JMS 2021;4(2):57-65
UDC:616.348/.35-006.6-073.756.8:004

THE VALUE OF PET/CT IN DETECTING COLORECTAL CANCER RECURRENCE IN PATIENTS WITH NEGATIVE CT FINDINGS

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Abstract

Computed tomography (CT) is widely accepted imaging modality used to detect recurrent colorectal cancer (CRC) in the routine follow up, though further imaging may be required. The objective of this research is to investigate the value of PET/CT in detecting colorectal cancer recurrence despite negative CT findings.

A retrospective review of colorectal cancer patients referred for 18F-FDG PET/CT imaging to the University institute of positron emission tomography in Skopje, between July 2018 and January 2020. All of the patients had a stage III disease and were clinically suspicious of recurrence (elevated CEA or presence of symptoms) despite recent negative CT findings.

Twenty one patients (10 women and 11 men, mean age 56.95) met the above criteria. In 6 patients (28%) cancer recurrence was detected. Negative PET/CT findings were reported in eleven patients and in only one patient (1/11, 9%) recurrence was detected within one year of PET/CT. Equivocal PET/CT finding were reported in three patients, further work-up proved metastasis. In eight (8/9, 88%) patients with abnormal level of CEA, PET/CT detected or initiated further work-up that led to malignancy detection. Patients with stage III CRC had the most positive PET/CT findings 4/7 (57%) compared to others. PET/CT could detect disease recurrence in patients when clinically suspicion persists in spite of negative CT findings.

Elevated CEA and the primary tumor stage were dominant features of the patients with recurrent disease. Negative predictive value of PET/CT is high enough to reassure clinicians and reduce patient anxiety.

Kew words:colorectal cancer, cancer recurrence, PER/CT, CEA, CT

Introduction:

Colorectal cancer (CRC) accounts for approximately 10% of all annually diagnosed cancers and cancer-related deaths worldwide [1]. Radical resection and postoperative chemotherapy are widely accepted as treatment of choice in stage III disease.

Unfortunately, metachronous metastasis occurs in one third of patients within the first year after resection. As a result, follow-up protocols have been developed so relapse could be detected on an early basis, thereby maximizing patient survival in the metastatic setting. Present follow-up protocols for colorectal cancer include clinical assessment, blood carcinoembryonic antigen (CEA) monitoring, imaging and colonoscopy in predefined time intervals up to five years after surgery.

In pre-CEA period follow up was generally limited to periodical examination and the outcome was often delayed or inaccurate recurrence or metastasis detection [2]. Since Gold and Freedman [3] isolated carcinoembryonic antigen (CEA) from human colorectal cancer tissue, CEA is constantly part of various follow-up strategies. In the 1970s and 1980s CEA was used to identify recurrent disease in colorectal cancer due to limited capabilities of the available imaging techniques. "Second-look"

operations were advocated based on elevated CEA with the hope that early recurrent disease would be identified and curable resection would be performed [4]. Advancement in imaging modalities gradually replaced "second-look" operations.

Current guidelines for colorectal cancer follow-up advocate computed tomography (CT) as a routine imaging modality to identify and pinpoint recurrent disease [5-7].

Elevated serum CEA without identified relapse poses a major challenge for clinicians due to the fact that treating patients with false-positive CEA increase could cause harm. Additionally, other imaging methods have been introduced including positron emission tomography/computed tomography (PET/CT) to determine whether disease recurrence is the cause of elevated serum CEA.

The objective of this research was to investigate the association between the primary tumor site, tumor stage, symptoms and serum CEA (symptoms and elevated CEA indicate disease recurrence) and PET/CT findings and therefore estimate the value of PET/CT in detecting CRC recurrence despite negative CT findings.

Materials and methods

2.1. Study design and patient population

A retrospective review of 144 patients referred for 18F-FDG PET/CT imaging to the University institute of positron emission tomography in Skopje, between July 2018 and January 2020, for surveillance of CRC was performed.

Patients were deemed eligible for inclusion in the study if they met the following requirements: 1. stage III colorectal cancer, 2. primary surgery for treating colorectal cancer, 3. standard post-treatment surveillance regimen (history and physical examination, CEA measurement every 3-6 months and CT chest/abdomen/pelvis every 6-12 months), 4. clinical suspicion of recurrent disease, 5. negative CT findings and 6. PET/CT performed no later than two months after the CT examination.

