

## Post-Operative Follow-up of Colorectal Cancer: Computed Tomography or F-18 Positron Emission Computed Tomography? That is the Question

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### Abstract

**Background:** In Egypt, the Colorectal cancer is considered the 7th commonest cancer, local recurrence, distant metastasis or both occurs in 30-50% of patients after operations. Both Computed Tomography (CT) and Positron Emission Tomography (PET) are well established in the diagnosis of Colorectal Cancer Recurrence (CRCR).

**Aim of Study:** In this study, we aimed to evaluate the diagnostic performance of 18F-FDG PET/CT in postoperative follow-up of CRC patients and the detection of local recurrence and distant metastasis as compared with CT.

**Patients and Methods:** 62 post-operative patients with colorectal carcinoma underwent whole body FDG PET/CT. The final histopathological and formal clinical follow-up findings were used as gold standard to determine the sensitivity and specificity of FDG PET/CT and enhanced CT of the same periods.

**Results:** The sensitivity, specificity and accuracy of PET/CT in diagnosis of local recurrence was 92%, 91.89% and 94.44% respectively. The sensitivity, specificity and accuracy of contrast enhanced CT in diagnosis of local recurrence was 72%, 89.19% and 82.5% respectively. The sensitivity, specificity and accuracy of PET/CT in diagnosis of distant metastasis was 91.12%, 81.08% and 88.64% respectively. The sensitivity, specificity and accuracy of contrast enhanced CT in diagnosis of local recurrence was 72.55%, 86.49% and 78.41% respectively.

**Conclusion:** In patients with suspected CRCR, FDG-PET/CT appears to be a significantly more accurate method than CT alone for detection of local recurrence and distant metastasis, FDG-PET/CT is sufficiently accurate to become a routine follow-up of patients after colorectal resection.

**Key Words:** Post-operative colorectal cancer – PET – PET/CT – CT.

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### Introduction

**IN** Egypt, the colorectal cancer is considered the 7th commonest cancer, with incidence 3.47% of male cancers and 3% of female cancers. In 2015, more than three thousands new cases were diagnosed as having colonic carcinoma [1].

The main lines of treatment of colorectal carcinoma still radical colectomy and post-operative chemotherapy. However, local recurrence, distant metastasis or both occurs in 30-50% of patients after operations [2-4]. To improve survival rates, early detection of local recurrence and/or distant metastasis plays a pivotal role to select patients who will benefit from surgical intervention or chemotherapy [5].

Both Computed Tomography (CT) and Positron Emission Tomography (PET) are well established in the diagnosis of Colorectal Cancer Recurrence (CRCR). CT is considered the workhorse of follow-up in patients with colorectal cancer. Though CT is effective in detection of metastatic deposits especially in the liver, it shows low accuracy in discrimination between local recurrence and post operative changes (CT: Sensitivity of 82% and a specificity of 50% with an accuracy of 68%) [6,7]. On the other hand, 18F-Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) provides accurate information about glucose metabolism and colorectal cancer and its recurrence are well known to have high uptake of FDG. However FDG-PET provide little information about the anatomical localization and the morphology of the lesion. So, the combined use of PET and CT would theoretically combine the advantages of both modalities and avoid the disadvantages of each technique, and would be able to differentiate between

the local recurrence and the changes attributable to surgery or radiotherapy [8]. The role of FDG PET/CT has expanded for large number of human solid tumors [9-12].

In this study, we aimed to evaluate the diagnostic performance of 18F-FDG PET/CT in postoperative follow-up of CRC patients and the detection of local recurrence and distant metastasis as compared with CT.

## Material and Methods

### *Patients:*

We prospectively included 62 patients in this study from November 2013 to September 2014 in Radiology and Oncology Departments in Tanta University and Cairo University. A total number of 62 colorectal cancer patients were included in this study, 42 males and 20 females. The age of the patients ranged from 17 to 73 years (mean 55.4 years). The inclusion criteria included: (1) Confirmation of previous CRC by pathological examination; (2) Patient's completed their treatment including curative surgical resection and/or chemotherapy or radiotherapy; (3) Regular clinical follow-up including carcino-embryonic antigen detection and regular chest and abdominal CT examination; (4) Patients underwent FDG PET/CT examination; (5) At least six months follow-up after the PET/CT examination. This study was approved by the Institutional Review Board at our institution. Informed consent was taken from every patient.

### *PET/CT scanning:*

The patients were instructed to fast for at least six hours, remove metallic objects and avoid exhausting activities following the injection and before the examination to avoid excessive muscle uptake. The encouraged to empty their bladder before the examination. Measurement of blood glucose level was performed for all patient to ensure it less than 150mg/dl. The timing of the examining was adjusted to be 4-6 weeks after surgery or chemotherapy and at least 8 weeks after radiotherapy to decrease the chance of false negative and false positive results. Combined PET/CT system (Siemens Biograph 64, Siemens Medical Solutions, Erlangen, Germany) was used. The patient was asked to drink at least one and half liters of water one hour before the examination. Also, about 45-90 minutes before the examination the patient was injected with 10-20mCi (1ml/10kg) 18F-FDG. At first, whole body contrast enhanced CT was performed and then whole body PET study. The average duration of the study was 20-30 minutes. The CT was performed following

injection of 1-2ml/kg of ultravist at a rate of 2.5-3.5ml/sec by automatic injector. Patients were instructed to breath quietly.

