FDG-PETCT versus contrast-enhanced computed tomography in diagnosis of post-therapeutic colorectal cancer recurrence and metastases

Nivine Abdel Moneim Chalabi[1], Reem Hassan Bassiouny[1*] and Mohamed Abobakr El Sedek[2]

Abstract

Background: This study was designed to assess the role of 18F-FDG CT was able to detect additional/CT in post-therapeutic surveillance of colorectal cancer patients as compared with contrast-enhanced CT to allow early detection of recurrent and metastatic cases amenable for curative surgery and thus improve the overall survival of patients.

Results: Of the total 100 patients, 70 proved to have metastasis or local recurrent disease by the standard reference modalities. One hundred eighty-two diseased regions were detected in these 70 patients. PET/CT was positive in 174 regions (95.6%) whereas CECT was positive in 118 regions (64.8%). PET/CT was superior to CECT in detection of hepatic focal lesions, metastatic lymph nodes, pulmonary metastases, and peritoneal and suprarenal metastases whereas both were equal in detection of osseous deposits. CECT detected four lesions that were missed by PET/CT, and these were hepatic metastases from mucinous adenocarcinoma.

Conclusion: PET/CT is a better method to evaluate post-therapeutic colorectal cancer patients. It detected viable residual tumor cells in operative bed scar, small LNs, hepatic focal lesions, peritoneal deposits, pulmonary masses, bone deposits, and suprarenal deposits with significantly higher specificity and sensitivity than CECT avoiding unnecessary surgeries.

Keywords: PET/CT, Recurrent and metastatic colorectal cancer

Background

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females, and is one of the leading causes of cancer-related morbidity and mortality that accounted for almost 835,000 deaths in 2015 [1]. Despite the fact that radical surgery is curative in up to 70% of colorectal cancer patients, 30–50% of them will still develop post-operative locoregional recurrence or metastasis within 2 years of primary surgery with or without adjuvant chemotherapy and will die with their disease [2, 3]. However, a good proportion of patients with recurrent or metastatic CRC still have the chance of curative-intent surgery which is associated

with a 5-year survival rate of 30–40% in selected patient populations with single organ metastasis [4]. The principal aim of follow-up programs after radical resection of colorectal cancer is to allow early detection of the recurrence and metastasis in order to enhance the proportion of potentially resectable cases and thus improve the prognosis and survival of patients [5]. The post-operative follow-up of CRC patients includes regular physical examination, estimation of the serum carcinoembryonic antigen (CEA) level, endoscopy, and conventional imaging techniques such as contrast-enhanced computerized tomography (CECT), magnetic resonance imaging (MRI) and ultrasound of the liver [4]. Elevated CEA values cannot provide accurate localization to the sites of recurrence [6]. CT has been considered the primary imaging investigation for detection of recurrent

* Correspondence: rhbassiouny1592@gmail.com
[1]Ain Shams University, Radiodiagnosis Department, Cairo, Egypt
Full list of author information is available at the end of the article

CRC because of its low cost, widespread availability, and high resolution of anatomic details; however, it cannot discriminate recurrent neoplastic disease from nonmalignant changes, such as scars, inflammation, and radiation necrosis and may under-estimate the actual tumor burden by overlooking small tumor clusters in areas of distorted anatomy after treatment [7]. 18 Fluorine (18F) fluorodeoxyglucose (FDG) positron emission tomography (PET/CT) is an integrated imaging modality of anatomic and functional imaging that can readily detect the cancer-related metabolic changes which usually precede the morphological ones [8, 9]. It was considered by many authors to be more sensitive than the conventional imaging modalities in the early detection of local recurrence and distant metastases and in evaluation of tumor viability following radiotherapy and chemotherapy in colorectal patients with elevated or normal CEA [2, 10]. However, the diagnostic value and efficacy of FDG PET/ CT in surveillance of CRC patients are not yet fully established [11].

