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18F-FDG PET/CT IN DIFFERENTIATING EQUIVOCAL CT LESIONS INPATIENTS WITH COLORECTAL CANCER

Goran Spirov[1], Simon Beshliev[2], Niki Matveeva[3], Ana Ugrinska[4], Vasilco Spirov[5]
[1,2,4] University Institute of Positron Emission Tomography R. North Macedonia, Faculty of Medicine, Ss Cyril and Methodius University in Skopje, R.North Macedonia
[3] Institute of Anatomy, Faculty of Medicine, Ss Cyril and Methodius University in Skopje, R.North Macedonia
[5] University Institute of Radiology-Skopje, Faculty of Medicine, Ss Cyril and Methodius University in Skopje, R.North Macedonia

Abstract

Imaging is vital in the follow-up strategy of patients with colorectal cancer. Computed tomography is widely accepted as a method of choice, but further work up is required when equivocal findings are present. The objective of this study was to investigate the potential of positron emission tomography (PET)/computed tomography (CT) as a problem-solving tool of dubious CT findings in patients with colorectal cancer (CRC) in the follow-up period. This was a retrospective review of thirty-two patients referred for 18F-fluorodeoxyglucose (FDG) PET/CT imaging due to suspicion of recurrent disease solely based on CT exam. The diagnosis of a malignancy lesion was based on intensity of the lesion, location, shape, size, as well as CT findings. There was a follow-up period of at least six months after the PET/CT examination.

The most common site of detected lesions that could not be characterized by CT were the lungs (13/32; 40.5%), followed by liver (8/32, 25%) and lymph nodes (5/32, 15.6%). Additionally, lesions were reported at adrenal gland, spleen, peritoneum, ovary and at surgical site. In almost half of the patients (15/32; 46.8%) lesions were detected by PET/CT and characterized as disease recurrence. Metastases at additional site were detected in five patients (6/15, 40%). In the follow-up period recurrent disease was detected in two patients (2/32, 6.2%) with negative PET/CT findings. Only one person had a false positive finding. The overall positive and negative predictive value of FDG-PET/CT was 93.3% and 84.6% respectively.

PET/CT offers a high overall positive and negative predictive value in distinguishing CRC metastasis. Furthermore, it exceeds CT performance in detecting extrahepatic recurrent disease.

Keywords: PET scan, CT scan, imaging, colorectal cancer.

Introduction

Colorectal cancer (CRC) is the fourth most commonly diagnosed and the third most deadly cancer in the world with nearly 2 million new cases and about 1 million deaths that had been expected in 2018[1]. Screening programs and novel treatment procedures gave hope in tackling the problem that resulted in decreasing morbidity and mortality in developed countries. On the other hand, developing countries still report rising incidence and death of CRC. Furthermore, new trend of rising incidence has been recognized in young adults especially in developed countries. Much is needed to be done for successfully tackling the problem.

Imaging is the cornerstone of modern medical practice. Various imaging modalities are available nowadays, starting with radiography, through ultrasound, computed tomography, magnet resonance imaging to molecular imaging. Pros and cons of each of them in various scenarios define their clinical appropriateness. The way of treating oncology patients is largely based on the stage that is the extent of the cancer already determined by pathology and imaging. In this respect colorectal cancer is no exception. Computed tomography (CT) is widely used imaging tool in determining initial disease extend as well as in follow up [2]. Recent studies report contradictory findings regarding follow up protocols of CRC patients [3], nevertheless routine CT imaging, except in stage one, is widely

accepted and recommended by relevant societies [4,5]. At the moment other imaging modalities like magnetic resonance imaging (MRI) and positron emission (PET)/computed tomography (CT) are part of the imaging process but labeled as complementary imaging techniques reserved for problem solving. So far, MRI have been proved to be superior in liver imaging using liver-specific contrast agent as well as in detecting local recurrence in rectal cancer [6,7]. Furthermore, PET/CT demonstrated superiority in detecting extrahepatic disease [8]. Both techniques are valuable tools in the follow up imaging though high cost and limited availability make them less accessible. Defining clinical scenarios in which CRC patients could benefit of such examinations is vital.

The objective of this research was to investigate the potential of PET/CT as a problem-solving tool of dubious CT findings in patients with CRC at the follow up period.

