RESEARCH

Can PET/CT detect recurrence in post-operative colorectal carcinoma patients with elevated CEA level?

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Abstract

Background: PET is considered to be the most sensitive and specific modality for the detection of recurrent colorectal cancer. This study is to assess the role of F18-FDG PET/CT in post-operative assessment in a patient with colorectal cancer with elevated CEA level to rule out local recurrence and/or metastasis and hence guiding the clinician to the proper management strategy.

Results: This study was performed on 45 patients who underwent surgical resection of the colon and/or rectal cancer; they were referred for PET/CT assessment at least 3 months after surgical resection. F18-FDG PET/CT sensitivity and specificity in detecting the recurrence and/or metastasis were 96.9 % and 83.3%, respectively. The positive predictive value was 94.2% while the negative predictive value was 90%.

Conclusion: For post-operative detection of loco-regional recurrence and metastasis in patients with colorectal cancer and elevated CEA level, 18F-FDG PET/CT can be considered as an efficient diagnostic imaging tool due to its high sensitivity and specificity which extensively affect further management.

Keywords: Colorectal cancer, 18F-FDG PET/CT, Recurrence, Carcinoembryonic antigen

Background

Colorectal cancer is one of the most common cancers worldwide and associated with a high mortality rate [1]. Radical resection is still the primary therapy for colorectal carcinoma, but local recurrence and/or metastasis rate in 2 years after operation is up to 30–40% [2]. Recurrence after initial surgery is responsible not only for significant morbidity and mortality but also for impairment for quality of life [3].

Early detection and accurate post-operative staging are very helpful for designing the subsequent therapeutic scheme, for example, secondary operation, radiotherapy, and/or chemotherapy [2].

For the early detection of recurrence, there are multiple imaging modalities that can be used including computed tomography (CT), magnetic resonance imaging (MRI), and

fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) [4]. Positron emission tomography (PET) is a non-invasive molecular imaging technique that can differentiate between cancer cells and non-cancerous cells by detecting differences in their metabolic activities [5].

Currently, PET is combined with CT to provide both metabolic and anatomic imaging data with a single device during a single diagnostic session. When PET and CT are combined, the sensitivity and specificity of detecting recurrent colorectal cancer range from 87% to 95% and 85 % to 95%, respectively [6]. PET/CT is recommended for determining management and prognosis if conventional imaging cannot confirm the presence of metastatic disease [7].

PET is the most sensitive and specific modality for the detection of recurrent colorectal cancer when used for patients with increasing carcinoembryonic antigen (CEA) levels that had done non-diagnostic CT imaging [8] as we

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will discuss in this study. More recently, there have been studies indicating that PET/CT may be useful in detecting recurrence in patients with normal CEA levels [9].

Methods

Our study was a retrospective analysis study carried out in the radiodiagnosis department at our university on 45 patients (17 were females and 28 were males) with known colorectal cancer undergone surgical resection (at least 3 months after surgical resection) in the period from June 2018 to June 2019. An informed consent was obtained from all patients.

The patient's age ranged from 34 to 81 years with the median age 58.7 years. The indication of the examination varied from elevated tumor markers (CEA), assessment of treatment response, routine follow-up, abnormality in other imaging modalities, or abnormal endoscopic findings. Some patients were referred for more than one cause.

Inclusion criteria:

- Patients with pathologically proven colorectal carcinoma and underwent radical resection
- No age or sex predilection

Exclusion criteria:

- Patients with blood glucose level > 390 mg/dl at the time of the study
- Patients with a history of previous hypersensitivity reaction to contrast material
- Bad general condition
- Patients with renal impairment (elevated serum creatinine > 2 mg/dl or decreased glomerular filtration rate < 30 mg/dl)

Most patients followed a post-operative follow-up program including clinical and radiological follow-up. The measurement of serial carcinoembryonic antigen (CEA) was integrated in the post-operative monitoring. Recurrence was suspected on the basis of elevated levels of CEA.