In this prospective study, our goal was to assess the role of 18F-FDG PET/CT in comparison with enhanced CT in post-therapeutic surveillance of CRC patients and its sensitivity for early detection of post-therapeutic colorectal cancer recurrence and metastasis

Methods
Patients
This prospective study included 100 patients with histopathologically proven colorectal cancer who were referred to perform post-therapeutic follow-up by PET/CT in the period between January 2014 and January 2018. The study took place in an Egyptian military hospital and was approved by its ethical committee. The inclusion criteria were as follows: (1) histopathologic confirmation of primary CRC including TMN classification; (2) curative resection of the tumor either or not followed by chemoradiation therapy; (3) regular follow-up program every 3 or 6 months, including physical examinations, serum CEA level estimation, and conventional imaging including ultrasound of the liver and CT chest and pelviabdomen; (4) patients with suspected local recurrence or metastasis by routine follow-up program. (5) No age predilection and both sexes were included. Exclusion criteria included patients with strong history of atopic disorders, and those with serum creatinine level above 2 mg/dl, recent surgery less than 6 weeks, radiotherapy within less than 3 months, or chemotherapy within less than 3 weeks.

Technique
PET/CT was performed on an integrated scanner (Philips 128 slice CT) that combines both CT and PET

Table 1 Patient characteristics

Total number of patients	100
Male patients	54
Female patients	46
Mean age for males (age range from 40 to 76) years	59.9
Mean age for females (age range 26–76) years	56.8

capabilities in two sequential gantries, to avoid the need to move the patient between the two components of the study. Patients fasted for at least 6 h before the examination, except for water. Blood glucose levels were measured and should be less than 200 mg/dl. An intravenous dose of (0.18–0.21 mCi/kg, 5–14 mCi) FDG was injected and after 45–60 min; the patients were asked to void just before entering the examination room. Multi-detector CT examination from the base of the skull to the upper thighs was planned with the following parameters: 120 mA, 140 kVp, table speed = 13.5 mm per rotation, and thickness of 4 mm. After CT acquisition, PET scan of the same axial range started with the patient in the same position on the table for 2–3 min per bed position. PET data were acquired by using a matrix of 128 × 128 pixels. CT-based attenuation correction of the emission images was used. Contrast-enhanced CT was performed by the same scanner 20–50 s after giving bolus injection of non-ionic iodinated contrast at dose about 2–3 ml/kg of body weight. Scanning was acquired from the base of the skull till the mid-thigh and may involve the whole body in case of extensive skeletal deposits, using the 2.5-mm thickness section.

Image interpretation
The reconstructed attenuation corrected PET images, CT images, and fused images of matching pairs of PET and CT images were reviewed by two experienced nuclear medicine physicians and a radiologist in axial, coronal, and sagittal planes, as well as in maximum intensity projections and in three-dimensional cine mode. Qualitative assessments for the presence of hyper-metabolic lesions were evaluated on

Table 2 Local recurrences or metastases proved by reference modalities

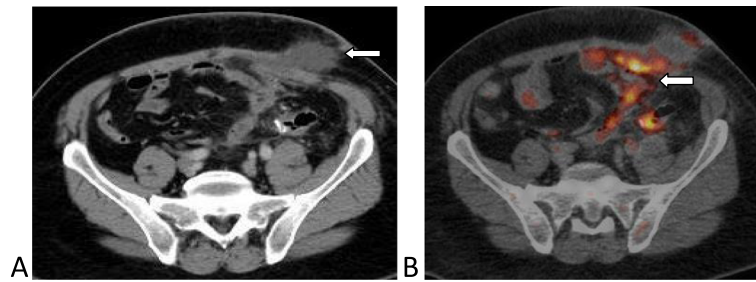| Region	Number of regions	PET/CT	CECT
Local recurrence	38	38 (100%)	28 (73.68%)
Hepatic deposits	52	48 (92.3%)	40 (76.9%)
Metastatic lymph nodes	40	40 (100%)	12 (30%)
Pulmonary metastasis	28	24 (85.7%)	22 (78.8%)
Peritoneal deposits	16	16 (100%)	10 (62.5%)
Suprarenal metastasis	2	2(100%)	2(100%)
Osseous deposits	6	6(100%)	4(66.6%)
Total	182	174(95.6%)	118(64.8%)

Fig. 1 A 52-year-old male patient who underwent surgical resection for pathologically proven colonic adenocarcinoma followed by chemotherapy and radiotherapy and follow-up 6 months later revealed a normal tumor marker level. **a** Axial post-contrast CT image showing operative bed fluid collection (seroma) with no enhancing component (arrow), **b** axial fused PET–CT image showing avid metabolic activity at the operative bed

corrected PET images. Semi-quantitative evaluation was performed using the standardized uptake value (SUVmax). Lesions which exceeded SUVmax of 2.5 were considered positive for disease involvement whereas findings with SUVmax below 2.5 were considered insignificant. Contrast-enhanced CT images were evaluated for the presence of hepatic focal lesions, lymph node size (more than 10 mm in its short axis), lymph node morphology, pulmonary nodules, peritoneal masses, operative bed masses, and skeletal lesions. Comparison with other clinical and diagnostic methods including laboratory tests (tumor markers) and other pathological findings was performed.

