Role of positron emission tomography/computed tomography for the staging of primary colorectal cancers

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Objective
The aim of this paper was to evaluate the role of positron emission tomography (PET) combined with contrast-enhanced computed tomography (CECT) in staging patients with primary colorectal cancer (CRC).

Background
CRC is the second leading cause of cancer-related deaths and the fourth most common malignancy worldwide. Cross-sectional imaging studies such as CT and MRI have evolved as the best modalities for staging rectal cancer. PET combined with CT is widely used not only for preoperative staging, but also for assessing the outcomes of rectal carcinoma.

Patients and methods
This prospective study was carried out on 50 patients: 30 (60%) men and 20 (40%) women in the age range from 27 to 74 years, who were diagnosed or suspected to have cancer colon by other radiological imaging.

Results
Our results showed that PET-CT had equal sensitivity (95.4%) and specificity (82%), positive predictive value (PPV) (80.7%), negative predictive value (NPV) (95.8%), and accuracy (88%) for the detection of regional lymph node metastasis compared to CECT. But PET-CT and CECT had higher sensitivity and higher specificity, PPV, NPV, and accuracy more than PET for detection of metastatic lymph nodes and PET-CT had equal sensitivity (92.8%) and specificity (86.2%), PPV (72.2%), NPV (96.8%), and accuracy (88%) for detection of lung metastasis compared to PET. But PET-CT and PET had higher sensitivity and higher specificity, PPV, NPV, and accuracy more than CECT for detection of pulmonary deposits.

Conclusion
According to our results, fluorine-18 fluorodeoxyglucose PET/CT has contributed positively to the staging of primary CRC patients.

Keywords:
colorectal neoplasms, lymph node, magnetic resonance imaging, positron emission tomography/computed tomography, rectal neoplasms

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Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths and the fourth most common malignancy worldwide [1]. Accurate tumor staging is a prerequisite for therapy planning and for a successful therapy of patients suffering from CRC [2]. Cross-sectional imaging studies such as computed tomography (CT), MRI, and endorectal ultrasound have evolved as the best modalities for accurately staging rectal cancer [3]. The most useful tumor-related factors in the preoperative staging of rectal cancers include the depth of tumor penetration through the rectal wall, the presence or absence of metastasis to regional lymph nodes (LNs), the adjacent organ involvement, and the presence of distant metastases [4].

Positron emission tomography (PET)/CT plays an important role regarding lesion detection and characterization, when staging patients with malignancy especially those with CRC [5]. PET/CT is widely used not only for preoperative staging, but also for assessing the oncologic outcomes of rectal carcinoma [3].

Staging of colon cancer is performed surgically. The T stage is based on tumor depth, and the N stage is based on LN dissection. Although PET can assess regional lymph-node involvement, it has proved most effective for the M stage, especially for detecting metastatic disease of the liver. PET has been reported to have an impact on patient staging in up to 65% of cases, usually by upstaging the patient's disease [6].

PET/CT is costeffective when included in the evaluation of patients with CRC and results in substantial potential savings as a result of detecting nonresectable disease thereby avoiding unnecessary surgery [7]. The major role of PET/CT in CRC is in restaging. Indications for restaging of CRC are potential curative surgery for isolated metastatic disease, differentiation of scar from recurrent tumor, particularly in the presacral space, and evaluation of increased carcinoembryonic antigen level [8].

The most common sites of metastases include the liver, lung, and the brain. Resection of isolated metastases is associated with improve survival while multifocal metastatic lesions are associated with less favorable prognosis. Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) PET can be considered as a useful tool in preoperative staging by producing superior results compared with conventional diagnostic modalities, especially in excluding or detecting hepatic or extrahepatic metastatic disease [8].

PET/CT is more helpful than contrast-enhanced computed tomography (CECT) for detection of recurrent hepatic metastases after hepatectomy, extrahepatic metastases, and local recurrence at the site of initial colorectal surgery [9]. However, conventional imaging techniques have limited sensitivity for detecting recurrent disease in such patients. ^{18}F-FDG PET has been proved to be an effective whole-body imaging technique that detects metabolic changes preceding structural findings [8].

In our study, we prospectively studied the role of ^{18}F-FDG PET/CT in the staging of CRC in comparison to separate CECT and PET scans.

Patients and methods

This prospective study was carried out at the National Liver Institute, Menoufia University during the period between March 2016 and June 2018. The study included a total of 50 patients, 30 (60%) men and 20 (40%) women in the age range from 27 to 74 years, who were diagnosed after colonoscopy and biopsy or suspected to have cancer colon by other radiological imaging. The Local Ethics Committee approved the study protocol. Formal consents were obtained from the patients or their relatives.