PET/CT acquisition and processing

Combined PET/CT scan was performed using a hybrid PET/CT system (Ingenuity, TF PET/CT/Philips, the Netherlands). The integrated CT system is a 64 multi-slice scanner. The acquisition of co-registered CT and PET images was performed in one session. Adequate patient preparation rules were strictly followed. Patients were instructed to fast except for glucose-free hydration for 4–6 h before injection of 18F-FDG. The scan was performed 40–60 min after IV injection of 3.7 MBq/kg (maximum dose 370 MBq) equivalent to 0.1 mCi/kg (maximum dose = 10 mCi) of 18F-FDG. The patients were examined in supine position. A whole-body examination was performed starting from the skull base to mid thighs. A PET emission scan was performed over several bed positions (5–7), each with an axial field of view of approximately 15 cm per bed position with an in-plane spatial resolution of 4 mm covering the same field of view as with CT. The acquisition time of emission data was 2 min per bed position in the time range that was between 13 and 17 min.

A fully diagnostic CT scan was performed using the following parameters: 350 mA, 120 kV, 0.5 s tube rotation time, slice thickness 5 mm, 8-mm table feed, and 3 mm incremental reconstruction. A IV contrast administration (80–120 ml) of a low-osmolarity iodinated contrast agent and negative oral contrast agent (water) for bowel was used.

All PET, CT, and PET/CT images were reconstructed and viewed on a Philips workstation, which provided multi-planar reformatted PET, CT, and fused PET/CT images with linked cursors as well as 3D maximum intensity projection (MIP).

Image analysis

A combined team, including one experienced nuclear medicine physician and one experienced radiologist (each has 10 years of experience), interpreted the PET, CT, and fused PET/CT images. The PET images were reviewed by the nuclear medicine physician. Fused PET/CT images were then analyzed separately by each of them, and each was blind to the other's findings.

Interpretation of the PET/CT findings

Visual assessment alone was adequate for interpreting PET findings as positive or negative. According to the IHP definitions, residual masses of 2 cm or more in greatest transverse diameter (GTD) with 18F-FDG activity visually exceeding that of mediastinal blood pool structures are considered PET-positive, whereas residual masses 1.1 to 1.9 cm are considered PET-positive only if their activity exceeds surrounding background activity. A smaller residual mass or a normal-sized lymph node (e.g., < 1 × 1 cm) should be considered positive for the disease if its activity is higher than that of the surrounding background.

Hepatic or splenic lesions should be considered as positive if their uptake is higher than or equal to that of the liver or spleen and negative if their uptake is lower than that of the liver and spleen.

Lung nodules of 5 mm in patients should be considered as positive if the FDG uptake is greater than the mediastinal blood pool. Metastasis cannot be excluded in lung nodules less than half a centimeter.

If there was a clearly multifocal increase in the FDG uptake in the bone marrow, the patient was considered as PET-positive. The diffuse pattern of uptake of reactive bone marrow hyperplasia after chemotherapy can mimic or mask diffuse bone marrow involvement; therefore, appropriate history was critical. A delay of 3 to 4 weeks after completion of therapy permits the physiologic marrow activity to abate.

The existence of recurrent colorectal cancer was determined based on histopathological examination or follow-up. In the absence of a positive pathology, clinical follow-up was done for at least 12–18 months of observation either with PET/CT or conventional imaging modalities showing progression in measurable lesions by the RECIST criteria or by adequate response to therapy (some patients received radiotherapy and/or chemotherapy as well as target therapy).

Results

Recurrent colorectal cancer was suspected on the basis of an elevated level of CEA. The study included 45 patients. PET/CT was positive for recurrent colorectal cancer (either local recurrence or distant metastasis) in 34 patients (75.5%) and negative in 11 patients (24.5%).

Out of the 34 patients with positive PET/CT (Figs. 1, 2, 3, 4, 5 and 6), 32 were true-positive cases. Five patients had a recurrence of CRC confirmed by histopathological examination. Twenty-seven patients had recurrent CRC based on clinical and radiological follow-up associated with the measurement of CEA level, and 24 of them showed regression of the detected lesions and a decrease of CEA level after receiving appropriate treatment. Three patients showed progression in the size and activity of the detected lesions with persistent elevation of the CEA level. Serum CEA was elevated in 30 patients with positive PET/CT findings, and its level ranged between 0.6 ng/ml and 100 ng/ml.

Two cases showed hypermetabolic mesenteric lymphadenopathy in PET/CT pathologically proven to be negative for malignancy (false-positive cases). Out of the eleven patients with negative PET/CT findings, ten of them proved to be true-negative cases based on the serial measurement of CEA and clinical and radiological follow-up. One patient had negative initial PET/CT and normal CEA levels with abnormal FDG accumulation in follow-up PET/CT and elevation of the CEA level (false-negative).