Reference standard
Our reference standard included histopathological or cytological confirmation or at least 6 months of clinical and radiological follow-up to confirm the final diagnosis of recurrence or metastasis.

Statistical analysis
IBM SPSS statistics (V. 23.0, IBM Corp., USA, 2015) was used for data analysis. Diagnostic validity test was used: it includes agreement and disagreement between PET/CT and CECT. The Chi-square test was used to compare the differences between the two studied imaging modalities. The probability of error equal 0.05 was considered significant; while values at 0.01 and 0.001 are highly significant. PET/CT findings and CECT findings were classified as true positive (TP), false positive (FP), true negative (TN), and false negative (FN), as compared with those of the reference standard. Standard statistical formulas were used to calculate the sensitivity, specificity, and accuracy of 18F-FDG PET/CT and CECT in both the case-based and lesion-based analyses.

Results
The sociodemographic variables and lesion characteristics of the 100 patients included in the study are shown in Table 1. Seventy out of the hundred patients (70%) proved to have metastasis or local recurrent disease by the standard reference modalities. Forty-two patients were confirmed by histopathology while 28 patients by follow-up regimes. One hundred eighty-two diseased regions were detected in these 70 patients with distribution as shown in Table 2. By comparing the results of 18F-FDG PET/CT and CECT (Table 2), we found that 18F-FDG PET/CT was superior to CECT by detection of all 38 local recurrent lesions (100%) compared with only 28 (73.6%) detected by CECT (e.g., Figs. 1 and 2). PET/CT accurately detected 48 out of the 52 hepatic focal
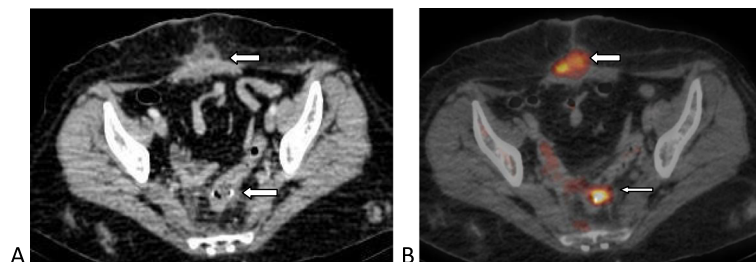