*Reconstruction:* Reconstruction of the PET data using ordered-subset expectation maximization iterative reconstruction with four iterations and eight subsets. Parameters were: Full width 5mm, pixel 4.07mm, and 3mm slices. PET data were corrected for decay, scatter, and random events, and attenuation-corrected using the CT-data. CT data were reconstructed using filtered back projection, slice increment 1 and 2mm slices.

### *Image analysis:*

The analysis of axial and multiplanar reconstruction images for CT and PET was performed. Initially, areas with abnormal focal FDG were noted on PET images. Then CT was used to detect the site of high FDG uptake. Also, CT was used to detect anatomical changes, as increased colonic wall thickness more than 3mm, pelvic masses, enlarged lymph nodes (more than 15mm short axis in the abdomen and more than 10mm in the pelvis), bone lesions, liver metastasis, lung nodules, and nodules in other organs.

The interpretation of integrated PET/CT was considered positive if the area of high focal FDG uptake corresponded to morphological abnormality on CT. The increased uptake in the kidneys, ureters, urinary bladder and brown fat was reported as normal or physiological. The presence of morphological changes on CT without abnormal increase in FDG uptake was considered benign postoperative changes. The presence of abnormal focal FDG uptake in normal structures without morphological changes was considered positive. The presence of lung or liver nodules <1cm on CT was considered positive even if the FDG was normal.

In the current study we adopted both visual interpretation and semi-quantitative analysis. The region of interest was placed in the lesion at the section of most radio-activity, and the maximum standardized uptake value (SUVmax) was calculated. In the early images, the diagnosis of positive lesions was based on SUVmax >2.5. In the delayed images, ASUVmax >20% was considered positive (ASUVmax=SUVmax, delayed-SUVmax, early). The diagnosis was confirmed by pathological examination after secondary operation, colonoscopy, rectoscopy, laparoscopy and formal follow-up.

### *Statistical analysis:*

The final diagnosis was based on either histopathological or cytological confirmation or at

least six months of clinical follow-up. The True Positive (TP), False Positive (FP), True Negative (TN), and False Negative (FN) for PET/CT and contrast enhanced CT findings were calculated as compared to those of the gold standard. The sensitivity, specificity, and accuracy of 18F-FDG PET/CT and CT were calculated using standard statistical formula. The chi-square test was used to compare the differences between the two imaging modalities.

**Results**

Among the 62 patients, recurrence and/or metastasis were later diagnosed in 50 patients, including 19 local recurrences, 25 metastases, and 6 recurrence and metastases.

*Patient characteristics:* This study included 62 patients. Patient demographics, tumor histology, tumor location, tumor stage, treatment details, have been summarized in (Table 1). This study included 42 males (76.6%) and 20 females (23.3%). Carcinoembryonic Antigen (CEA) was elevated in 39 patients (62.9%). The anatomical location of the primary tumor was colon in 49 patients (79%) and rectal in 13 patients (21%).

Table (1): Characteristics of 62 patients included in the study.

Characteristics	No	%
<i>Age:</i>		
• <40 years	9	14.5
• 40-<50 years	13	20.9
• 50-<60 years	28	45.1
• ≥ 60 years	12	19.3
<i>Sex:</i>		
• Male	42	67.7
• Female	20	32.3
<i>Tumor location:</i>		
• Colonic	49	79
• Rectal	13	21
<i>Histology:</i>		
• Adenocarcinoma	34	54.8
• Mucoïd carcinoma	9	14.5
• Squamous cell carcinoma	12	19.3
• Undifferentiated carcinoma	7	11.3
<i>CEA before PET/CT:</i>		
• Elevated	45	72.5
• Normal	17	27.5
<i>Treatment received:</i>		
• Surgery and adjuvant chemotherapy	31	50.0
• Surgery and radiotherapy	10	16.1
• Surgery and adjuvant chemotherapy and radiotherapy	11	17.7
• Surgery only	10	16.1

*Performance of contrast enhanced CT and PET/CT:*

In the current study, 25 patients with local recurrence. PET/CT correctly diagnosed 23 patients (2 false negative patients), and there was three false positive cases (two cases diagnosed by endo-

scopic biopsy as post-operative fibrosis and one case diagnosed as post-operative inflammatory process and resolved by follow-up). The sensitivity, specificity and accuracy of PET/CT in diagnosis of local recurrence was 92%, 91.89% and 94.44% respectively. The sensitivity, specificity and accuracy of contrast enhanced CT in diagnosis of local recurrence was 72%, 89.19% and 82.5% respectively (Tables 2,3).

Table (2): Comparison between lesions detection on CT and PET images in the studied 62 patients.