The sensitivity, specificity, and positive and negative predictive values were estimated using a standard statistical formula for calculating the diagnostic
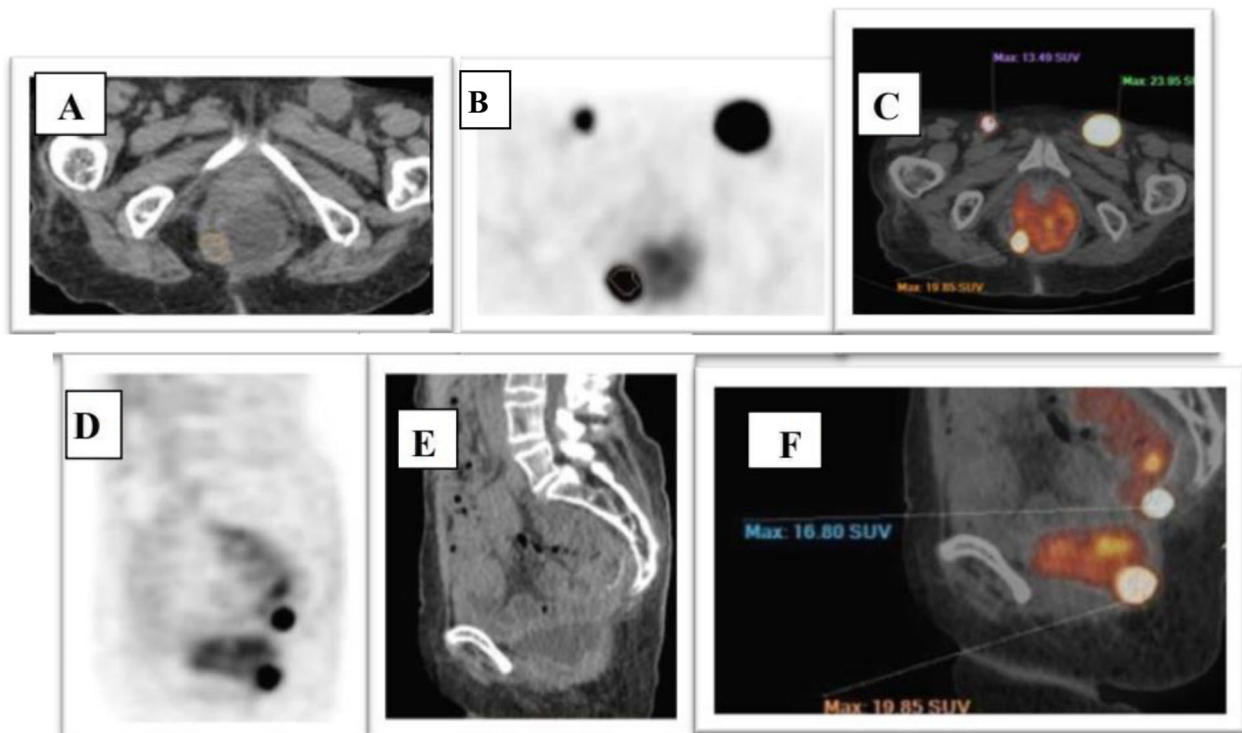
Fig. 1 A 66-year-old female patient with a history of rectal carcinoma received chemo-irradiation followed by surgical resection, presented by elevated CEA. Her PET/CT assessment shows **a** axial CT, **b** axial PET, **d** sagittal PET, **c** axial PET/CT, **f** sagittal PET/CT PET CT showing the following: heterogeneous hypermetabolic soft tissue nodule at the operative bed (along the right basal aspect of mesorectal fascia) measuring 19 × 10 mm achieving 19.8 SUV$_{max}$ (**a**, **b**, **f**); another smaller intensely avid one measuring 14 × 10 mm is seen opposite the tip of coccyx achieving 16.8 SUV$_{max}$ (**f**); and bilateral enlarged hypermetabolic inguinal lymph nodes achieving 23 and 13 SUV$_{max}$ (**c**)

Table 1 Demonstrates the sensitivity, specificity, and positive and negative predictive values of 18F-FDG PET/CT in detecting recurrent colorectal cancer

Sensitivity	Specificity	Positive predictive value	Negative predictive value
96.9%	83.3%	94.2%	90%

efficacy of PET/CT in detecting recurrent colorectal cancer (Table 1).

Comparisons between CECT and PET/CT findings were done using crosstabs and kappa value as well as confidence interval 99% (Table 2).