Fig. 2 A 64-year-old female patient who underwent surgical resection for pathologically proven colonic adenocarcinoma, presented with an elevated tumor marker. **a** Axial post-contrast CT image showing early post-operative enhancing scar and minimal thickening at the anastomotic site (arrows), **b** axial fused PET–CT image showing corresponding metabolic activity in the base line PET–CT (arrows)
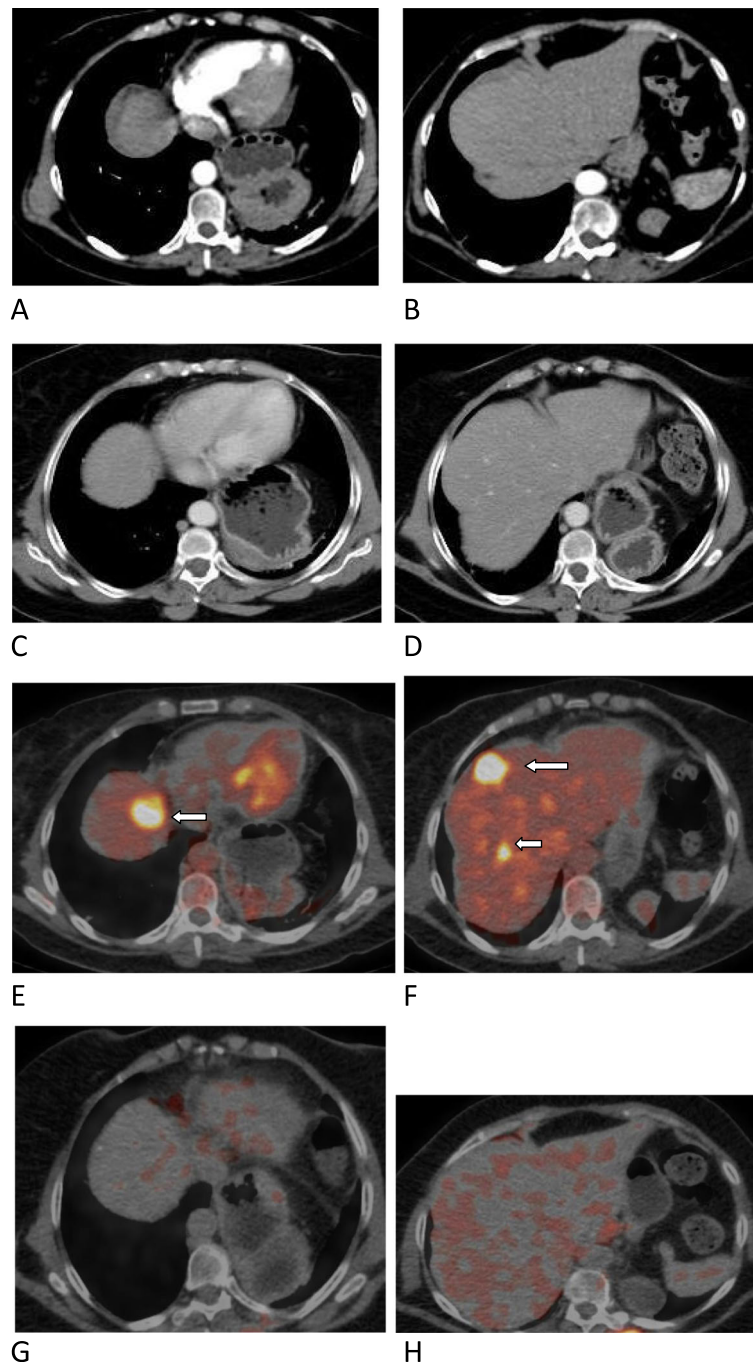
Fig. 3 A 64-year-old female patient who underwent surgical resection for pathologically proven colonic adenocarcinoma, presented with an elevated tumor marker. **a**, **b** Axial post-contrast CT images in arterial phase showing no enhancing focal lesion. **c**, **d** Axial post-contrast CT images in porto venous phase showing no enhancing focal lesion. **e**, **f**, **d** Axial fused PET–CT images at the same level of the enhanced CT images showing metabolically active hepatic focal lesions (arrows). **g**, **h** Post-therapeutic axial fused PET–CT images showed good therapeutic response with disappearance of the metabolically active hepatic focal lesions

lesions (92.3%) and CECT detected 40 lesions (76.9%). PET/CT was able to detect additional 8 hepatic deposits, not detected by CT (e.g., Fig. 3), while CECT detected 4 lesions that were missed by PET/CT and were hepatic metastases from mucinous adenocarcinoma (e.g., Fig. 4).

PET/CT detected all 40 metastatic lymph nodes (100%), while the CECT detected only 12 (30%). PET/CT accurately detected 24 out of the 28 pulmonary metastases (85.7%) whereas CECT detected only 22 (78.8%) (e.g., Fig. 6). PET/CT accurately detected other lesions
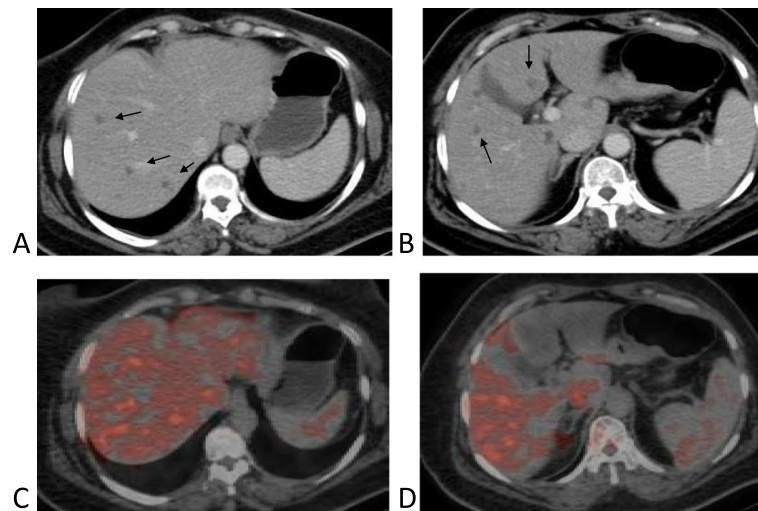
Fig. 4 A 40-year-old male patient who underwent rectal resection for pathologically proven mucinous adenocarcinoma, not followed by chemo or radiotherapy. Follow-up revealed elevated level of tumor markers. **a, b** Axial post-contrast CT images showing multiple small sized hypodense non-enhancing hepatic focal lesions (arrows). **c, d** Axial fused PET/CT images showing no avid metabolic hepatic focal lesions at the same levels which proved to be metastatic deposits