Findings	No. of lesions detected on CT images	No. of lesions on PET/CT images	Final results by pathology and formal follow-up
• No abnormal findings	14	8	12
• Local recurrence	22	26	25
• Enlarged lymph nodes	18	24	22
• Pulmonary nodules	6	7	7
• Hepatic deposits	8	9	8
• Peritoneal deposits	3	4	5
• Osseous lesions	5	7	6
• Anterior abdominal wall scar tissue lesion	2	4	3

Table (3): Diagnostic performance of CT and PET/CT in detection of local recurrence.

	TP	FN	TN	FP
	18	7	33	4
Contrast enhanced CT	Sensitivity	Specificity	PPV	NPV
	72.00%	89.19%	81.82%	82.50%
Overall accuracy: 82.26%				
	TP	FN	TN	FP
	23	2	34	3
PET/CT	Sensitivity	Specificity	PPV	NPV
	92.00%	91.89%	88.46%	94.44%
Overall accuracy: 91.94%				

TP : True Positive. TN: True Negative.  
FN : False Negative. FP : False Positive.

Fifty one metastasis was found in 31 patients in the current study: PET/CT correctly diagnosed 48 cases (true positives), while contrast enhanced CT diagnosed only 37 cases. There was seven false positive cases on PET/CT. The diagnosis was confirmed by pathological examination or formal follow-up: Hepatic abscess (1 case), lymphadenitis (3 cases), pathological fracture (1 case), spondylodiscitis (1 case) and pneumonia (1 case). The sensitivity, specificity and accuracy of PET/CT in diagnosis of distant metastasis was 91.12%, 81.08% and 88.64% respectively. The sensitivity, specificity and accuracy of contrast enhanced CT in diagnosis of distant metastasis was 72.55%, 86.49% and 78.41% respectively (Tables 2,4). We have three

false negative results on PET/CT in detection of distant metastasis, one case with military metastasis in the liver, one case with sclerotic bone lesion and one case with lung nodule, all cases failed to show any pathological uptake of FDG.

Table (4): Diagnostic performance of CT and PET/CT in detection of metastasis (at all sites, no of metastases 61 in 39 patients).

	TP	FN	TN	FP
Contrast enhanced CT	37	14	32	5
	Sensitivity	Specificity	PPV	NPV
	72.55%	86.49%	88.10%	69.57%
	Overall accuracy: 78.41%			
	TP	FN	TN	FP
PET/CT	48	3	30	7
	Sensitivity	Specificity	PPV	NPV
	94.12%	81.08%	87.27%	90.91%
	Overall accuracy: 88.64%			

TP : True Positive.                      TN: True Negative.  
 FN : False Negative.                  FP : False Positive.

The distribution of FDG lesions assessed as positive for recurrent CRC is shown in (Table 5). Most PET/CT positive lesions have SUVmax >4.1 |. In comparison to other regions, pulmonary lesions were frequently small with half of them with

SUVmax <4.1. The height mean SUVmax was found in the hepatic lesions.

*Carcino-embryonic antigen:*

The carcino-emryonic antigen was found to be elevated in 45 patients. The elevated CEA as a predictor of recurrent colonic carcinoma and/or metastasis has a sensitivity 82.22%, specificity 52.94%, PPV 82.22%, NPV 52.94% and accuracy 71.84%.

Table (5): Distribution of SUVmax assessed as positive for recurrent CRC on PET/CT.

	Local recurrence	Lymph nodes	Hepatic	Pulmonary	Others
• SUVmax (range)	8.1 (3.1-17.5)	8.5 (3.2-18.7)	9.2 (5.2-19.5)	6.4 (2.3-9.8)	14.2 (3.7-18.8)
0-2	0	0	0	0	0
2.1-4	11	8	2	3	2
>4.1	12	13	6	3	15

Table (6): The sensitivity, specificity, PPV and NPV value of carcino-embryonic antigen.

	TP	FN	TN	FP
CEA	37	8	9	8
	Sensitivity	Specificity	PPV	NPV
	82.22%	52.94%	82.22%	52.94%
	Overall accuracy: 74.19%			