The study excluded pregnant and lactating women, patients with renal impairment with a serum creatinine of more than 1.5 mg/dl, patients with uncontrolled diabetes or elevated blood sugar of more than 200 mg/dl and patients who received prior treatment of CRC chemotherapy or radiotherapy.

All patients were subjected to full history taking including drug history to exclude any contraindications to contrast media, detailed clinical history such as bleeding per rectum, chronic constipation and family history of familial polyposis, full clinical examination, complete blood picture, kidney function tests, random blood glucose, and pregnancy test of women in the childbearing period. Patients were instructed to have a high-protein, low-carbohydrate diet 24 h before the scan, complete fasting at least 6 h, minimal physical activity to decrease muscle uptake, and to wear warm clothes to avoid brown fat uptake. ^{18}F-FDG PET-CT scan was performed using Siemens (Biograph, Knoxville, USA) PET/CT scanner with a 128 MDCT tube. All data were acquired with a combined PET/CT. This dedicated system integrates a PET scanner with a multislice helical CT scanner and permits the acquisition of co-registered CT and PET images in one session.

Statistical analysis

The data collected were tabulated and analyzed by SPSS (the Statistical Package for Social Sciences, SPSS; SPSS Inc., Chicago, Illinois, USA) version 22.0 on an IBM compatible computer. Two types of statistics were done descriptive statistics, for example, percentage, mean and SD and analytic statistics, for example, χ^2 test was used to study the association between two qualitative variables. Sensitivity, specificity, positive and negative predictive value, and diagnostic accuracy were calculated. Level of significance was set at a P value of less than or equal to 0.05.

Results

The age of the patients included in this study ranged between 27 and 74 with a median age of 50.55, mean 56.08 and 10.19 SD. They were 30 (60%) men and 20 (40%) women. According to the pathology of the biopsy taken by colonoscopy, 44 patients were diagnosed as being of adenocarcinoma (42 cases were mucinous adenocarcinoma and two cases were signet-ring adenocarcinoma) and six patients were of non-Hodgkin's lymphoma. The site of lesion was involved in 16 (32%) patients at the ascending colon, rectum in 12 (24%) patients, sigmoid colon in 10 (20%) patients, rectosigmoid colon in six (12%) patients, and at descending colon in six (12%) patients. Regarding regional LN metastasis (N staging) by CT, 28 (56%) patients were positive for metastasis and 22 (44%) patients were negative, measured short axis of the positive LNs ranged between 1 and 8 cm with a mean ± SD of 2.4 ± 1.4, while by PET 26 (52%) patients were positive and 24 (48%) patients were negative.

Regarding liver metastasis it was considered positive for metastasis in 14 (28%) patients and negative in the remaining 36 (72%) patients by CT. While by PET it is considered positive for metastasis in 18 (36%) patients and negative in the remaining 32 (64%) patients, and by PET/CT 18 (36%) patients were positive for metastasis and 32 (64%) patients were negative and for lung metastasis 14 (28%) patients were considered to have lung metastasis with the size of nodules ranged between 8 and 25 mm with a mean ± SD of 15.5 ± 5.9 while the remaining 36 (72%) patients were considered negative by CT, while by PET 12 (24%) patients were considered to have lung metastasis while the remaining 38 (76%) patients were negative and by PET/CT 22 (44%) patients were considered to have lung metastasis while the remaining 28 (56%) patients were considered negative.

Accuracy of CT, PET, and PET/CT in relation to reference (histopathology) as regards regional LNs PET-CT had equal sensitivity (95.4%) and specificity (82%), positive predictive value (PPV) (80.7%), negative predictive value (NPV) (95.8%), and accuracy (88%) for detection of LN metastasis to CECT. But PET-CT and CECT had higher sensitivity and higher specificity, PPV, NPV, and accuracy of more than PET for detection of metastatic LNs. All of these results are shown in Table 1.

Accuracy of CT, PET, and PET/CT in relation to reference as regards liver metastasis PET-CT had equal sensitivity and specificity, PPV, NPV, and accuracy for detection of liver metastasis to PET. But PET-CT and PET had higher sensitivity, specificity, and accuracy more than CECT for detection of liver metastasis. All of these results are shown in Table 2.