Discussion

Highlighting on postoperative patients with colorectal carcinoma is to detect whether recurrence and metastasis exist or not, which can be detected by traditional imaging only when lesion sites present morphological changes. But it is difficult to distinguish early recurrence and metastasis from the inflammatory process and anatomic changes caused by operation and radiotherapy. A quarter of the recurrent colorectal carcinoma confines to the original operative site, and these patients can be cured by a second operation. The only way to reduce metastasis is early detection of recurrence. 18F-FDG PET shows metabolism changes that happen before morphological changes, which makes it detect recurrence earlier than conventional imaging [2].

In the current study, we evaluated 45 patients for the presence of recurrence and/metastasis. According to the recommendations of ASCO, carcinoembryonic antigen is considered the best marker for monitoring metastatic colorectal cancer, and its measurement can be useful in the detection of asymptomatic recurrences. After surgical resection, it was found that the tumor has recurred in almost 90% of patients who have elevated postoperative CEA levels [10]. In the current study, 30 patients had elevated serum CEA levels. The sensitivity, specificity, and positive and negative predictive values of FDG PET/CT in detecting CRC recurrence/metastasis in patients with elevated serum CEA as the following: 96.9%, 83.3%, 94.2%, and 90%. That was in accordance with Metser et al. [10] who reported that the sensitivity ranges from 79–100% and the specificity ranges from 50–100%. The results of the current study fall within this range, so recurrent CRC was detected by FDG PET/CT with high sensitivity and specificity (Figs. 2, 3, 4, 5, and 6).

Agarwal et al. [9] reported that FDG PET/CT is more sensitive than conventional imaging in the evaluation for recurrence of CRC patients with rising CEA levels. In the current study, we also concluded that PET/CT is useful in the detection of recurrence in patients with normal CEA values but with suspicious clinical symptoms or radiologic findings. In the current study, two patients had normal serum CEA levels with positive PET/CT findings.

The diagnosis of local recurrence and differentiating it from post-operative and/or radiotherapy changes constitute a diagnostic challenge for conventional imaging as these changes may appear on CT images for many years and be indistinguishable from tumor recurrence [11]. In the current study, the detection of local recurrence by PET/contrast-enhanced CT was higher compared with enhanced CT. Ten lesions were detected as local recurrence and/or operative bed findings by CECT while PET/CT detect 17 lesions. So, PET/CT revealed additional information by detecting occult malignant lesions which were not detected in CECT. These results agree with Kitajima et al. [4] and Chiewvit et al. [12] which showed that the sensitivity of detecting local recurrence by PET/contrast-enhanced CT was relatively high compared with enhanced CT (96.7 vs 80.0%). Also, the study done by the study of Kitajima et al. [11] demonstrated that FDG-PET/CT seems to be the method of choice in the evaluation of presacral fibrotic tissue in patients who have undergone rectal amputation [12]. In the current study, out of the 16 patients diagnosed with recurrence, PET/CT detected 4 patients with pararectal soft tissue masses and 3 patients with presacral soft tissue lesions.

Liver metastasis is very common in patients with colorectal cancer with an incidence of approximately 50–60% [11]. The presence of hepatic metastasis is the main determinant of survival and guides the therapeutic strategy, particularly in patients with colorectal carcinoma [13]. In the current study, 12 patients proved to have

Table 2 Demonstrates the number of lesions detected in CECT and PET/CT in different sites