including (16 peritoneal, 2 suprarenal, and 6 osseous deposits, e.g., Fig. 7), and CECT detected 19 lesions only (10 peritoneal, 2 suprarenal, and 4 osseous deposits) as shown in Table 3. In the assessment of the 100 patients 252 sites of recurrent sites were suspected by both PET/ CT and CECT. PET–CT agreed with reference modalities in 238 lesions as it was true positive in detection of 174 lesions and true negative in detection of 64 regions.

PET–CT disagreed with reference modalities in 14 lesions (5.8%) as it was false negative in 8 lesions (two hepatic and two pulmonary) and false positive in 6 operative bed recurrence regions. The level of agreement between the results of both PETCT and reference modalities was about 94.4% with p value = 0.000 which is highly significant (Table 3). CECT agreed with reference modalities in 148 lesions as it was true positive in detection
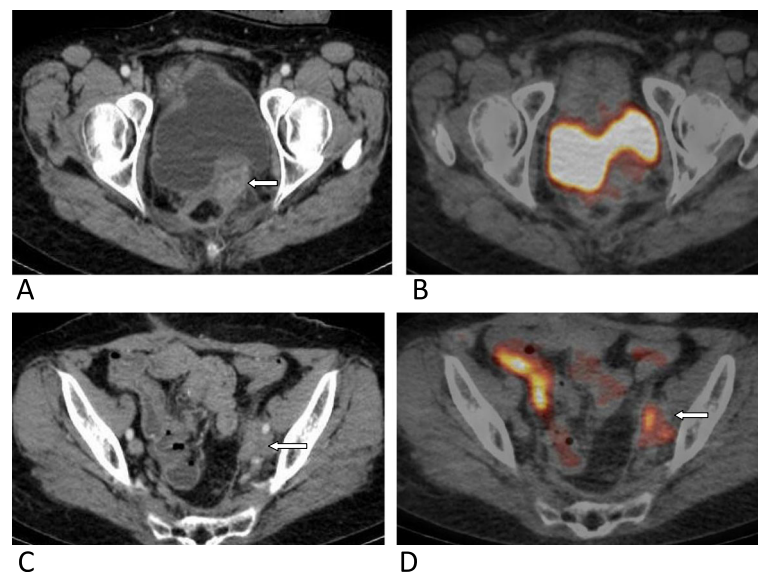