TNM staging by CECT, PET, and PET-CT in comparison with that of reference. Stage IIA: there were 22 patients by reference. CECT detected 10 of them (45.5%) and caused upstaging of four (18.2%) patients to stage IIIB, six (27.3%) patients to stage IVA and two (9.1%) patients to stage IVB; FDG-PET detected 10 of them (45.5%) and caused upstaging of four (18.2%) patients to stage IIIB, four (18.2%) patients to stage IVA and four (18.2%) patients to stage IVB and PET/CT detected 12 of them (54.5%) and caused upstaging of four (18.2%) patients to stage IIIB, four (18.2%) patients to stage IVA, and two (9.1%) patients to stage IVB.

Stage IIIB: there were two patients by reference. No patients were detected by CECT but these two (100%)

Table 1 Accuracy of computed tomography, positron emission tomography, positron emission tomography/computed tomography vs reference for lymph node metastasis among colorectal cancer cases

	Reference regional LN [*n* (%)]		Total [*n* (%)]	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
	Yes	No						
CT regional LN								
Yes	21 (95.4)	5 (18.0)	26 (52.0)	95.4	82.0	80.7	95.8	88
No	1 (4.6)	23 (82.0)	24 (48.0)					
PET regional LN								
Yes	20 (90.9)	6 (21.4)	26 (52.0)	90.9	78.6	76.92	91.6	84
No	2 (9.1)	22 (78.6)	24 (48.0)					
PET/CT regional LN								
Yes	21 (95.4)	5 (18.0)	26 (52.0)	95.4	82.0	80.7	95.8	88
No	1 (4.6)	23 (82.0)	24 (48.0)					

LN, lymph node; NPV, negative predictive value; PET/CT, positron emission tomography/computed tomography; PPV, positive predictive value.

Table 2 Accuracy of computed tomography, positron emission tomography, positron emission tomography/computed tomography versus reference for liver metastasis among colorectal cancer cases

	Reference liver [*n* (%)]		Total [*n* (%)]	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
	Yes	No						
CT liver								
Yes	11 (91.6)	2 (5.5)	13 (28.0)	91.6	94.5	84.61	97.29	94
No	1 (8.4)	36 (94.5)	37 (72.0)					
PET liver								
Yes	12 (100)	0 (0.0)	12 (24.0)	100	100	100	100	100
No	0 (0.0)	38 (100.0)	38 (76.0)					
PET/CT liver								
Yes	12 (100)	0 (0.0)	12 (24.0)	100	100	100	100	100
No	0 (0.0)	38 (100.0)	38 (76.0)					

NPV, negative predictive value; PET/CT, positron emission tomography/computed tomography; PPV, positive predictive value.

patients were upstaged to stage IVA, FDG-PET, and PET/CT detected all patients (100%) as stage IIIB.

Stage IVA: there were 12 patients by reference. CECT detected six of them (50.0%) and caused upstaging of six (50.0%) patients to stage IVB, FDG-PET detected eight of them (66.7%) and caused upstaging of two (16.7%) patients to stage IVB and downstaging of two (16.7%) patients to stage IIA and PET/CT detected eight of them (66.7%) and caused upstaging of four (33.3%) patients to stage IVB (Figs. 1 and 2).

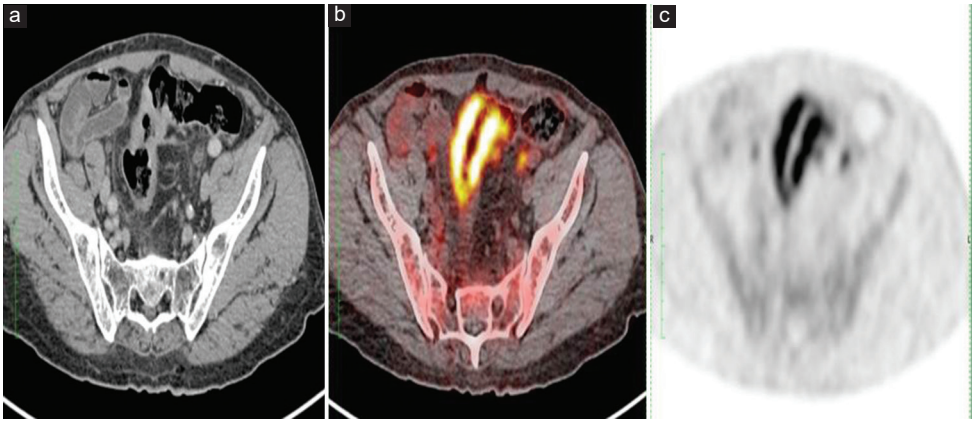
Stage IVB: there were 14 patients by reference. CECT detected 12 of them (85.7%) and caused downstaging of two (14.3%) patients to stage IVA, FDG-PET detected 12 of them (85.7%) and caused downstaging of two (14.3%) patients to stage IVA and PET/CT detected all 14 (100%) patients as stage IVB. All these data are shown in Table 3.