Material and methods

1.1. Study design and patient population

A retrospective review of 224 patients referred for 18F- fluorodeoxyglucose (FDG) PET/CT imaging to the University institute of positron emission tomography in Skopje, between July 2018 and June 2021, for surveillance of CRC was performed.

Patients were considered adequate to enroll the study if they met the following requirements: 1. curable resection for treatment of colorectal cancer, 2. no distant metastasis, 3. pretreatment staging included CT abdomen and pelvis with intravenous contrast and chest CT or radiography, 4. suspicion of recurrent disease solely based on CT exam, 5. PET/CT performed no later than three months after the CT examination.

Exclusion criteria for participation in the study were synchronous or metachronous malignant disease. The follow-up time was at least four months.

1.2. 18F-FDG PET/CT imaging

All patients intended to undergo PET/CT imaging were instructed to fast for at least 4-6 hours before administering the 18F-FDG injection along with oral hydration. Furthermore, they were advised to avoid any unnecessary physical activity two days prior to the examination.

Free-breathing skull base-to-thigh examinations were performed on a hybrid PET/CT scanner (Biograph 40mCT, Siemens, Germany) sixty minutes following 18F-FDG injection (200–400MBq). Blood glucose levels were recorded prior to administering FDG. Elevated serum glucose (>11.1 mmol/l) would have postponed the examination.

Low dose CT scanning was done using automatic exposure control system (Care Dose 4D) with the following parameters: ~35 mA, 120 kV, 5 mm collimation, 0.8 s gantry rotation speed and table feed of 18 mm per rotation, a pitch of 1.5:1, and a detector row configuration of 40×0.625 mm. The raw CT data were reconstructed into three planes with a 5-mm section thickness.

Data acquisition in PET was done in 2D with 2 minutes 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 three 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.

1.3. Imaging evaluation

Nuclear medicine physician and radiologist interpreted each PET/CT study with consensus using Syngo multimodality workplace (Siemens AG). Full medical record of all patients was available prior to the examination. Initially, PET images were evaluated visually and semi-quantitatively. Any significant uptake of FDG was recorded using maximum standardized uptake values (SUVmax). Afterward, comparison was done with the CT images to determine any lesion or morphological/structural alteration. All measurements were done in axial planes.

The diagnosis of a malignancy lesion was based on intensity of the lesion, location, the shape, size, 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).

1.4. Follow up

There was a follow up period of at least six months after the PET/CT examination. All of the patients with negative PET/CT results had a follow up with cross sectional imaging within six months. Further investigation (imaging/biopsy) to characterize the lesions was done in patients with equivocal findings. Patients with positive findings were referred for treatment. Pathology report or follow up imaging after therapy was used to confirm the findings.

Results

Table 1 shows the baseline characteristics of the included patients. Thirty two (mean age 62 years (range 32-79), 20 men and 12 women) met the inclusion criteria. The most common tumor site was left colon in 13 patients (40.5%), followed by rectum in 11 (34,5%), and right colon in 8 (25%) patients.

Based on the imaging prior to surgery and histological analyses of the resected specimens a more than half of the patients were classified in stage III (19/32, 59,4%), 11 patients in stage II (34,4%) and only two patients (6,2%) in stage I. Almost four-fifths of the patients (81,2%) were treated with some form of chemotherapy. Two patients in stage I as well as three patients in stage II (2 patients in IIA, and 1 patient in IIB stage) did not receive systemic treatment due to oncologist recommendation. Three patients had neoadjuvant and one patient adjuvant radiotherapy (4/32, 12.5%).

PET/CT examination was done on average in 16 months (range of 2-91 months) of surgery. Five patients (15.6%) had their PET/CT examination within the first six months of surgery, 21 patients (65,6%) between 6 and 18 months and 6 patients (18.8%) later than a year and a half.

Table 1. Patient characteristics.

	N = 32
Age [years; median (range)]	62 years (range 32-79)
Gender	
Male	20 (62,5%)
Female	12 (37,5%)
Primary tumor	
Right colon	8 (25%)
Left colon	13 (40.5%)
Rectum	11 (34,5%)
Stage	
I	2 (6,2%)
IIA	6 (18.6%)
IIB	3 (9,4%)
IIC	2 (6,3%)
IIIA	2 (6,3%)
IIIB	14 (43,7%)
IIIC	3 (9,4%)
Treatment	
Surgery	32 (100%)
Chemotherapy	26 (81.3%)
Radiotherapy	4 (12,5%)

Table 2 shows the lesion sites identified by PET/CT and compared to CT findings. The most common site of detected lesions that could not be characterized by CT was lung (13/35; 37,1%), followed by liver (8/35, 22,9%) and lymph nodes (5/35, 14,3%). Additionally, lesions were reported at adrenal gland, spleen, peritoneum, ovary and at surgical site. Single site lesions were present in most of the patients (29/32, 90,6%).