Fig. 5 A 57-year-old female patient who underwent rectal resection for pathologically proven adenocarcinoma, followed by chemotherapy, presented 4 months later by left loin pain and elevated tumor markers. **a** Axial post-contrast CT image showing operative bed faintly enhancing mass (arrow) encasing the distal left ureter (arrow). **b** Axial fused PET–CT image showing no metabolically active lesions noted in the operative bed. **c** Axial post-contrast CT image showing left iliac enlarged LNs (arrow). **d** Axial fused PET–CT image showing left iliac metabolically active LNs (arrow)
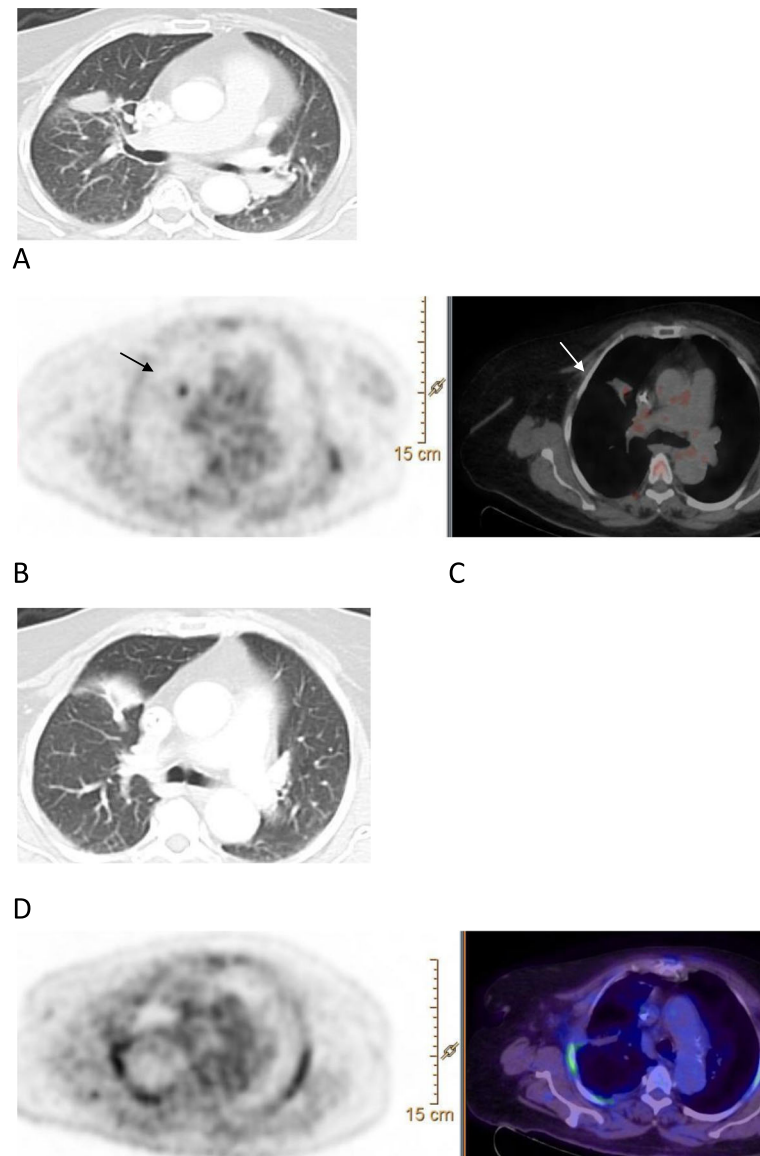
Fig. 6 A 70-year-old female patient who underwent colonic mass surgical resection for pathologically proven adenocarcinoma, presented 4 months later by elevated tumor markers. **a** Axial CT image in lung window showing right upper lobe pulmonary nodule. **b** Axial PET attenuated corrected image and axial fused PET–CT image of right upper lobe metabolically active nodule (arrows). **c** Post-radiofrequency ablation assessment for the pulmonary nodule by contrast-enhanced CT showed stationary size depending on the size criteria (appreciable change in size needs time). **d** PET–CT revealed a photopenic area corresponding to the ablated nodule with no metabolically active lesion within

of 114 lesions and true negative in 34 lesions, yet CECT disagreed with reference modalities as it was false negative (Fig. 6), false positive (Fig. 5) as shown in Table 4 and figure. The agreement between the results of both CECT and reference modalities was about 58.7% and p value = 0.51 which is insignificant. The diagnostic performance of PET/CT and CECT in the detection of locoregional recurrence and metastases is shown in Table 5 with higher sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic efficacy of PET/CT as compared with enhanced CT. The sensitivity and accuracy of FDG PET/

CT significantly differed from those of CECT in lesion-based analyses ($p < 0.05$), whereas for the specificity, the PET/CT results did not show a significant difference from those of CECT.

