million newly-developed cases of CRC worldwide, in 2015, with a trend of rising morbidity [4]. It was also reported that CRC will become the most prevalent malignancy worldwide, in place of lung and gastric cancers, in the next three years [5]. Clinically, CRC is managed by

surgical resection with adjuvant radiotherapy and chemotherapy [6]. Siegel et al. provided evidence that management of CRC at an early stage is effective and the prognosis is excellent. However, the cancer tended to be neglected due to its obscure characteristics at early stages. Most patients present with moderate or advanced stage CRC at diagnosis [7]. With the proliferation and metastasis of cancer cells, treatment has been increasingly difficult and incomplete resections of tumor lesions result in poor prognosis of patients [8]. According to Tejpar et al., 5-year survival rates are, merely, 26.8% in patients with CRC [9]. For conventional oncological diseases, "early detection and treatment" is recommended to improve prognosis of patients [10].

Table 1. PET-CT parameter setting

	Parameter
Matrix	128*128
Scan duration	3 min
Axial scan visual field	15 cm
Slice thickness	5 mm
Slice gap	3 mm
Current	120 kV
Voltage	200 mA

Currently, CRC is more often initially diagnosed by relevant tumor markers than by imaging tools. It is finally confirmed by pathological biopsy in clinical settings. Imaging tools for early diagnosis of CRC are still, primarily, CT and MRI. Nevertheless, Chapiro et al. argued that the sensitivity and specificity of CT and MRI in diagnosing CRC are unsatisfactory [11]. ¹⁸F-FDG PET-CT, a new technology integrating functional and anatomical imaging, has been shown to be of value in detecting various oncological diseases [12-14]. However, few studies have explored the diagnosis of CRC in China and other countries. In this study, it was presumed that ¹⁸F-FDG PET-CT had high efficiency for detecting CRC and the combination of ¹⁸F-FDG PET-CT, carcinoembryonic antigen (CEA), and CA199 (cancer biomarkers) could further improve efficiency for detecting CRC. Therefore, this study aimed to investigate whether the combination of ¹⁸F-FDG PET-CT, CEA, and CA199 is a more accurate and specific diagnostic modality for clinical diagnosis of CRC.

Materials and methods

Study participants

From January 2012 to November 2016, 546 patients with suspected CRC, according to findings on the colonoscopy and their clinical symptoms, admitted to The Weifang Traditional Chinese Hospital, were recruited for this retrospective analysis. Inclusion criteria included: patients 40 to 60 years of age if they were confirmed as having CRC or benign tumor by biopsy in The Weifang Traditional Chinese Hospital; patients that did not receive any relevant treatment (surgery, chemotherapy, or hormones) at admission; complete clinical records and data on relevant tests were available; patients that underwent standardized examinations by ¹⁸F-FDG PET/CT, CEA, and CA199. Exclusion criteria

included: patients that had comorbidities of cardiovascular and cerebrovascular disease or other major organ dysfunction; had a history of other tumors; patients that were bedridden or disabled; patients that had an immunological disease; binge eating patients or patients referred to another hospital. This study was approved by the Medical Ethics Committee of Weifang Traditional Chinese Hospital and all patients provided written informed consent.

The standard process of PET-CT examination was as follows: Gemini PET-CT system (Philips, the Netherlands) was applied, with GSO crystals and transverse and vertical resolutions of respective 4.8 mm and 4.0 mm. Imaging agent used was ¹⁸F-FDG (Siemens, Germany) and scanning sites were the chest, abdomen, pelvis, and perineum. PET emission scans were acquired in 3D mode and the details of setting parameters are shown in **Table 1**. PET and CT images were fused to acquire transverse, sagittal, and coronal PET/CT images.

Standard procedures for determining serum content of CEA and CA199 were as follows: 2 mL of venous blood was extracted from each patient and centrifuged (at 3,000 dpm/5 min), followed by determination of serum CEA and CA199 content by an automated immunoassay analyzer (Beckman Coulter, USA). Test images were reviewed by four experienced imaging chief physicians in a double-blind manner. They also evaluated the clinical significance of the images.