Discussion

The age of the patients included in this study ranged between 27 and 74 years with a median age of 50.55, mean 56.08 and 10.19SD. They were 30 (60%) men and 20 (40%) women. According to the pathology of the biopsy taken by colonoscopy, 44 patients were diagnosed as being of adenocarcinoma and six patients were of non-Hodgkin's lymphoma.

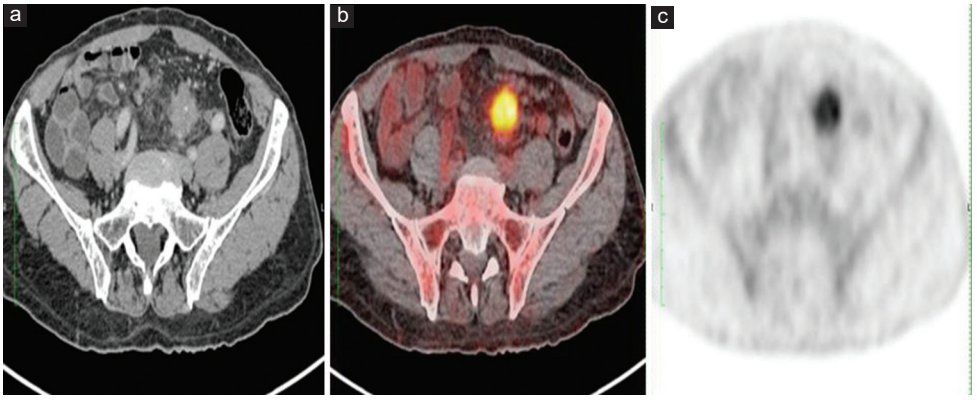
The Golfam *et al.* [10] study indicated that the rate of male patients has been more than female patients (male-to-female rate = 1.8:1). The mean age of patients was 53 years with a range of 15–87 years. In

Figure 1



A 52-year-old male patient presented with bloody diarrhea; axial CT image (a) shows mural thickening involving sigmoid colon reaching the rectosigmoid junction, it measures 20 mm in thickness, 7 cm in length. There is stranding of adjacent fat. CT stage: T3 N2a M0. Fused PET/CT (b) and PET image (c) show FDG avid lesion (SUV ma × 25.3) involving sigmoid colon reaching the rectosigmoid junction and pericolic tissue. PET/CT stag: T4 N2b M0. On histopathology, the tumor was perforating the visceral peritoneum with multiple metastatic lymph nodes (T4a N2b M0). FDG, fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography.

Figure 2



A 52-year-old man with colorectal cancer. Axial CT image (a) shows an abnormally enhancing iliac lymph node on contrast-enhanced CT. Suggestive lymph node metastasis: N2a stage. Fused PET/CT (b) shows increased uptake on FDG-PET correlates with multiple enlarged lymph nodes seen on CT and PET and is consistent with a malignant deposit. And PET image (c) shows multiple avid radiotracer uptake on the left side of the pelvis on FDG-PET. (b) and (c) show sigmoid and rectosigmoid carcinoma spreading to the internal iliac chain lymph nodes suggestive of lymph node metastasis: N2b stage. FDG, fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography.

Table 3 TNM staging of reference in comparison with that of contrast-enhanced computed tomography, positron emission tomography, or positron emission tomography/computed tomography among colorectal cancer cases