Discussion

Although contrast-enhanced computed tomography is considered the primary imaging modality in the detection of local recurrence in patients with colorectal cancer, its limitations include its reliance on size criteria in the diagnosis of metastatic LNs, enhancing
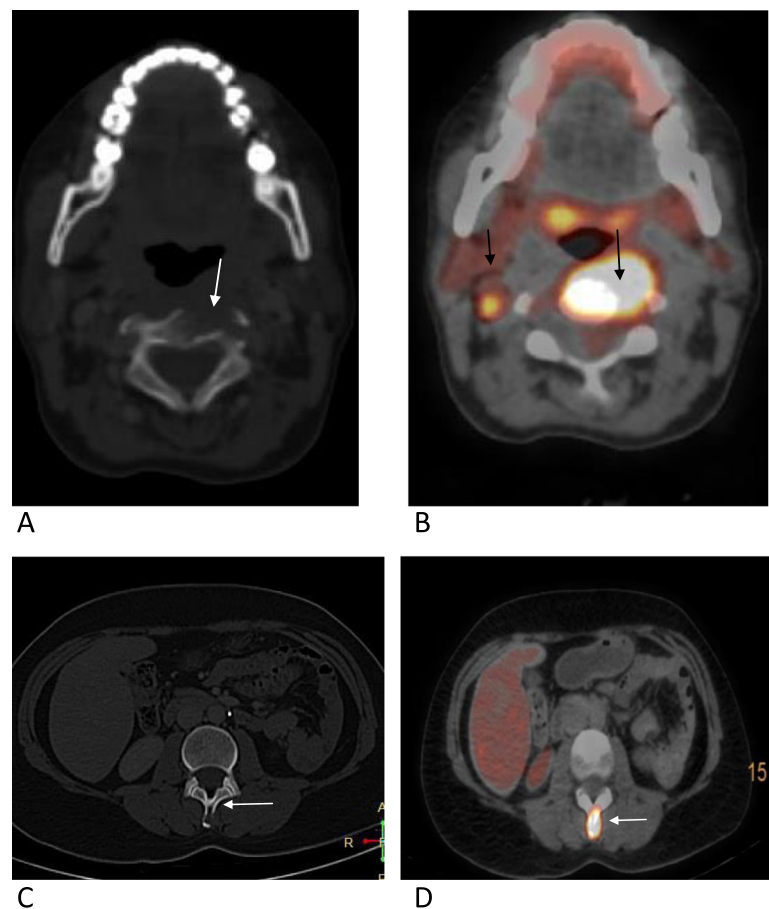
Fig. 7 A 38-year-old female patient who underwent rectal surgical resection for pathologically proven adenocarcinoma, not followed by chemo or radiotherapy. Recently, she presented with neck pain, low back pain, and elevated tumor markers level. **a** Axial CT image in bone window showing destructive cervical vertebral body lesion (arrow). **b** axial fused PET–CT image at the same level showing metabolically active lesion destroying the vertebral body of C2 as well as avid right deep cervical LN (arrows). **c** Axial CT image in bone window showing a small osteolytic lesion in the spinous process of the second lumbar vertebra (arrow). **d** Axial fused PET–CT image at the same level showing metabolic activity within the lesion of the spinous process of the second lumbar vertebra (arrow)

pattern of hepatic deposits and the inability to differentiate between post-therapeutic viable and non-viable malignant lesions. According to previous studies PET/CT has showed better sensitivity and specificity for detection of hepatic and extra-hepatic metastasis than CECT [12, 13]. In some studies, the sensitivity of PET/CT for hepatic lesions was similar to that of MRI [9, 14]. The final diagnosis of distant metastasis and/or local recurrence by PET/CT in post-therapeutic CRC in our study based on lesions

Table 3 Agreement of PET–CT with the reference modalities in detection of post-therapeutic colon cancer recurrence and metastasis (lesion-based analysis *n* = 252) crosstab

			Reference		Total
			Negative	Positive	
PET–CT result	Negative	Number of Patients	64	8	72
		%	91.4%	4.4%	28.6%
	Positive	Number of Patients	6	174	180
		%	8.6%	95.6%	71.4%
Total		Number of Patients	70	182	252
		%	100.0%	100.0%	100.0%

Table 4 Agreement of CECT with the reference modalities in detection of post-therapeutic colon cancer recurrence and metastasis (lesion-based analysis *n* = 252) crosstab

			Reference		Total
			Negative	Positive	
CE-CT result	Negative	Number of Patients	34	68	102
		%	48.6%	37.4%	40.5%
	Positive	Number of Patients	36	114	150
		%	51.4%	62.6%	59.5%
Total		Number of Patients	70	182	252
		%	100.0%	100.0%	100.0%