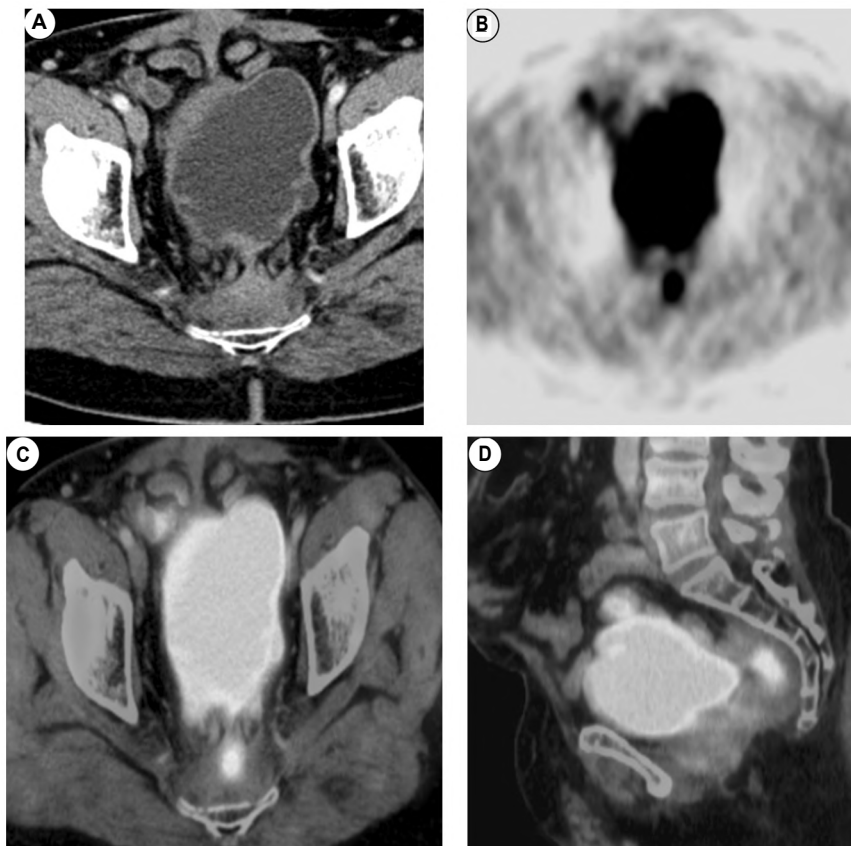


Fig. (1): Sixty-one year old male patient, pathologically proven to have rectal carcinoma, underwent tumor resection and colostomy, received chemotherapy and radiotherapy ended 1 year before this study (A) Contrast enhanced CT showing irregular shaped pre-sacral enhancing soft tissue mass measuring 3 X 2cm. (B,C,D) The lesion incorporating a central metabolically active FDG avid area with maximum SUV (SUVmax) ~11.4. The lesion proved to be local metastasis.

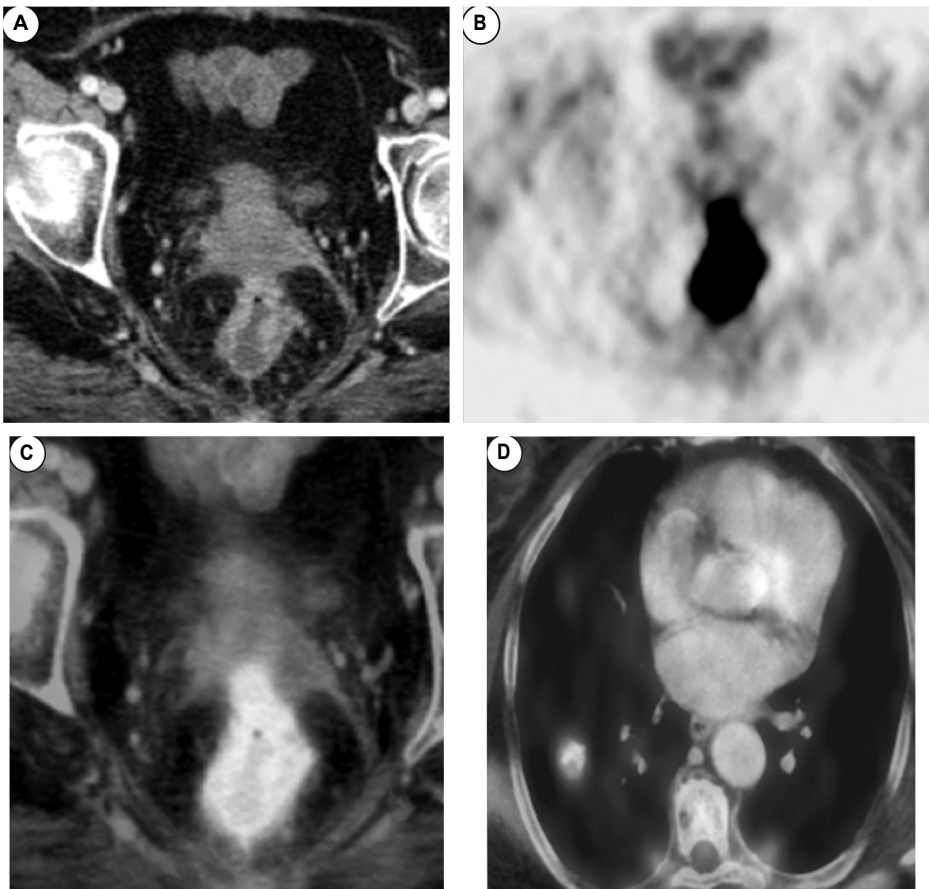


Fig. (2): Seventy-four year old female patient, pathologically proven to have rectal carcinoma, underwent surgical resection 3 years ago and received chemotherapy and radiotherapy. (A) Contrast enhanced CT reveals marked irregular wall thickening at site of the anastomosis. (B,C) Metabolically active rectal wall is seen evident local recurrence SUVmax ~19 (D) Metabolically-active pulmonary nodule seen at the posterior segment of the left lower lung lobe measuring about 1.7cm in diameter with SUVmax ~16.