Table 2. Total CT equivocal lesion sites compared to PET/CT findings of disease recurrence.

Lesion site	**CT**	**PET/CT**	**Corresponding**	**Newly detected by PET/CT**
Lung	*13 (37.1%)*	*4 (19,0%)*	*4 (33.3%)*	*/*
Liver	*8 (22.9%)*	*6 (28.6%)*	*5 (41.7%)*	*1 (11%)*
Lymph nodes	*5 (14.3%)*	*6 (28.6%)*	*2 (16.7%)*	*4 (44%)*
Spleen	*2 (5.7%)*	*/*	*/*	*/*
Ovary	*1 (2.8%)*	*/*	*/*	*/*
Surgical site	*1 (2.8%)*	*2 (9.5%)*	*1 (8.3%)*	*1 (11%)*
Peritoneum	*2 (5.7%)*	*2 (9.5%)*	*/*	*2 (22%)*
Adrenal	*3 (8.6%)*	*/*	*/*	*/*
Skeleton	*/*	*1 (4.8%)*	*/*	*1 (11%)*
	35 (100%)	21 (100%)	12 (100%)	9 (100%)

Table 3 shows the correlation of PET/CT to CT findings per patient. In almost half of the patients (15/32; 46,8%) lesions were detected by PET/CT and characterized as disease recurrence. Compared to the CT findings, in 11 patients there was a match at the location site (11/15, 73%). Metastasis at additional site were detected in five patients (6/15, 40%). Furthermore, in four patients (4/32; 12,5%) the nature of detected lesions could not be established by PET/CT and further work-up was required (Fig.1). In the follow up period recurrent disease was detected in two patients (2/32, 6,2%) with negative PET/CT findings. In the first case, the lesion was not detected by PET/CT although it was pinpointed by the previous CT exam. In the second case, detected metastasis was at a site different that it had been suggested by CT (Table 3). In one patient (1/32, 3,1%) reported mediastinal lymph node metastasis by PET/CT turn out to be sarcoidosis after biopsy (Table 3). Most of the liver lesions (5/8, 62,5%) were characterized as metastasis by PET/CT (Figure2, Figure 3). On the other hand, most of the lung lesions (9/13, 69,2%) were dismissed as benign. Greatest discrepancy of CT vs PET/CT findings was registered in lymph nodes. In two out of five patients PET/CT detected recurrent disease in lymph nodes. Additional lymph node metastases were detected in two patients who had no signs of lymph node involvement on the CT exam.

Table 3. Correlation of PET/CT to CT findings per patient.

	True positive	**True negative**	**False positive**	**False negative**	**Total**
Match	6	/	/	/	6 (18.7%)
Partial match	4	/	1		5 (15.6%)
No match	4	11	/	2	17 (53.2%)
Undefined					4 (12.5%)
	14 (43.7%)	11 (34.4%)	1(3.1%)	2 (6.3%)	32 (100%)

The overall positive and negative predictive value of FDG-PET/CT was 93,3% and 84,6% respectively.

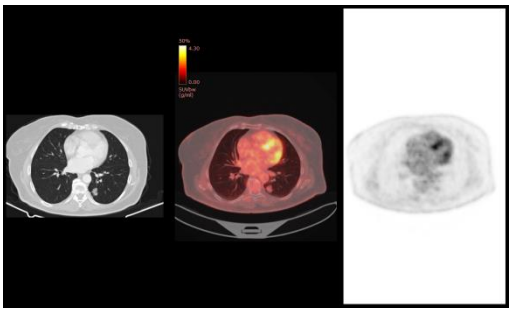

Fig. 1. 62 years old patient treated of left colon cancer, stage I. 2cm lung nodule is spotted on the first follow up CT. PET/CT showed low avid lung nodule, most likely benign. Follow up CT exams showed no signs of progression nor other malignant lesions were detected.