	Reference stage [*n* (%)]				Total [*n* (%)]	χ^2	*P*
	IIA (*n*=22)	IIIB (*n*=2)	IVA (*n*=12)	IVB (*n*=14)			
CT stage							
IIA	10 (45.5)	0 (0.0)	0 (0.0)	0 (0.0)	10 (20.0)		
IIIB	4 (18.2)	0 (0.0)	0 (0.0)	0 (0.0)	4 (8.0)		
IVA	6 (27.3)	2 (100.0)	6 (50.0)	2 (14.3)	16 (32.0)	24.2	<0.001
IVB	2 (9.1)	0 (0.0)	6 (50.0)	12 (85.7)	20 (40.0)		
PET stage							
IIA	10 (45.5)	0 (0.0)	2 (16.7)	0 (0.0)	12 (24.0)		
IIIB	4 (18.2)	2 (100.0)	0 (0.0)	0 (0.0)	6 (12.0)		
IVA	4 (18.2)	0 (0.0)	8 (66.7)	2 (14.3)	14 (28.0)	24.6	<0.001
IVB	4 (18.2)	0 (0.0)	2 (16.7)	12 (85.7)	18 (36.0)		
PET/CT stage							
IIA	12 (54.5)	0 (0.0)	0 (0.0)	0 (0.0)	12 (24.0)		
IIIB	4 (18.2)	2 (100.0)	0 (0.0)	0 (0.0)	6 (12.0)	18.6	<0.001
IVA	4 (18.2)	0 (0.0)	8 (66.7)	0 (0.0)	12 (24.0)		
IVB	2 (9.1)	0 (0.0)	4 (33.3)	14 (100.0)	20 (40.0)		

PET/CT, positron emission tomography/computed tomography.

addition, the most common sites for tumor were rectum and thereafter sigmoid. In Molanae's study regarding the tumor type, 90% were of adenocarcinoma, 7% were of lymphoma, and 3% were of carcinoid tumors [10].

In CRC, accurate assessment of the T stage and tumor size may aid in determining the correct way to access the lesion (local endoscopic excision, laparotomy, laparoscopy, or transanally) or the modality of surgery (radical or limited resection, palliative derivative surgery) [11].

Regarding regional LN metastasis (N staging): our study showed that PET-CT had equal sensitivity (95.4%), specificity (82%), and accuracy (88%) for detection of LN metastasis to CECT. But PET-CT and CECT had higher sensitivity and higher specificity, PPV, NPV, and accuracy more than PET for detection of metastatic LNs.

Kwak *et al.* [12] in a study of 473 patients with CRC found that in detecting proximal LNs, FDG-PET/CT had a sensitivity of 66%, a specificity of 60%, a PPV of 63%, an NPV of 62%, and an accuracy of 63%, whereas CT had a sensitivity of 87%, specificity of 29%, PPV of 57%, NPV of 68%, and accuracy of 59% ($P = 0.245$). FDG-PET/CT and CT also showed similar accuracy in detecting distal LNs (87 vs 88%, $P = 0.620$) and concluded that preoperative FDG-PET/CT and CT scanning had comparable accuracy in detecting LN metastases of CRC [12].

Ye *et al.* [13] in a meta-analysis including 2283 patients aimed to assess the diagnostic value of fluorine-18 fluorodeoxyglucose (^{18}F-FDG) PET-CT/PET in the preoperative evaluation of TNM staging in patients with primary cancers. A total of 28 studies including 2283 CRC patients were analyzed and the results have shown that the global measure of diagnostic accuracy of PET-CT and PET was 0.71 and 0.79, respectively. Though the pooled sensitivity of PET-CT (0.70) was superior to those of PET (0.36) and PET-CT/PET (0.62) the pooled specificity of PET was highest in the three groups. Interestingly, the overall diagnostic accuracy of PET was higher than that of PET-CT, maybe because PET was a specific examination in the preoperative N staging of primary CRC. In a word, the overall accuracy of PET-CT or PET for the detection of preoperative N staging of primary CRC is not ideal [13].

Regarding M staging and distant metastasis our data has shown that PET-CT had equal sensitivity and NPV to CECT while both PET-CT and CECT had higher sensitivity than PET. PET has higher specificity, PPV, and accuracy than PET-CT and CECT for detection of metastatic LNs.

Kwak *et al.* [12] found that FDG-PET/CT and CT showed similar accuracy in detecting distal LNs (87 vs 88%, $P = 0.620$). And concluded that preoperative FDG-PET/CT and CT scanning had comparable accuracy in detecting LN metastases of CRC [12].

For liver metastasis, this study showed that PET-CT had equal sensitivity and specificity, PPV, NPV, and accuracy for detection of liver metastasis to PET. But PET-CT and PET had higher sensitivity, specificity, and accuracy more than that of CECT for detection of liver metastasis.

FDG PET is highly sensitive for the detection of liver metastases. A meta-analysis demonstrated the sensitivities of CT, MR, and FDG PET for detecting

hepatic metastases from CRC to be 83.6, 88.2, and 94.1%, respectively [14].

Ali and Abd Elkhalek [15] concluded that PET/CT improved our ability to detect and characterize metastatic liver deposits, for proper staging which significantly affect further management planning [15].