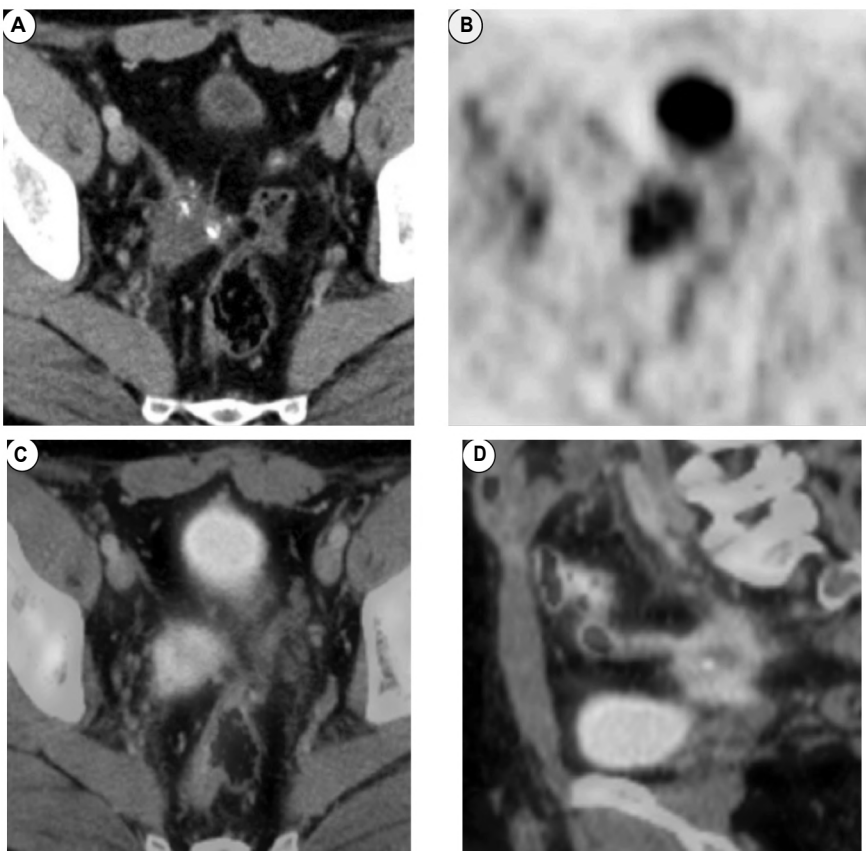


Fig. (3): Forty-two year old male patient, pathologically proven to have cancer colon, underwent hemicolectomy, received chemotherapy and radiotherapy ended 2 years before this study (A) Contrast enhanced CT showing irregular shaped soft tissue mass with calcification, and no significant enhancement, and was reported as post-operative fibrosis. (B,C,D) The lesion appears metabolically active with maximum SUV (SUVmax) ~3.6. The lesion proved to be local recurrence.

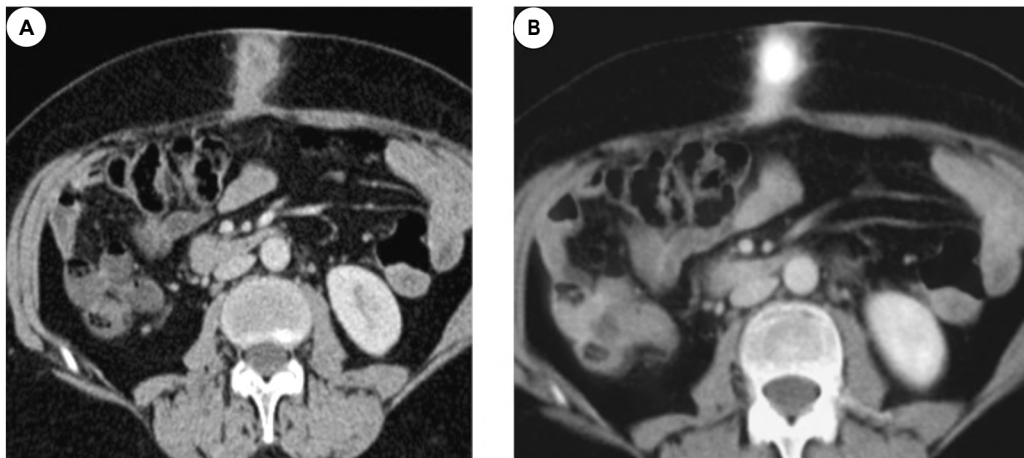


Fig. (4): Forty-eight year old female patient, pathologically proven to have sigmoid colon carcinoma, underwent surgical resection, followed by multiple cycles of radiotherapy ended 2 month before this study (A) Contrast enhanced CT showing irregular shaped soft tissue mass at the site of the scar, (B) PET/CT revealed metabolically active lesion confirming scar tissue/ parietal wall metastasis.