	CT no. of lesions	PET/CT no. of lesions	Agreement	Kappa value	Confidence interval 99%
Local recurrence	10	17	(61.1%)	0.147	0.437–0.462
LN metastasis	38	58	(63.5%)	0.112	0.123–0.140
Hepatic deposits	50	65	(82.5%)	0.013	0.013–0.029
Peritoneal deposits	9	14	(76.5%)	0.469	0.048–0.059
Osseous deposits	6	13	(46.2%)	0.646	0.005–0.009
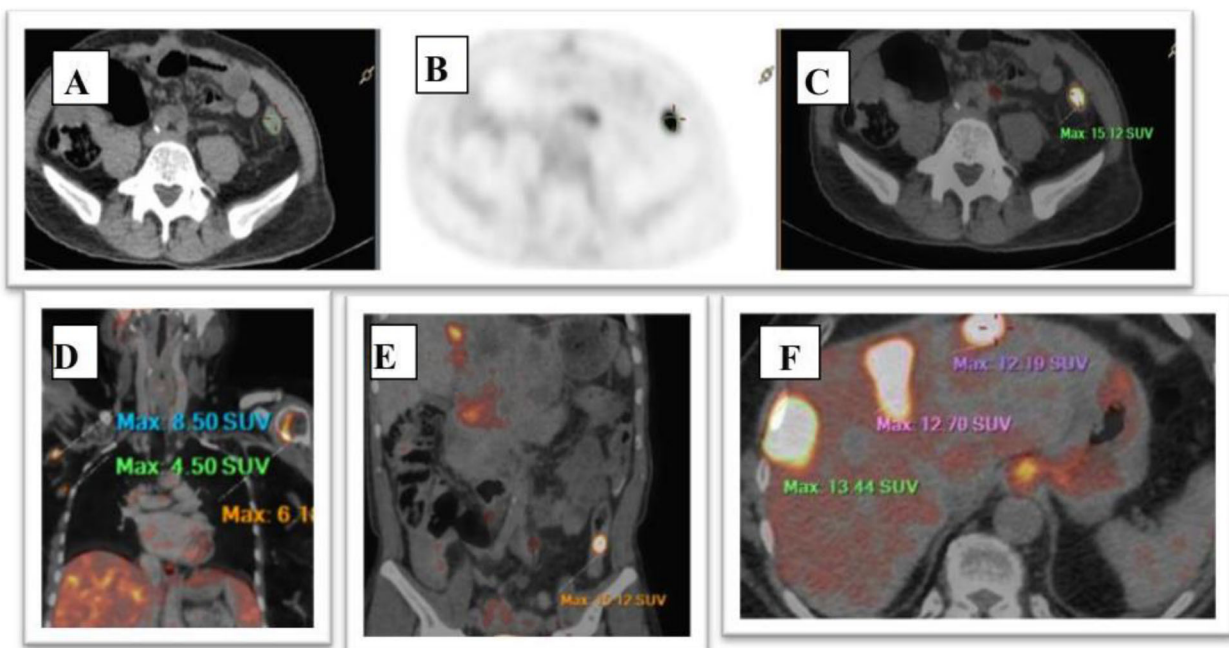
Fig. 2 A 75-year-old male patient with a history of colon cancer treated by surgical resection. He was referred for routine follow-up by PET/CT. **a** Axial CT, **b** axial PET, **c**, **e** axial PET/CT, **d**, e coronal PET/CT showing the following: focal mural increased FDG uptake is noted at the distal aspect of the descending colon, just below the surgical anastomotic site achieving 15.12 SUV$_{max}$ proved to be recurrent by endoscopy and histopathology (**a**, **b**, **c**); multiple hypermetabolic metastatic hepatic focal lesions achieving SUV$_{max}$ up to 13.44 (**f**); and multiple hypermetabolic focal osseous deposits, achieving SUV max of 8.50 (**d**)
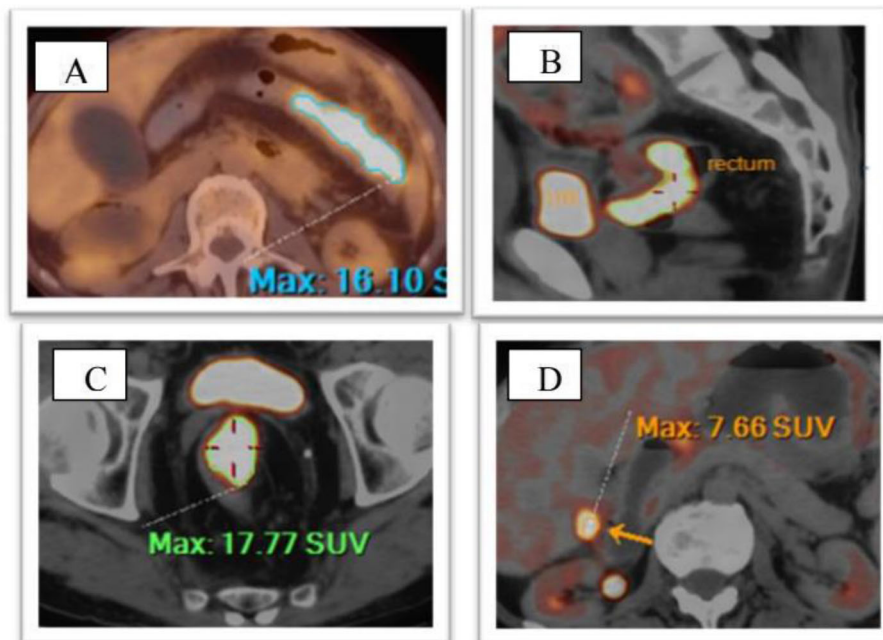