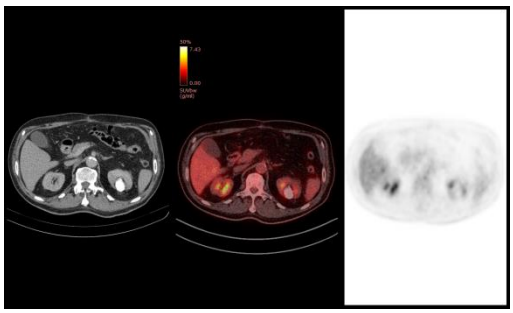

Fig. 2. 75 years old patient treated of rectal cancer, stage IIIA. Patient was referred to PET/CT due to suspected peritoneal lesions. PET/CT did not detect peritoneal metastasis but FDG avid liver lesion in segment 6 was identified.

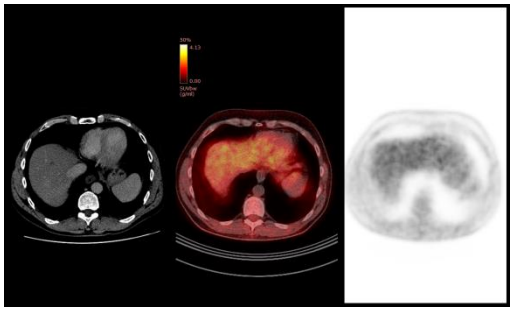

Fig. 3. 45 years old patient treated of rectal cancer, stage IIIB. Patient was referred to PET/CT due to sub centimetric liver lesion suspected of metastasis. PET/CT did not detect FDG avid lesion. Four months later liver MRI was performed, and metastasis was identified with signs of progression compared to previous CT exam.

Detailed information of most common lesion sites is presented in Table 4.

Table 4. PET/CT findings of most common lesion sites.

	True positive	**True negative**	**False positive**	**False negative**	**PPV**	**NPV**
Lung	4	25	0	0	100%	100%
Liver	6	25	0	1	100%	96,1%
Lymph nodes	5	26	1	0	83%	100%

Discussion

About 80% of colorectal cancer patients are initially diagnosed with non-metastasized disease [9]. Curative surgery with or without adjuvant chemotherapy is treatment of choice for most of them. Nevertheless, recurrent disease is expected in one-third of the patients, mostly depending on the initial stage of the disease. Most of the metachronous metastases are detected in the first three years after the treatment. After the fifth year, recurrence is unlikely [10]. Early detection of metastasized disease should lead to effective treatment and better clinical outcome. Based on the patterns, timing, and predictors, guidelines for the surveillance have been published by relevant societies and most of them recommended CT as an imaging tool for chest, abdomen and pelvis in regular intervals in the first few years after treatment [4,5]. Despite its notable accuracy, occasionally further work up is necessary to differentiate detected lesions. 18F-FDG PET/CT is a very sensitive whole-body imaging technique providing unique molecular and metabolic information that proofed to be useful for patient assessment and management in oncology settings.

In our study quarter of the undifferentiated lesion were located in the liver. Almost two thirds of them were labeled as metastasis. Focally increased FDG uptake at previously detected liver lesion with contrast enhanced CT was sufficient enough to reach the conclusion. Tan et al. reported that in more than 90% of the patients with focal liver lesions showing increased FDG uptake were malignant. Additionally, in 5% of the patients, lesions remained indeterminate despite biopsy. Only 8 lesions out of 217 were histologically proven to be benign, half of them were abscesses [11]. According to Patel et al. there was no significant difference between the five studies regarding sensitivity (78% to 100%) and specificity (75% to 100%) on detection of hepatic metastasis [12], a conclusion that do not correspond to our findings. Results presented in this research are more consistent to findings of Deleau et al. that states greater accuracy of PET/CT over CT in detection of liver metastasis [13]. In only one patient, a lesion under one centimeter was not detected by PET/CT although it was pinpointed by contrast enhanced CT. Wiering et al. reported that CT and FDG-PET are inadequate for detection of small liver lesions [14]. Liver MRI using hepato specific contrast agents is considered as a superior method for detecting metastasis especially for lesions under one centimeter [15-17].