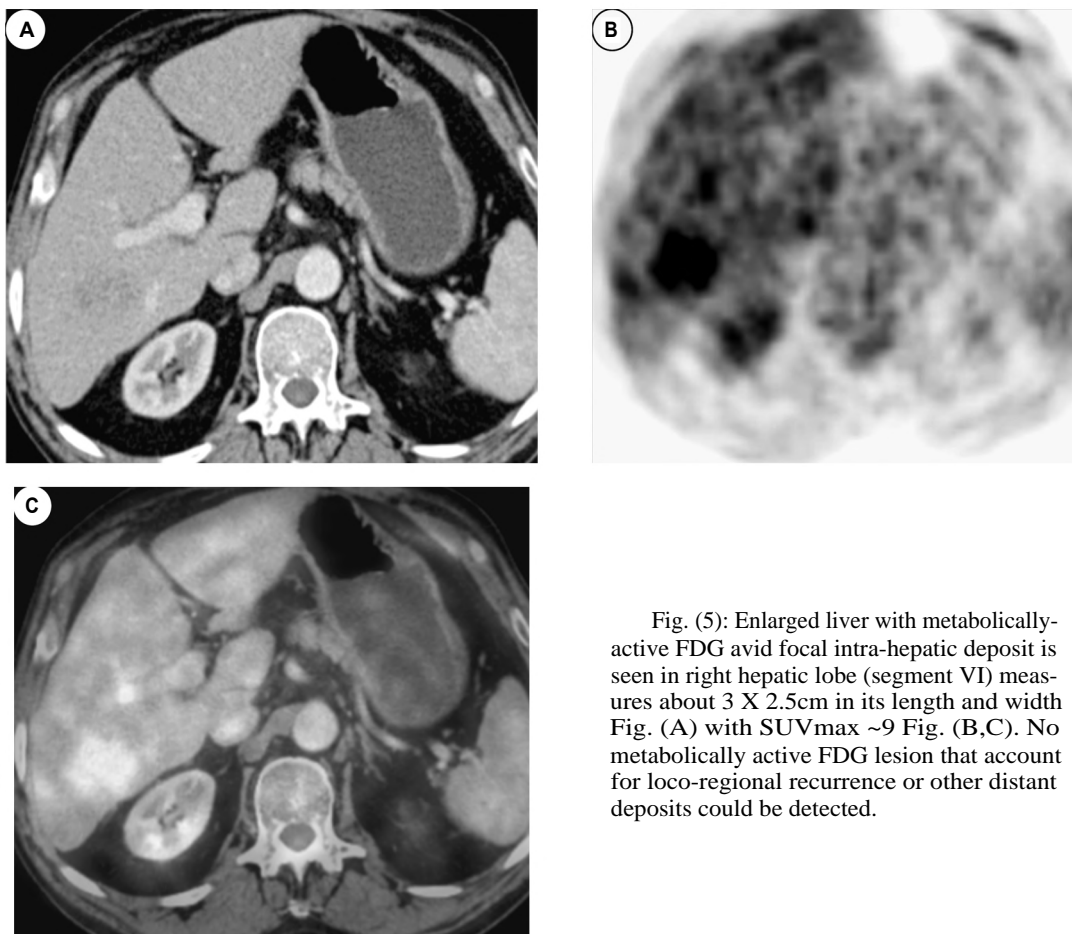


Fig. (5): Enlarged liver with metabolically-active FDG avid focal intra-hepatic deposit is seen in right hepatic lobe (segment VI) measures about 3 X 2.5cm in its length and width Fig. (A) with SUVmax ~9 Fig. (B,C). No metabolically active FDG lesion that account for loco-regional recurrence or other distant deposits could be detected.