After retrieval and screening, 519 patients met the abovementioned conditions and 319 of them were confirmed as having CRC upon biopsy performed by physicians from the Department of Pathology in Weifang Traditional Chinese Hospital. The 319 CRC patients were assigned to the test group. Among them, 186 were male and 133 were female, ranging from 35 to 65 years of age (mean, 44.27±9.62 years). Rectal cancer was reported in 154 patients and sigmoid colon carcinoma in 165 patients; there were 49 cases of stage I, 77 cases of stage II, 132 cases of stage III, and 61 cases of stage IV. CRC staging was performed in accordance with guidelines listed in the AJCC Gastric Cancer Staging System in 2010 [15]. In contrast, the remaining 200 patients were confirmed with benign colorectal tumors and enrolled in the control group.

Table 2. Clinical characteristics of patients in the test group and control group (n, %)

Characteristics		Test group (n=319)	Control group (n=200)	X ²	P
Age (year)	<44	118 (37.0)	68 (34.0)	0.48	0.489
	≥44	201 (63.0)	132 (66.0)		
Sex	Male	186 (58.3)	121 (60.5)	0.24	0.621
	Female	133 (41.7)	79 (39.5)		
Place of residence	Urban	164 (51.4)	104 (52.0)	0.02	0.896
	Rural	155 (48.6)	96 (48.0)		
Marital status	Married	264 (82.8)	168 (84.0)	0.14	0.713
	Single	55 (17.2)	32 (16.0)		
Smoking	Yes	209 (65.5)	130 (65.0)	0.01	0.904
	No	110 (34.5)	70 (35.0)		
Drinking	Yes	218 (68.3)	136 (68.0)	0.001	0.936
	No	101 (31.7)	64 (32.0)		
Exercise	Yes	132 (41.4)	86 (43.0)	0.13	0.716
	No	187 (58.6)	114 (57.0)		
Body weight (KG)	<70	125 (39.2)	72 (36.0)	0.53	0.467
	≥70	194 (60.8)	128 (64.0)		

Outcome measures

Outcomes were the diagnostic efficiency of combination of SUV, CEA, and CA199 for rectal cancer and predictive value of combination of SUV, CEA, and CA199 for postoperative metastasis of rectal cancer. Other outcomes included differences among SUV, CEA, and CA199 in diagnosis of various tumor types, lesion types, and pathological stages. Cutoff values for all indexes were defined based on the findings of Niekel et al., shown as follows: SUV≥2.5 was adjudicated as presence of malignant tumor; CEA>3.4 ng/mL as presence of malignant tumor; CA199>27 U/mL as presence of malignant tumor; combination of SUV≥2.5, CEA>3.4 ng/mL, and CA199>27 U/mL as presence of malignant tumor [16].

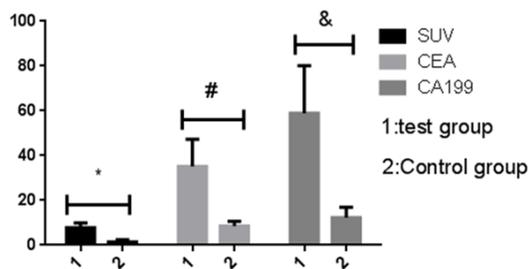


Figure 1. SUV, CEA, and CA199 findings of the test group and control group. The values of SUV, CEA, and CA199 in the test group were (7.82±2.16), (35.14±12.15) ng/mL, and (58.87±21.26) U/mL, respectively; those in the control group were (1.42±1.02), (8.54±2.08) ng/mL, and (12.33±4.62) U/mL, respectively; *P<0.001, comparison of the findings of the SUV test between the two groups; #P<0.001, comparison of the findings of the CEA test between the two groups; &P<0.001, comparison of the findings of CA199 test between the two groups.

Statistical analysis

Data were processed using SPSS statistical software, version 22.0. Count data are presented as rates and compared by Chi-square tests. Measurement data are described as mean ± SD and compared with application of two independent samples t-tests. Specificity and sensitivity were compared between the two groups by Chi-square test. P<0.05 was deemed to indicate statistical significance.