Clinical suspicion of recurrent disease was defined as presence of symptoms (abdominal or pelvic pain, change in bowel habits, fatigue) or elevated blood CEA (above 5 ng/ml). Exclusion criteria for participation in the study were synchronous or metachronous malignant disease. The follow-up time was at least 6 months.

The Ethics Committee of our Institute approved the research protocol.

2.2 18F-FDG PET/CT imaging

All patients intended to undergo PET/CT imaging were instructed to restrain from unnecessary physical activity and fast for at least 4 hours before the time of their appointment. Drinking water prior to the examination was encouraged.

Blood glucose levels were recorded prior to intravenous administration of 18F-FDG. If the serum glucose level was higher than 11.1 mmol/l (200 mg/dl), the examination was postponed. Sixty minutes following 18F-FDG injection (206–398 MBq), CT and PET images were consecutively acquired from the base of the skull to the upper thighs. Patients were instructed to breathe normally during the PET and CT acquisitions. 18F-FDG PET/CT examinations were performed on a hybrid PET/CT scanner (Biograph 40mCT, Siemens, Germany).

For the CT scan portion of the study, the settings were as follows: 120 kVp, ~35 mA [personalized settings determined by automatic exposure control system; automatically defined by the software used by manufacturer (CareDose 4D) depending on the patient and region assessed], a rotation time of 0.8 s, a table speed of 18 mm per gantry rotation, a pitch of 1.5:1, and a detector row configuration of 40×0.625 mm.

The raw CT data were reconstructed into transverse, sagittal and coronal images with a 5-mm section thickness. For the PET portion of the study, a two-dimensional acquisition was performed, images were acquired using 2 min. per bed position and nine to eleven bed positions per patient, depending on patient height.

Raw PET data were reconstructed with and without attenuation correction and images were presented in axial, coronal, and sagittal planes as well as maximum intensity projection (MIP) images. Attenuation correction was based on the CT attenuation coefficients, which were determined by Filtered back-projection. PET/CT fusion images of the whole body were also displayed in three planes.

2.3 Imaging evaluation

Each PET/CT study was interpreted by nuclear medicine physician(s) and radiologist with consensus using Syngo Multimodality workplace (Siemens AG). Both physicians had an access to the full medical record prior to the examination. First, PET images were evaluated alone, both visually and semi-quantitatively. The maximum standardized uptake values (SUVmax) were determined if there was a significant uptake (SUVmax cut-off value of 2.5).

Furthermore, comparison of the CT images in the above-mentioned sites was done to evaluate any detectable lesion or morphological/structural alteration. At axial images diameters were measured, maximum diameter of the lesions and short axis of the lymph nodes.

The diagnosis of a malignancy lesion was based on the shape, size, intensity of the lesion as well as the CT findings.

PET/CT results were classified as positive (suspicious for malignancy), equivocal (ambiguous findings) or negative (no apparent sign of malignancy). All of the patients with positive or equivocal findings were referred to further diagnostics and/or therapeutic interventions.

An additional radiology review of the previous diagnostic CT scans of patients with new evidence of disease recurrence on PET/CT was done to determine whether lesions were truly occult or the lesions had been overlooked. Radiologist was informed of the PET/CT findings before reevaluating previous CT scans.

Data were analyzed with SPSS for Windows (version 20, SPSS, Chicago, IL, USA). Chi squared or Fischer's exact test were used to test differences in the PET/CT scan outcomes associated with tumor site, primary tumor stage, symptoms and serum CEA.

Results

Twenty-one patients (mean age 56.95±13.62 years (range 27-81), 10 women and 11 men) met the inclusion criteria. The most common tumor site was left colon in 8 patients (38%), followed by right colon in 7 (33%), and rectum in 6 (29%) patients.

Histological analyses of the resected specimens revealed: 9 (42%) cases as T3 and T4 and 3 (16%) cases as T2 regarding the tumor and 13 (62%) cases N1 and 8 (38%) cases N2 apropos lymph node involvement. Only 3 (16%) patients were classified as stage IIIA disease, 7 (33%) patients as stage IIIC and the rest 11 (51%) patients as stage IIIB disease. Majority of the patients (18, 85%) were treated with some form of chemo- and/or radiotherapy. Elevated blood CEA levels were recorded in 9 (43%) patients and symptoms were present in 17 (81%). PET/CT examination was done within 2-12 months of the surgery, with mean period of 8 months.

In 6 patients (28%) cancer recurrence was detected. Liver metastasis were identified in four patients (4/6, 66%). Additionally, metastasis was depicted in peritoneum and lymph nodes. More than one site of metastasis was noted in three patients. Synchronous colon and pancreatic cancer were also detected (2/21, 10%).