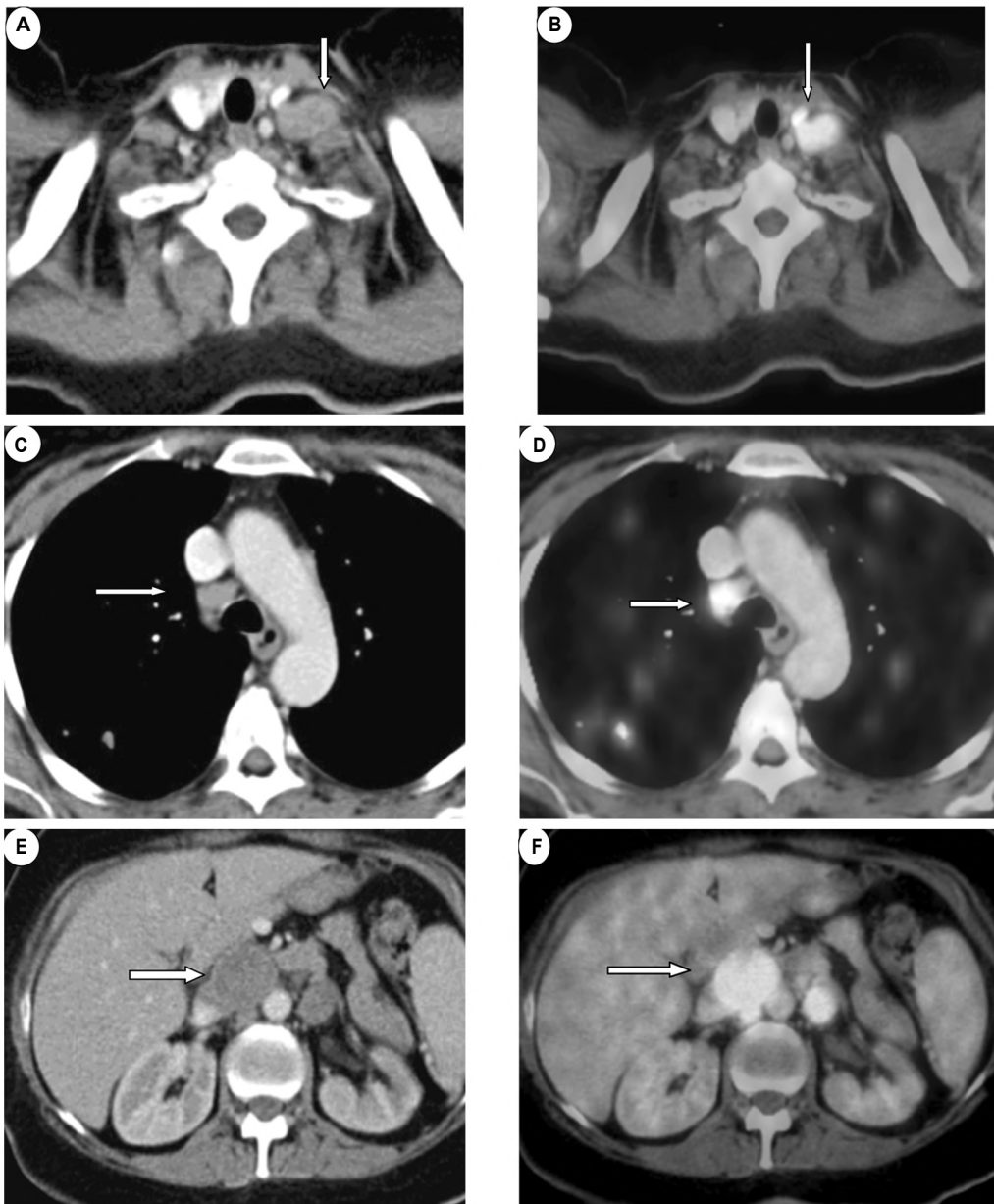


Fig. (6): Multiple enlarged metabolically active lymph nodes in different partients. A, B: Left lower deep cervical lymph node; C, D: Pretracheal lymph nodes; E, F: Enlarged metastatic retroperitoneal lymph nodes.

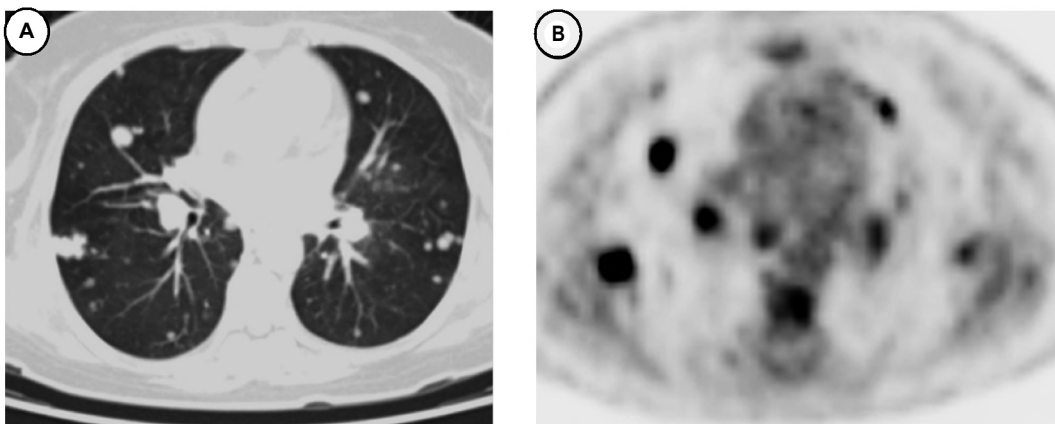


Fig. (7): Multiple variable sized metastatic lung nodules scattered in both lungs, appear metabolically active on FDG-PET/CT.