Regarding pulmonary deposits our data has shown that PET-CT had equal sensitivity and specificity, PPV, NPV, and accuracy for detection of lung metastasis to PET. But PET-CT and PET had higher sensitivity and higher specificity, PPV, NPV, and accuracy more than that of CECT for detection of pulmonary deposits. The value of PET compared with CT has been studied in the preoperative staging of patients with CRC. Furukawa *et al.* [16] looked at PET versus CT in the staging of 44 CRC patients. For pulmonary metastases, CT detected metastases for three patients, whereas one was missed on PET. This made no difference to the overall patient treatment. For overall staging, the authors concluded that PET was not superior to CT in routine CRC staging. Sensitivity and specificity of PET-CT for the detection of malignant solitary pulmonary nodules are 96 and 83%, respectively [17].

This study showed that PET-CT and PET were of higher specificity than CECT, while PET-CT was equal to CECT and PET as regards sensitivity, PPV, NPV, and accuracy for detection of BM metastasis. Also, CECT, PET, and PET-CT had equal sensitivity for detection of another metastasis. Both CECT and PET-CT were equal in specificity but PET was higher in specificity.

Peritoneal implants due to colon cancer can be difficult to detect on CT alone particularly in cachectic patients without careful attention to technique and interpretation. FDG PET images are very useful for locating peritoneal implants of 7–8 mm or greater in size [17].

Regarding TNM staging of reference in comparison with that of CECT, PET, or PET-CT: our data in the present study showed that PET/CT was more accurate than CECT and FDG-PET for detecting patients with stage IIA and IVB, whereas FDG-PET and PET/CT were more accurate than CECT for detecting patients with stage IIIB and IVA.

Engelmann *et al.* [18] in a study of 66 patients with CRC, PET/CT for preoperative staging was performed in 66 prospectively included patients with primary CC. Diagnostic accuracy for PET/CT and CT was analyzed. The major finding in this study is that contrast-enhanced ^{18}F-FDG PET/CT is a valuable tool for primary staging of CC. PET/CT readers identified 97–98% of primary tumors, similar to previously reported detection rates. In this prospective head-to-head comparison, PET/CT-based M-staging showed robust reproducibility and better specificity and higher total correct classification rate than CT. Organ-specific M-staging accuracies confirm previous findings of overdiagnosis of suspicious lung lesions in CC patients by CT [18].

This prospective study added to the sparse evidence on contrast-enhanced FDG PET/CT for primary staging of unselected CC patients. It suggests PET/CT as a robust tool in all aspects of CC staging. Especially in the detection of distant metastases and T4 disease, PET/CT shows advantages of overstaging with CT alone. The follow-up part of our study has shown that optimized preoperative staging does not eliminate the need for intensive postoperative surveillance [18].

Ozis *et al.* [19] conducted a study of 97 patients diagnosed with primary rectal adenocarcinoma. Preoperative staging was performed by evaluating contrast-enhanced thoracic, abdominal, and pelvic CT. After staging by conventional methods, all patients underwent an ^{18}F-FDG PET/CT [19].

Regarding primary rectal cancer studies, it has been reported that ^{18}F-FDG PET imaging leads to changes in cancer stage in one-third of patients [19].

According to the results, ^{18}F-FDG PET/CT has contributed positively to the staging of primary rectal cancer patients and led to changes in the treatment strategy of 14.4% of the patients. It seems to be complementary to CECT in patients with suspected findings [19].

Ye *et al.* [13] in a meta-analysis including 2283 patients aimed to assess the diagnostic value of ^{18}F-FDG PET-CT/PET in the preoperative evaluation of TNM staging in patients with primary cancers. A total of 28 studies including 2283 CRC patients were analyzed. The meta-analysis concluded that ^{18}F-FDG PET-CT/PET had good performance in the preoperative tumor detecting rate, T staging, and M staging in patients with primary CRC when compared with CT, which might alter the therapeutic strategy. However, the diagnostic value of ^{18}F-FDG PETCT/PET in preoperative N staging in CRC patients was not ideal, which could be used combining with other conventional imaging in pretherapeutic CRC patients with suspected LN involvement [13].

Conclusion

According to our results, ^{18}F-FDG PET/CT has contributed positively to the staging of primary CRC patients. It seems to be complementary to CECT in patients with suspected findings. Thus, we recommend ^{18}F-FDG PET/CT as one of the methods to be consulted in the staging of patients with primary rectal cancer. More studies are required on a large number of patients who might benefit from PET/CT during initial staging.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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