Fig. 3 A 61-year-old male patient with a history of colon cancer treated by surgical resection. He was referred for PET/CT assessment due to elevated CEA. **a**, **c**, **d** Axial PET/CT cuts through the abdomen and the pelvis, **b** sagittal PET/CT through the pelvis showing the following: irregular thickening of the wall of distal transverse colon with hypermetabolic activity reaching up to 16 SUV$_{max}$ proved to be malignant on endoscopy and biopsy (**a**); irregular mucosal mass at the rectum projecting into its lumen with hypermetabolic activity reaching up to 17.7 SUV$_{max}$ (**b**, **c**); and the liver showing a small hypermetabolic focal lesion measuring 1 cm and achieving 7.6 SUV$_{max}$ (**d**)
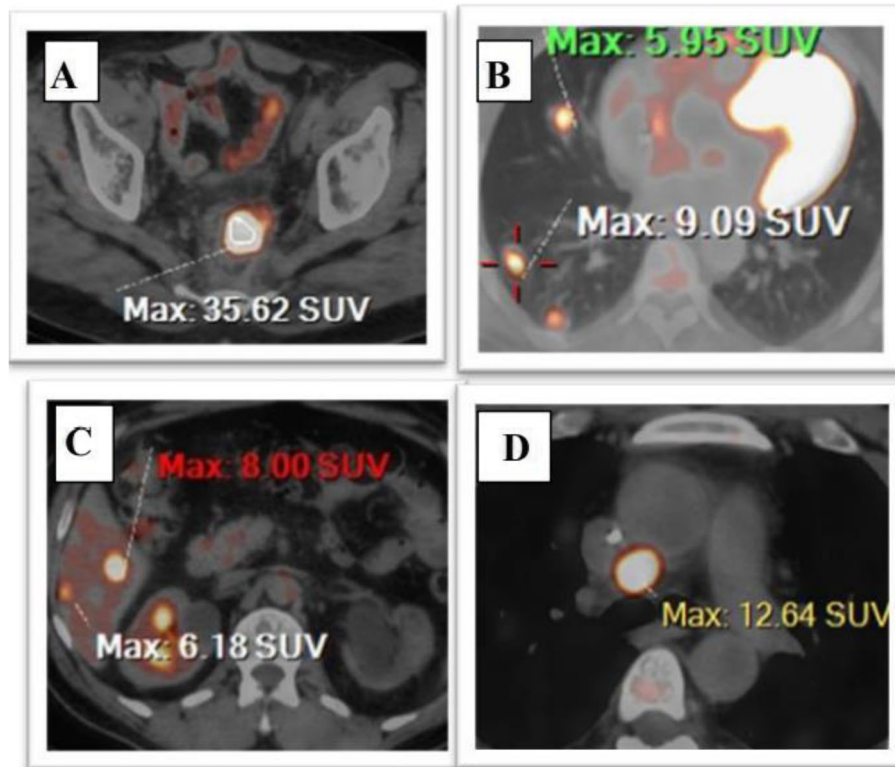
Fig. 4 A 55-year-old male with a surgically resected rectal cancer, presented by elevated CEA and was referred for PET/CT assessment. **a**, **b**, **c**, **d** Axial PET/CT images through the pelvis, chest, and abdomen showing the following: left pararectal hypermetabolic soft tissue lesion achieving 35.62 SUV$_{max}$ (**a**); multiple hypermetabolic metastatic pulmonary deposits, the most active of them achieved 9.09 SUV$_{max}$ (**b**) associated with hypermetabolic mediastinal lymph nodes, the most active of them achieve 12.64 SUV max (**d**); multiple hypermetabolic metastatic hepatic focal lesions, the most active of them achieve 8 SUV$_{max}$ (**c**)

