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*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 SUV≥2.5 was adjudicated as the presence of malignant tumor. Serum CEA>3.4 ng/mL and CA199>27 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 rising 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]. $^{18}$F-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 $^{18}$F-FDG PET-CT had high efficiency for detecting CRC and the combination of $^{18}$F-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 $^{18}$F-FDG PET-CT, CEA, and CA-199 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 $^{18}$F-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 $^{18}$F-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 sage 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) | | |

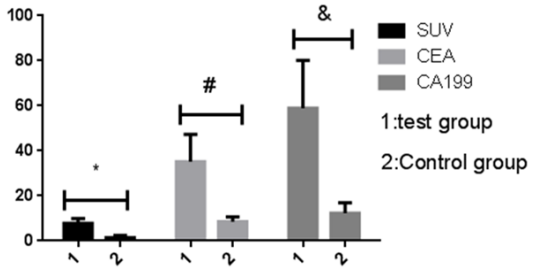


**Figure 1.** SUV, CEA, and CA199 findings of the test group and control group. The values of SUV, CEA, and CA199 in the test group were (7.82±2.16), (35.14±12.15) ng/mL, and (58.87±21.26) U/mL, respectively; those in the control group were (1.42±1.02), (8.54±2.08) ng/mL, and (12.33±4.62) U/mL, respectively;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

*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.

*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].

*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**).

*$^{18}$F-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±

**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.** $^{18}$F-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, $^{18}$F-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 $^{18}$F-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 $^{18}$F-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, $^{18}$F-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 $^{18}$F-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 $^{18}$F-FDG PET-CT imaging is that glucose metabolism is elevated in tumor tissues and $^{18}$F-FDG PET-CT shows a high sensitivity to the metabolism of tumor tissues. In the process of tumor proliferation, images of local accumulation of $^{18}$F-FDG tracer due to uptake can be formed on $^{18}$F-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 $^{18}$F-FDG are shown on $^{18}$F-FDG PET-CT. The fusion of images by $^{18}$F-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, $^{18}$F-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 $^{18}$F-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

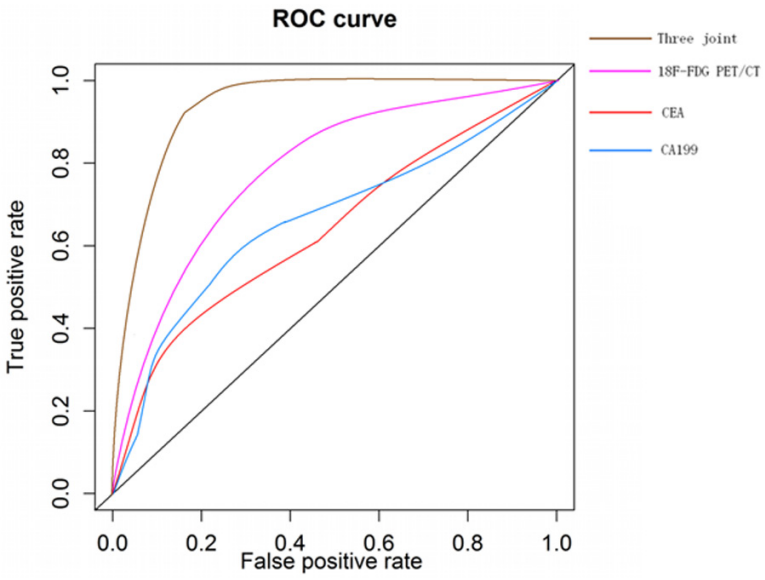


**Figure 2.** Findings of the combination of $^{18}$F-FDG PET-CT, CEA, and CA199, as well as those of the three modalities alone in detection of CRC in the ROC curve analysis. The sensitivity and specificity of CEA test for detecting CRC were 79.94% and 50.00%, respectively; those of CA199 test were 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 CA-199 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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