In four patients, findings were histologically confirmed with surgery, colonoscopy and endobronchial ultrasound-guided biopsy. In the rest of the patients, follow up CT or PET/CT was performed. Equivocal PET/CT finding of lymph nodes and ovary were reported in three patients. Negative PET/CT findings were reported in eleven patients and in only one patient (1/11, 9%) recurrence was detected within one year of PET/CT.

PET/CT detected or initiated further work-up that led to malignancy detection in eight (8/9, 88%) patients with abnormal level of CEA, half of them were asymptomatic. Furthermore, in two (2/12, 16%) patients recurrent disease was identified even though normal serum CEA levels were presented.

In three out of four patients, detected liver metastases were present on the previous CT exams as well as one of the two peritoneal metastases. Ovary lesions in both cases were also present on previous exams, but there were no signs of malignancy.

The metastatic lymph nodes were present on previous CT exams, but they did not meet the criteria for metastasis. Both synchronous cancers were also present on previous CT exams.

There was no association between the tumor site and PET/CT findings. In four out of 8 patients with primary left colon tumor site positive PET/CT was detected, in 2/7 (28.6%) patients with right colon and in 1/5 (16.7%) with rectum tumor site positive PET/CT was detected.

Patients classified as stage IIIC disease had more positive PET/CT findings 4/7 (57%) compared to patients with stage IIIB 2/11 (18.2%) and IIIA 1/3 (33%) (Fig. 1).

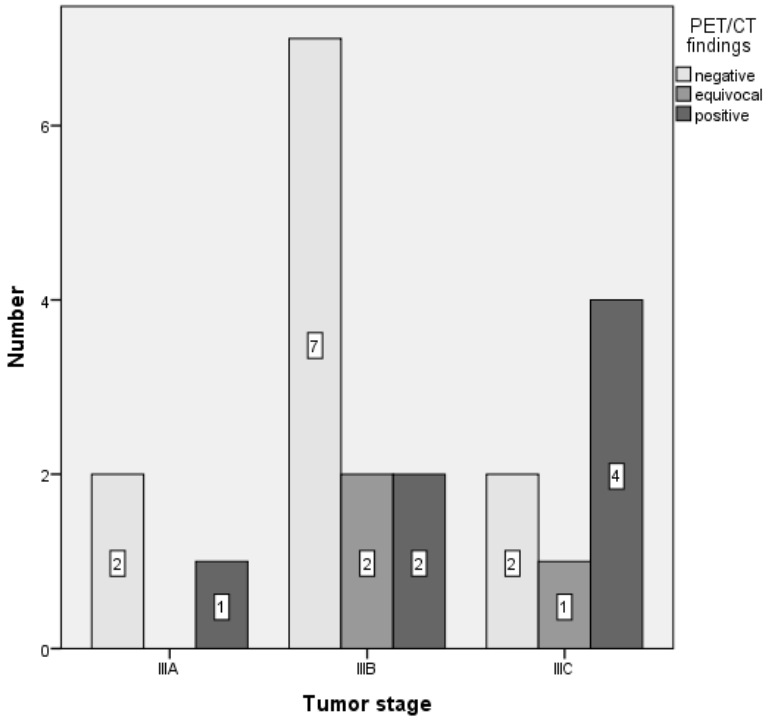

Fig. 1 PET/CT findings in patients with different primary tumor stage

Symptoms were not associated with the PET/CT findings. Only four out of 17 symptomatic patients (23.5%) had positive PET/CT findings.

In more 6/9 (66.7%) patients with elevated CEA, positive PET/CT was detected compared to 1/12 (8.3%) patient with normal CEA. Significantly more patients with elevated CEA had positive PET/CT findings, p=.004 (Fig. 2).