metastatic hepatic lesions with higher detection rate of PET/CT over CECT in the detection of metastatic hepatic deposits. Fifty lesions were detected by CT and 65 lesions were detected by PET/CT which detected occult metastatic hepatic focal lesions. The superiority of PET/CT over CECT owes to the latter's inability to diagnose small masses (less than 15 mm in diameter) as benign or malignant. These results are comparable to those of Ali and Abd Elkhalek [14] and Agarwal et al. [9] which demonstrated that FDG PET is highly sensitive for the detection of liver metastases, and the routine FDG-PET/CT assessment of patients with hepatic metastasis has a significant impact on disease staging and selection of candidates suitable for solitary liver metastasis resection.

PET/CT could also be used in monitoring the treatment efficacy of local therapy of isolated lung and liver metastatic lesions. The local therapy approaches of hepatic metastasis are radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE), and cryoablation. Traditional imaging techniques could not discriminate between tissue edema and tumor remnant. However, PET provides a functional imaging of the levels of metabolism within the suspected foci and also the whole body, so it

substantially helps the clinicians in recognizing tumor remnants [15]. In the current study, one patient underwent radiofrequency ablation for hepatic metastasis which showed successful ablation of the focal hepatic lesion with no residual FDG uptake. This is also comparable with the results of Veit el al [16]. which showed that PET/CT plays a distinctive role in the follow-up of patients undergoing RFA of the liver lesions.

In the current study, eight patients proved to have metastatic peritoneal deposits. The number of detected lesions by CECT was 9, and 14 lesions were detected by PET/CT which showed the superiority of PET/CT over CECT which detected occult peritoneal deposits.

Lymph node metastasis is an important prognostic factor in patients with colorectal cancer [17]. In the current study, 17 patients proved to have metastatic lymph nodes with higher detection rate by PET/CT over CECT as regards the number of the detected lesions. Thirty-eight lymph nodes were detected by CECT and 58 lymph nodes were detected by PET/CT which detected 18F-FDG avid subcentimetric lymph nodes; these additional sites of metastatic involvement would have been missed if assessment was done using CT alone, and this
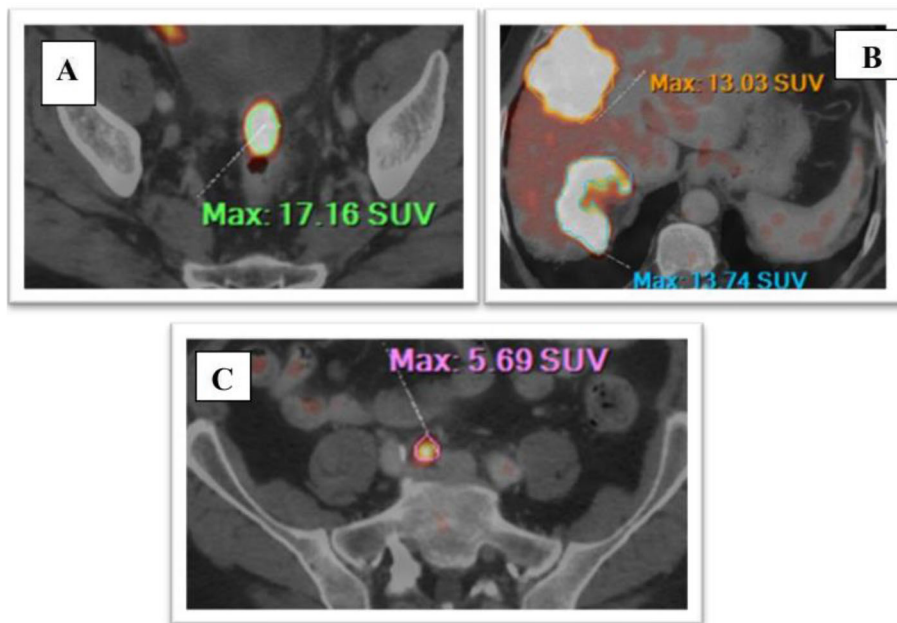
Fig. 5 A 65-year-old male patient with a history of rectal cancer treated first surgically followed by chemotherapy. He was presented with elevated CEA and referred for PET/CT assessment. **a**, **b**, **c** Axial PET/CT images through the abdomen and the pelvis showing the following: recurrent hypermetabolic soft tissue nodule at the pelvic operative bed achieving activity about 17.16 SUV$_{max}$ (**a**); hypermetabolic hepatic focal lesions achieving about 13 and 13.7 SUV$_{max}$ (**b**); hypermetabolic right internal iliac lymph nodes achieving activity about 5.69 SUV$_{max}$ (**c**)
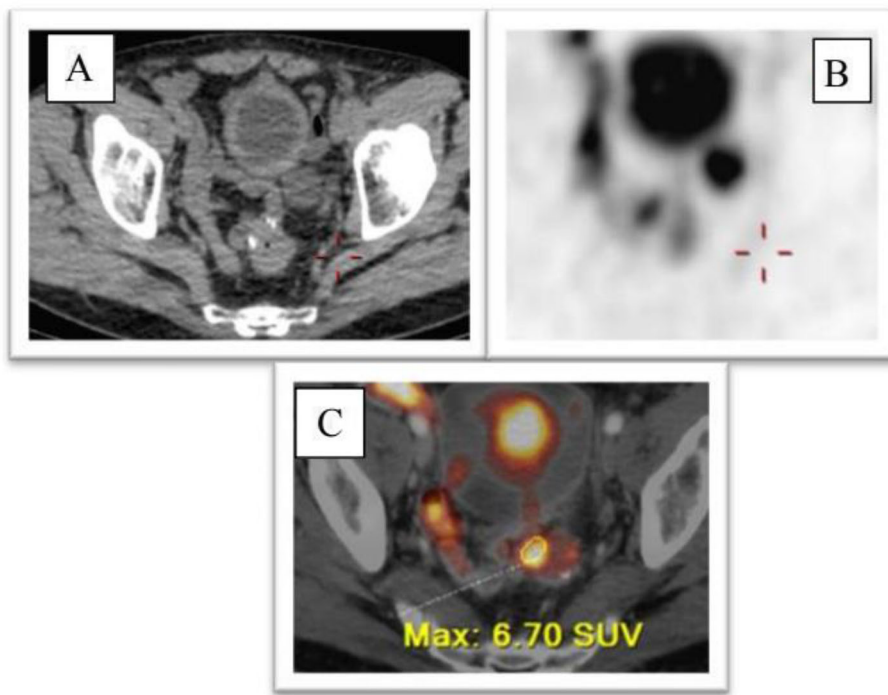
Fig. 6 A 70-year-old male patient with a history of surgically resected sigmoid cancer followed by chemotherapy, presented by elevated CEA and referred for PET/CT assessment. **a** Axial CT, **b** axial PET, and **c** axial PET/CT showing the following: ill-defined metabolically active soft tissue lesion at the left side of the pelvis related to the recto-sigmoid anastomotic site measuring 29 × 19 mm (**a**, **b**) and achieving 6.70 SUV$_{max}$ (**c**)