Greatest discrepancy of CT vs PET/CT findings in detecting disease presence was registered in lymph nodes. In two out of five patients PET/CT suggested recurrent disease in lymph nodes that were considered atypical. Furthermore, PET/CT findings indicate malignancy in lymph nodes in other two patients. These lymph nodes were considered normal-appearing using the widely used criteria: lymph node size, internal heterogeneity and irregular outer border. False positive PET/CT finding was verified in only one patient, sarcoidosis was diagnosed after biopsy of mediastinal lymph nodes. To date, there are no validated CT criteria for the assessment of lymph node metastases in colon cancer [18]. Furthermore, detecting metastasis in normal sized lymph node by CT is less likely. According to Kitajima et al. PET detected more nodal involvement than CT in lymph nodes smaller than one centimeter [19]. Deleau et at. reported significantly greater sensitivity (100% vs 35%) but less specificity (40% vs 60%) in detecting lymph node metastases compared to CT. Major setback of PET/CT in detecting lymph node malignancy is infection and inflammation [20].

Chest CT is highly recommended for initial staging in colorectal cancer patients [2,4,5], still chest X ray (CXR) is a modality of choice in staging work up. Higher detection rate of lung lesions with CT is not a guarantee for patients' benefit. Only one quarter of unspecified pulmonary lesions detected by CT are demonstrated to be metastases and in up to 40% definitive diagnosis cannot be reached [21].

Furthermore, Kim et al. reported that preoperative staging using chest CT is not beneficial for CRC patients without liver and lymph node metastasis on abdominal and pelvic CT who had a negative initial CXR finding [22]. Nonetheless, characterizing newly detected pulmonary nodes in the follow up period without initial CT to compare could be challenging. As anticipated, pulmonary nodules were most frequent lesions that could not be characterized by CT (13/32; 40,5%), despite lung is the second most common location of metastasis in CRC. Pulmonary nodules of ten millimeters or larger were addressed in this study because previous research imply that FDG PET is not suitable for subcentimeter nodules [23,24]. Our results show that two thirds of the pulmonary nodules (9/13, 69,2%) were benign.

Additionally, lesions (8/32, 25%) were reported at adrenal gland, spleen, peritoneum, ovary and at surgical site. Most of them were identified as benign except for one lesion at the surgical site the was characterized as local recurrence. Most patients with rectal cancer developed a fibrotic mass in the presacral space following surgery and/or radiotherapy that could lead to false positive finding on CT. Londono et al. reported that presacral false positive findings were correctly evaluated as negative by PET [23]. Metser et al. reported that PET is more sensitive than CT in the identification of tumor recurrence in the presacral space in patients who have undergone abdominoperineal resection [25]. In meta-analysis by Yu et al., PET/CT in detecting local recurrence of CRC had pooled sensitivity and specificity of 0.94 [26].

Furthermore, additional metastasis in five patients (5/32, 15%) were detected by PET/CT that have not been identified previously. Greater detection rate of CRC metastases by PET/CT have been reported previously, especially for extrahepatic sites. Moore's retrospective study of 342 patients show that PET/CT helped identify metastatic disease in 10.8% of the patients usually in the liver, lymph nodes, peritoneum and lung [27]. Fehr et al. reported greater detection rate of CRC metastases by 12.2% by PET/CT compared to CT [28]. Maas et al. concluded that PET/CT has a greater accuracy over CT in detection extrahepatic metastasis [29].

Nevertheless, PET/CT did not help in determining the nature of the lesions in two patients (2/32, 6%) previously detected by CT. Also, new lesions detected by PET/CT that could not be characterized were present in other two patients. Overall, further work-up was required in four patients (4/32; 12%). Equivocal findings in PET/ contrast enhanced CT were reported in less than 10% of patients with elevated CEA by Vallam et al. [30].

In the follow up period recurrent disease was detected in two patients (2/32, 6%) with negative PET/CT. In the first case, the lesion was not detected by PET/CT although it was pinpointed by previous CT exam. In the second case, detected metastasis was at a site different that it had been suggested by CT. The negative predictive value (NPV) of PET/CT in our study was 84,6%. In the meta-analysis by Maas et al. [29], the reported NPV is as low as 44% and as high as 88% [31,32]. Negative predictive value of 100% was reported by Ince et al., in a study of 53 patients [33].

Conclusion:

PET/CT offers high overall positive and negative predictive value in distinguishing CRC metastasis. Furthermore, PET/CT exceeds CT performance in detecting extrahepatic recurrent disease. At certain clinical scenarios PET/CT performance could be limited predominantly as a result of low space resolution and non-tumor FDG uptake. Nevertheless, PET/CT is a method of choice for characterizing equivocal lesions detected on CT in CRC patients.

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