Results

Clinical characteristics of patients

Patients in the test group and control group were well-matched in clinical data including age, sex, place of residence, marital status, smoking and drinking habits, exercise habits, and body weight (all P>0.05), indicating that they were comparable (Table 2).

¹⁸F-FDG PET/CT, CEA, and CA199 findings

SUV values of the test group were remarkably higher than the control group (7.82±2.16 vs. 1.42±1.02; t=39.24, P<0.001), as were the values of CEA (35.14±12.15 ng/mL vs. 8.54±2.08 ng/mL, t=30.67, P<0.001) and CA199 (58.87±

Information retrieval

Information was retrieved by browsing the available electronic medical records and checking results of the tests. The pooled information included their basic data (age, sex, place of residence, marital status, smoking, drinking, exercise, and body weight), serum CEA and CA199 concentrations, maximum standardized uptake value (SUV) for PET-CT, biopsy and pathological findings, as well as metastasis profile within, 1 year after surgery.

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Table 3. CEA diagnostic efficiency

	Biopsy (+)	Biopsy (-)	Total
CEA (+)	255	100	355
CEA (-)	64	100	164
Total	319	200	519

Table 4. CA199 diagnostic efficiency

	Biopsy (+)	Biopsy (-)	Total
CA199 (+)	256	86	342
CA199 (-)	63	114	177
Total	319	200	519

Table 5. ¹⁸F-FDG PET-CT diagnostic efficiency

	Biopsy (+)	Biopsy (-)	Total
¹⁸ F-FDG PET-CT (+)	257	71	328
¹⁸ F-FDG PET-CT (-)	62	129	191
Total	319	200	519

Table 6. Diagnostic efficiency of the three-modality combination

	Biopsy (+)	Biopsy (-)	Total
Three-modality combination (+)	309	26	335
Three-modality combination (-)	10	174	184
Total	319	200	519

21.26 U/mL vs. 12.33±4.62 U/mL; t=30.50, P<0.001). Of note, ¹⁸F-FDG PET/CT, CEA, CA199 values of the test group were highly expressed (**Figure 1**).

Diagnostic efficiency assessment

For the 519 participants, the diagnostic efficiency of single tests of ¹⁸F-FDG PET-CT, CEA, and CA199 and the three-modality combination are shown in **Tables 3-6** and **Figure 2**.

Diagnostic efficiency of the three-modality combination in detection of postoperative metastasis

Of the 319 cases of confirmed CRC, 88 patients were detected with postoperative metastasis. Three-modality (CEA, CA199, and ¹⁸F-FDG PET-CT) combination was used for detecting patients with or without postoperative metastasis and the cut-off value was defined as 86.13. With the cut-off value as the threshold, 81 cases of postoperative metastasis of tumors

were detected by the three-modality combination, with a diagnostic accuracy rate of 92.05% (**Table 4**).

Discussion

In the present study, ¹⁸F-FDG PET-CT detection demonstrated that SUV, CEA, and CA199 were all highly expressed in CRC patients. Accuracy, sensitivity, and specificity of the combination of ¹⁸F-FDG PET-CT, CEA, and CA199 were superior to those of any one of the three modalities in detection of CRC. Furthermore, the three-modality combination yielded optimum efficiency for detecting postoperative tumor metastasis in patients, implying that the three-modality combination could be employed as an excellent indicator for clinical diagnosis of CRC and monitoring postoperative tumor metastasis in patients. The rationale for ¹⁸F-FDG PET-CT imaging is that glucose metabolism is elevated in tumor tissues and ¹⁸F-FDG PET-CT shows a high sensitivity to the metabolism of tumor tissues. In the process of tumor proliferation, images of local accumulation of ¹⁸F-FDG tracer due to uptake can be formed on ¹⁸F-FDG PET-CT [17, 18]. During tumor treatment, tumor cell proliferation in the lesion tissue is attenuated and metabolism is also reduced. In this case, images with more evenly-distributed ¹⁸F-FDG are shown on ¹⁸F-FDG PET-CT. The fusion of images by ¹⁸F-FDG PET-CT with those by CT can not only effectively detect the metabolism of tumor tissues but also yield better images of the pathological changes around the lesions. Consequently, ¹⁸F-FDG PET-CT demonstrates good performance in monitoring postoperative tumor metastasis in patients. This is consistent with the results of a study by Paspulati et al. in which ¹⁸F-FDG PET-CT was applied for detecting liver cancer in patients. It also provided evidence supporting the presumptions of the current study [19]. CEA may have different degrees of abnormal expression in blood. It is an optimum indicator for early detection of development and progression of tumors, thus, it is frequently utilized as a preferable marker for cancer diagnosis by combining multiple imaging tools. CEA is highly expressed in most cancerous tissues, with high sensitivity but low specificity. CA199 is a protein generated by rectal cells, belonging to the family of tumor-associated oligosaccharide