result in up-staging and consequently change the management plan in these patients. CT's strengths are its accurate depiction of anatomic abnormalities and its ability to define structures that are below the resolution of conventional nuclear medicine. A major limitation of CT however is its reliance on anatomic criteria in order to identify the pathological condition, for example using a 1-cm short axis dimension threshold for pathological lymphadenopathy.

However, lymph nodes smaller than 1 cm can contain malignant cells and, in addition to reactive or inflammatory processes, can result in nodes larger than 1 cm [1].

Nodal metabolic activity assessment using FDG PET is not directly reliant on the nodal size to determine the presence or absence of malignancy. Nodes that are not enlarged can contain tumor on FDG PET. However, PET can give false-positive results due to inflammation. In addition, some cystic or mucinous nodal metastasis may not show significant FDG uptake [18].

Bone metastasis from colorectal carcinoma is relatively uncommon [1]. In the current study, patients had metastatic bone deposits with higher detection rate by PET/CT over CECT. Six lesions were detected by CECT and 13 were detected by PET/CT with retrospective detection of 7 occult lesions missed on CT. That was in accordance with Ali and Abdelkhalek [19].

PET scanning can identify osseous metastases at an early stage of growth before host reactions to tumor cells occur (active osseous deposits without structural abnormalities) [18]. Early malignant bone marrow infiltration can be depicted by 18F-FDG PET because of the very early increased metabolism of glucose in the neoplastic cells. The combined PET/CT is unique as it can scan the whole body in one session, and it can provide us with the functional and anatomic data in co-registered images. Combined PET/CT improved the CT ability to detect and characterization of metastatic osseous deposits, which is essential for proper staging and further management planning [19].

The overall comparison between CECT and PET/CT in the current study showed significant superiority of PET/CT over CECT.

The limitations of our study were as follows:

- Relatively small number of the studied population.
- Patient referral bias and intra- and inter-observer variation for conventional imaging interpretation influenced the selection of eligible patients.

Conclusion
For post-operative detection of loco-regional recurrence and metastasis in patients with colorectal cancer and elevated CEA level, 18F-FDG PET/CT can be considered as an efficient diagnostic imaging tool due to its high sensitivity and specificity which extensively affect further management.

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