## Discussion

The differentiation between post-operative benign changes and the true local recurrence is challenging and difficult task [8]. Previous studies indicated the diagnostic value of CT, MRI [13-15] and FDG-PET [16-18] in diagnosis of primary CRC and its post therapy recurrence. Relatively recently multiple studies have stressed role of FDG PET/CT as an integrated modality in the evaluation of CRCR [19-22] and can change the stage of 10-65% of post-operative patients [8,23,24]. Patel et al., [25] in a systematic review evaluating the role of PET/CT found no sufficient evidence of the use of PET/CT in routine follow-up in patients with CRC. On the other hand Lu et al., [26] in a review of eleven studies, found that 18F-FDG PET and PET/CT were valuable in the follow-up of patients of elevated CEA and suspected disease recurrence. Also, Sanli et al., [27] observed that whatever the CEA levels, 18FFDG PET/CT still can detect rectal or colonic tumor recurrence. The same conclusion was shown by Ozkan et al., in a study included 76 patients [28]. In the current study, PET/CT had a sensitivity 92%, specificity 91.89%, PPV 88.46%, NPV 94.44% and overall accuracy 91.94% in detection of CRCR. We had three false positive cases and two false negative cases. The false positive cases were attributed to inflammatory processes at site of surgery. The false negative cases were recurrent mucinous adenocarcinoma which is know to be low FDG avid tumor. The PET/CT had considerably higher sensitivity and specificity than contrast enhanced CT, similar to results of votrobuva et al., [8] and Han et al., [29]. PET/CT combines the advantages of functional imaging and morphological imaging. The PET portion provides the useful functional information, which should be earlier than morphological changes. The CT element provides the important anatomical and morphological resolution. In addition, if the increased glucose utilization is due to post-operative changes, the CT morphology can suggest the correct diagnosis [8].

On PET/CT the false positive results may be due to post therapy inflammatory processes or granulation tissue and might be due to physiological causes, on the other hand the false negative results may be due to small lesions with few malignant cells and non detectable with FDG-PET [30,31]. Regarding metastatic deposits, including lymphadenopathy, PET/CT had seven false positive cases and three false negative cases, the overall accuracy of the PET CT in detection of metastasis is 88.64%. PET/CT is obviously superior over CT in detection of metastasis including lymph node metastasis,

hepatic, pulmonary, osseous and/or peritoneal dissemination. In the current study, the overall accuracy of CT was 78.41% in detection of distant metastasis. This means that FDG-PET/CT may provide chances to select suitable patients for surgical resection and unnecessary surgery would be avoided [32,33].

Serum CEA is a tumor marker used for detection of recurrent tumors and monitoring the therapy in CRC patients. In the current study, the CEA had sensitivity 82.22%, specificity 52.94%, PPV 82.22%, NPV 52.94% and accuracy 71.84. CEA is a conventional method in post-operative follow-up, but when a high serum level of CEA is encountered, the, imaging will be necessary to detect the site of possible recurrence or metastasis. Also, CEA has some pitfalls, like CEA levels may increase in smokers, in patients with inflammatory bowel disease, pancreatitis, liver disease and in patients with epithelial tumors at other sites. On the other hand a normal CEA level also does not rule out tumor recurrence [34].

One limitation of the study deserve mention. Pathological confirmation was not performed in all cases, depending on the assumption that regular follow-up may be sufficient in some cases.

## Conclusion:

In patients with suspected CRCR, FDG-PET/CT is significantly more accurate than CT alone for detection of local recurrence and distant metastasis. FDG-PET/CT is adequately discriminating to become a standard follow-up of patients after colorectal cancer resection.

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## متابعة ما بعد الجراحة لسرطان القولون والمستقيم: التصوير المقطعي أو التصوير المقطعي بالإشعاع البوزيتروني F-18؟ هذا هو السؤال

في مصر، يعتبر سرطان القولون والمستقيم سابع أكثر أنواع السرطان شيوعاً. ويحدث إرتداد الورم في 30-50% من المرضى بعد العمليات. كل من التصوير المقطعي المحوسب (CT) والتصوير المقطعي بالإشعاع البوزيتروني (PET) راسخان في تشخيص تكرار الإصابة بسرطان القولون والمستقيم.

في الدراسة الحالية، كنا نهدف إلى تقييم الأداء التشخيصي للتصوير المقطعي والتصوير المقطعي بالإشعاع البوزيتروني في متابعة ما بعد الجراحة لمرضى سرطان القولون.

إشتملت الدراسة على 62 مريضاً وإستخدمت النتائج النهائية للمتابعة السريرية للنسج المرضى والرسمية كمييار لتحديد حساسية التشخيص للتصوير المقطعي والتصوير المقطعي بالإشعاع البوزيتروني.

كانت حساسية وخصوصية ودقة التصوير المقطعي بالإشعاع البوزيتروني في تشخيص إرتداد الورم 92%، 91.89% و 94.44% على التوالي. كانت حساسية وخصوصية ودقة الأشعة المقطعية في تشخيص إرتداد الورم 72%، 89.19% و 82.05% على التوالي. كانت حساسية وخصوصية ودقة التصوير المقطعي بالإشعاع البوزيتروني في تشخيص ورم خبيث بعيد 91.12%، 81.08% و 88.64% على التوالي.

في المرضى الذين يشتبه في وجود إرتداد الأورام القولون، يبدو أن التصوير المقطعي بالإشعاع البوزيتروني طريقة أكثر دقة من الأشعة المقطعية وحدها للكشف عن التكرار المحلي والإنبثاث البعيد.