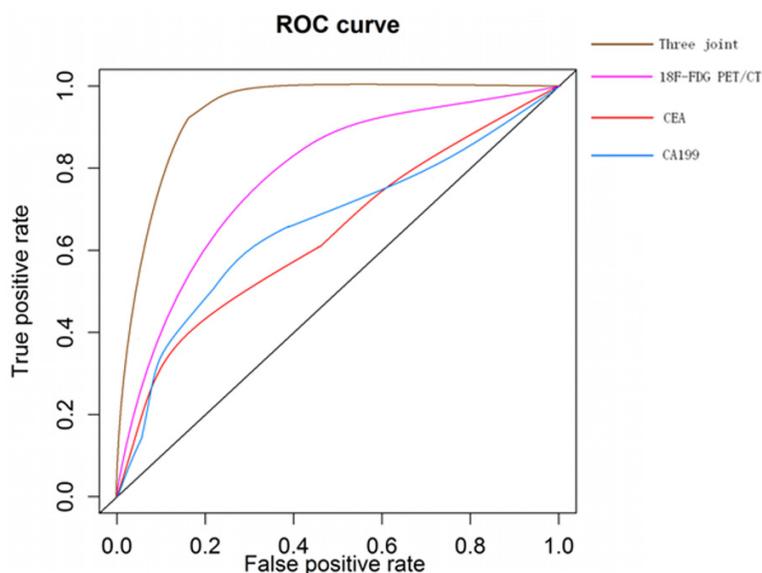


Figure 2. Findings of the combination of ^{18}F -FDG PET-CT, CEA, and CA199, as well as those of the three modalities alone in detection of CRC in the ROC curve analysis. The sensitivity and specificity of CEA test for detecting CRC were 79.94% and 50.00%, respectively; those of CA199 test were 80.25% and 57.00%, respectively; those of ^{18}F -FDG PET-CT test were 80.56% and 64.50%; those of the three-modality combination were 96.87% and 87.00%, respectively.

antigens. Expression of CA199 is primarily elevated in pancreatic and gastrointestinal malignancies. Bacac et al. have proven that combination of CEA and CA199 has good sensitivity and specificity in diagnosis of early colorectal cancer [20]. For patients with CRC stages III and IV, dissemination of lesions and tumor cells and metastasis of lymph nodes lead to more significant elevation in cancer markers. In the present study, there were no significant differences in CEA and CA199 levels between patients with CRC of stages III and those with IV. It was speculated that expression of the cancer markers had reached cutoff values, hence, the increase was not significant. As a result, the combination of ^{18}F -FDG PET-CT, CEA, and CA199 is of value in diagnosis of early CRC.

However, there were still some limitations to this study, due to insufficient experimental conditions such as a small sample size. The possibility that ^{18}F -FDG PET-CT findings and that levels of CEA and CA199 might be different among CRC patients with different ages and genders cannot be ruled out. Therefore, longer periods of investigation and follow ups are necessary to confirm the results of this study.

In summary, combination of ^{18}F -FDG PET-CT, CEA, and CA199 was associated with high accuracy, sensitivity, and specificity in diagnosis of CRC. This combination yielded a better result in monitoring postoperative tumor metastasis of CRC patients. Thus, it is worthy of extensive use in clinical settings.

Disclosure of conflict of interest

None.

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