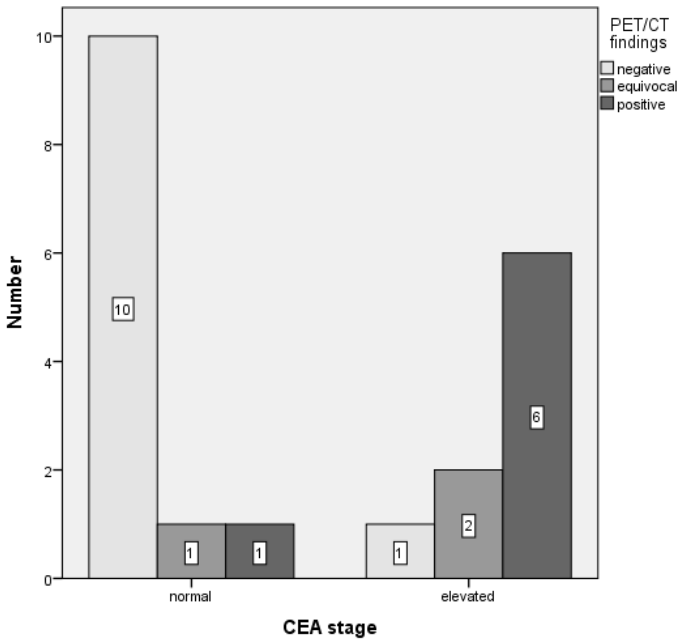

Fig. 2. PET/CT findings in patients with normal and elevated serum CEA

Discussion

Contrast enhanced CT is still the workhorse of diagnostic imaging in the follow-up process in patients with CRC according to the majority of the relevant guidelines due to its availability, cost effectiveness and superiority to conventional radiography and ultrasound. Nonetheless, CT is less reliable in some aspects than other advanced imaging modalities.

MRI using liver-specific contrast agent grants better accuracy in detection of liver metastases and PET/CT detects far more extrahepatic metastasis[8-9]. Many research has been done to evaluate the added value of PET/CT in the follow-up period in numerous clinical setups including monitoring colorectal cancer patients by 6-monthly PET/CT [10]. So far, some guidelines encourage the use of PET/CT in events of elevated CEA when recurrence cannot be detected [6].

Published data reveal greater sensitivity of PET/CT over contrast enhanced CT in recurrence detection in CRC patients in different scenarios. Deleau *et al*. compared PET/CT to contrast enhanced CT when CRC recurrence was suspected dominantly based on nonconclusive CT findings. Results showed significantly greater accuracy of PET/CT compared to CT (88% *vs*. 55%) (11).

Caglar *et al.* reported that PET-CT is more accurate than CT in detecting recurrent CRC in patients with elevated tumor marker (cancer antigen 19-9 and/or carcinoembryonic antigen) and/or suspicious chest or abdomen CT during follow-up. False negative rate was higher for CT examination (21%) compared to PET/CT (8%) (12). In pN2 subgroup of stage III colorectal cancer patients, Fehr *et al*. reported that early postoperative PET/CT detected metastases in 14% of the examined patents compared to preoperative CT examination [13].

Metser *et al.* compared PET/CT to contrast-enhanced 64-MDCT of the chest and abdomen in patients with elevated CEA. Although both techniques had similar specificity, FDG PET/CT had considerably higher sensitivity than CT (97.3% *vs* 70.3%) in identifying sites of recurrence [14].

Mittal *et al*. reported that PET/CT detected disease recurrence in 13 of 28 (46%) subgroup of patients with negative CT scan who had rising CEA levels [15].

In our study, we evaluated the value of PET/CT in detecting disease recurrence when suspicion rose due to elevated CEA and/or present symptoms, but CT could not confirm that. PET/CT led to detection of CRC recurrence in 9 patients (9/21, 42.8%) with recent negative CT findings. Subsequently,

in four of the patients identified lesions were present on the previous CT examination. In one patient liver metastasis was reported as hemangioma and in the remaining lesions were overlooked. After all, PET/CT led to detection of true occult recurrence in five patients (5/21, 23%).

Furthermore, PET/CT helped us detect metachronous malignancies in two patients (2/21, 9.5%), at cecum and pancreas. Both patients had elevated blood CEA, and the patient with pancreatic tumor was symptomatic. In both cases, tumors were overlooked on CT examination. Lee *et al.* reported five metachronous tumors (5/59, 8.5%) in patients group with normal CEA levels (thyroid, hepatocellular, mucoepidermoid, pancreatic, and esophageal cancer) [16]. Lower prevalence of metachronous tumors was reported by Chen *et al.*, in 3% (2/68 patients) [17].

Equivocal interpretations in PET/CT are not uncommon, usually resulting in additional imaging or biopsy for further characterization, thereby delaying clinical decision-making, increasing medical expenses, and resulting in additional inconvenience to the patient.

Fraum *et al.* reported 16% (31 patients) indeterminate reports of oncologic PET/CT in initial staging or subsequent restaging of malignancy [18]. Our results showed that equivocal findings were reported in three patients (3/21, 14,2%). In all three of them, lymph nodes were suspicious of disease recurrence. Histopathological analysis following PET/CT scan demonstrated metastasis in all of the patients.