analysis was evident in 70% of our patient population with sensitivity of 95.6%, specificity of 91.4%, NPV of 88.9%, PPV of 96.7%, and diagnostic efficacy of 94.4% compared with 62.6%, 48.6%, 76%, 33.3 and 58% for CECT respectively. It showed a great role in the detection of small sized LNs, local operative bed recurrence, small suprarenal metastasis, early osseous deposits, and post-therapeutic evaluation of viable and non-viable malignant lesions (post-chemotherapy, post-radiotherapy). These results were quite similar to those obtained by Metser et al. [15] whose study included 158 post-operative colorectal carcinoma patients who presented with increasing CEA levels and equivocal explanation of these elevated levels by conventional imaging modalities. He reported sensitivities of PET/CT and MDCT of 98.1% and 66.7%, and specificities of 75% and 62.5% respectively. The specificity in Metser et al. study for PET/CT was higher than that by Mittal et al. [16] in which he analyzed 73 post-operative CRC patients grouped into various categories depending on CEA level. PET/CT showed recurrences in 71% of CRC patients, CT showed recurrence in 23 (45%) patients, and the positive rate increased with the CEA level. The study results by Choi et al. [17] to assess the value of 18F-FDG PET/CT in detecting local or distant recurrence in 269 post-operative CRC patients and to compare its accuracy with conventional imaging studies, showed overall sensitivity, specificity, accuracy, PPV, and NPV of 94.7%, 96.0%, 95.8%, 78.2%, and 99.2% for PET/CT, and 86.8%, 97.6%, 96.2%, 84.6%, and 98.0% for conventional imaging studies, respectively. As reported previously and confirmed by our study, Chiewvit

Table 5 Diagnostic performance of PET/CT in comparison with CECT by regional lesion-based analysis

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Diagnostic efficacy
PET–CT	95.6%	91.4%	96.7%	88.9%	94.4%
CECT	62.6%	48.6%	76.0%	33.3%	58%

et al. [13] have shown that 18F-FDG PET/CT is a useful method in post-operative evaluation of patients with suspected recurrent colorectal cancerous lesions and a normal CEA level. When conventional imaging methods have shown equivocal findings, 18F-FDG PET/CT is effective and helpful to distinguish local recurrences or metastases from post-operative changes or benign disease findings that may not be meaningful. The sensitivity of FDG-PET imaging for detection of mucinous carcinoma was proven by many authors to be significantly lower than that for nonmucinous carcinomas owing to little or negligible uptake of the tracer [3]. In our study, mucinous adenocarcinoma metastases constituted the main factor responsible for false negative scans Therefore, it was suggested that for mucinous adenocarcinoma patients with negative FDG-PET imaging results, other imaging modalities should be recommended for further diagnosis [11, 18]. Limitations of this study were as follows: (1) the sensitivity, specificity, and PPV of PET/CT may be overestimated because the study population included only those patients with suspected local recurrence or metastasis by regular follow-up program and most (87%) of them have elevated serum CEA levels. According to Zhang et al. (11) the sensitivity, specificity, and accuracy of FDG PET/CT were 81.3%, 80%, and 80.6% in patients with normal CEA and equivocal or meaningless findings at conventional imaging modalities. (2) Histopathologic confirmation was lacking in 28 patients.

Conclusion
In conclusion, PET/CT proved to be a better method to evaluate post-therapeutic colorectal cancer patients. It detected viable residual tumor cells in operative bed scar, small LNs, hepatic focal lesions, peritoneal deposits, pulmonary masses, bone deposits, and suprarenal deposits with significantly higher specificity and sensitivity than CECT avoiding unnecessary surgeries

resolved, and the resolution documented in the literature. First author NAMC provided the main idea and the main design of the word; helped in collection of the clinical and pathologic data; contributed in the acquisition, analysis, and interpretation of the imaging studies; and revised and approved the submitted version. Third author MABS collected the clinical and pathologic data, contributed in the acquisition of the quantitative measures, contributed to drafting of the manuscript, and revised and approved the submitted version. All authors have read and approved the manuscript.

Availability of data and materials
All datasets used and/or analyzed during the current study are available in the radiology department of AL Maadi Egyptian military Hospital.

Ethics approval and consent to participate
The study was approved by the ethical committee of Al Maadi Egyptian military hospital on January 2014 (no reference number was given at that time). Written consent for participation in the study was obtained from all patients or relatives of patients.

Consent for publication
Written informed consent for publication of the study was obtained from the patients themselves.

Competing interests
This statement is to certify that all authors have seen and approved the manuscript being submitted. We warrant that the article is the authors' original work. We warrant that the article has not received prior publication and is not under consideration for publication elsewhere. On behalf of all co-authors, the corresponding author shall bear full responsibility for the submission.

Author details
[1]Ain Shams University, Radiodiagnosis Department, Cairo, Egypt. [2]Egyptian Military Hospital, Cairo, Egypt.

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