Kudura *et al*. also reported that the most frequent indeterminate findings on the FDG-PET/CT were lymph nodes (18.3%) of all findings in patients with melanoma [19]. Additionally, in two patients ovary lesions were also reported as indeterminate. Following surgery, metastasis was histologically proven.

Vallam *et al.* reported seven patients (7/104, 6.7%) with an equivocal PET–CECT report; five developed progressive disease, whereas two remained disease-free when asymptomatic rise in CEA values was present [20].

Presence of signs and/or symptoms of recurrence without a possibility to identify or rule out disease makes patients anxious and uncertain. One of the attributes of PET/CT is the high negative predictive value (NPV) of disease recurrence that could ease patients and reassure clinicians in an uncertain situation. Negative predictive value of 100% was reported in a study by Ince *et al*. that enrolled patients based on elevated blood CEA and/or Ca 19-9 levels or conventional imaging (CT or MRI) [21]. Negative predictive values over 90% in detecting colorectal cancer recurrence with PET/CT in patients with elevated CEA was reported by several authors [22-25].

Our results showed that disease recurrence was identified (liver metastases) in only one patient after negative PET/CT within a year. Negative predictive value of PET/CT in our study was 90%. In a similar study conducted by Khan *et al.*, which included patients with elevated CEA after normal findings on conventional investigations, negative predictive value of 80% was reported [26].

The diagnosis of recurrent disease may be made several months ahead of morphological imaging by investigating the first abnormal CEA level [27], though localization of the lesions is necessary for treatment planning. Our results showed that in a setting of elevated blood CEA, PET/CT managed to pinpoint recurrent disease in 5 patients (5/9, 55%) and initiated further work-up in other two patients (2/9, 22%), which turnout to be recurrence. Out of the remaining two patients, one had synchronous colon cancer at cecum and the other was disease-free in the follow-up period of one year. The true occult recurrence detection rate by PET/CT in the patients with elevated CEA after reviewing previous CT examination in our study was 33% (3/9 patients), which was more than reported in the study by Amin *et al*. where only one of ten patients had a positive yield from PET/CT in a case of unexplained rise in CEA [28].

Overall, PET/CT led to detection of malignancy in 8 (8/9, 88%) patients with elevated blood CEA. In a setting of elevated blood CEA without previous CT imaging, previous research data revealed a wide range of prevalence of recurrent disease detection with PET/CT. Surpassing rates of recurrence detection were reported by Chen *et al*. and Kyoto *et al*. with prevalence of 91.7% (22 patients) and 74% (54 patients), respectively [17,29].

On the other hand, studies by Gade *et al.*, Mital *et al.* and Vallam *et al*. included contrast enhanced CT and their detection rates were significantly lower, 44% (32 patients), 46% (13 patients) and 59.6% (62 patients), respectively[15,20,30].

Tumor marker testing, imaging, and colonoscopy in tight schedule, especially in the first three years after surgery have been introduced to maximize the efficiency of the postoperative surveillance. The goal is to detect early recurrences that might be amenable to curative surgery. Although it is believed that most of recurrence detection would be made before symptoms occur, some researches dispute this conjecture. Over forty percent of the recurrences after initial curative treatment for colon cancer were found during non-scheduled interval visits, mainly based on symptoms [31].

Hung *et al*. reported that in patients with low preoperative serum CEA level, suspicion of recurrence was based on positive physical signs and symptoms in 36.7% of patients [32].

In our study in two symptomatic patients (2/12, 16.6%) with normal blood CEA levels, recurrence was detected with PET/CT. Additionally, PET/CT helped in detection of 4 symptomatic patients with elevated blood CEA (4/5, 80%). The retrospective analysis of the previous CT examinations showed that PET/CT helped in detection of true occult metastases in three of four patients. There was only one symptomatic patient with elevated blood CEA with negative PET/CT. After one year of PET/CT, there were no signs of disease recurrence.

Conclusion

PET/CT modified clinical management in nearly half of the patients. Elevated CEA and the primary tumor stage were dominant features of the patients with recurrent disease. Symptomatic patients with negative diagnostic CT could benefit of PET/CT but selection criteria should be reevaluated. Negative predictive value of PET/CT in such clinical scenario is high enough to reassure clinicians and reduce patient anxiety. Second reading of the negative CT exams prior to PET/CT examination could be beneficial.

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