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Patient And Lesion-Based Analysis Of 18F-FDG PET/CT Compared With Conventional CT During Follow Up of Patients With Colorectal Carcinoma

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ABSTRACT:

Objective: The aim of this study was to evaluate the potential significance of 18F-FDG PET/CT in detection of local or distant disease recurrence during routine follow up of patients with colorectal cancer (CRC) in comparison with conventional CT. **Methods:** Sixty seven patients (43 males and 24 females; age range 32-72 years, mean 55.7±9.2 years) with histologically proven CRC previously treated by surgery and chemotherapy. 18F-FDG PET/CT and conventional CT were performed for all patients. Diagnostic ability was determined on a patient and on a lesion site basis (loco-regional recurrence, hepatic or extra-hepatic metastases that include LNs, bone and other sites). The final diagnosis was obtained from the results of histo-pathological examination after surgery or biopsy, or follow-up after at least 6-12 months on the basis of clinico-radiologic or follow up PET/CT. **Results:** On patient-basis analysis, PET/CT showed higher sensitivity, specificity and accuracy than CT in detection of local recurrence and metastatic lesions (94.6%, 100%, and 95.5% for PET/CT versus 83.9 %, 100% and 86.6% for diagnostic CT, respectively). On lesion-basis analysis, loco-regional recurrence was present in 23 patients, PET/CT detected all 25 lesions (100%) compared to 14/25 lesions (56%) detected by CT. Twenty-six Liver metastatic lesions were detected in 12 patients, PET/CT and CT accurately detected 22/26 (84.6%) and 21/26 (80.7%) hepatic lesions, respectively. PET/CT identified 32/42 LNs (76%) versus 23/42 LNs (55%) identified by CT in 19 patients. PET/CT had higher detectability of bone deposits than CT. PET/CT definitely changed the treatment modality in 28/67 patients (41.8%). PET/CT showed recurrent disease in 5/18 patients with elevated carcino-embryonic antigen who had negative CT.

Conclusion: 18F-FDG PET/CT provides high accuracy for detection of recurrent and distant metastases than conventional CT in CRC patients during regular follow up. PET/CT changed the management strategy in a significant number of patients on lesion-based analysis. The use of 18F-FDG PET/CT in the regular follow up of CRC patients is worth considering.

Key words: colorectal cancer; lesion-basis analysis; CT; 18F-FDG PET/CT.

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INTRODUCTION:

Colorectal cancer (CRC) is the third most common cancer diagnosed, and is associated with high rates of incidence and mortality for both men and women [(1)]. In Egypt, CRC accounts for 6.53% of all cancers according to the National Cancer Institute, Cairo University [(2)]. If colorectal cancer has already spread to distant organs, the long term survival is much lower [(3)]. Furthermore, despite progress that has been made in the treatment of advanced cases of CRC, the clinical outcome of this disease still remains poor with recurrence and/or metastasis occur in 30-50% of the patients after surgery [(4)].

Contrast-enhanced CT is currently the most established and important tool for restaging in patients with suspicion of CRC recurrence[(5)]. MRI is often used for detecting pelvic recurrence of colorectal cancer due to its excellent soft tissue resolution[(6)]. However, post therapy differentiated tumor recurrence or small intra-abdominal lymph node metastases may be missed in CT or MRI [(7)].

FDG-PET provides functional information and has been found to be accurate in the detection of CRC and its distant metastasis. However, based on its limited spatial resolution, FDG-PET, often makes exact anatomical localization and demarcation of the lesion difficult, thus Fusion of functional PET with CT morphological data has provided benefit for tumor restaging and detection of metastatic spread in clinical practice using combined PET/CT imaging [(8)]. There is no agreement as to whether FDG PET/CT screening for advanced colorectal neoplasms is meaningful[(9)].

Aim of work: The aim of this study was to evaluate the potential significance of 18F-FDG PET/CT in detection of local or distant disease recurrence during routine follow up of patients with CRC in comparison with conventional CT.

PATIENTS AND METHODS:

Patient population: This prospective study included 67 patients with histologically diagnosed CRC previously treated surgically and with chemotherapy. Patients were referred to PET/CT department at the International Medical Center (IMC) during the period between December 2008 and January 2011 with presence of recently increased serum tumor marker carcino-embryonic antigen (CEA), equivocal conventional radiological findings or clinical symptoms suspecting either loco-regional recurrence or distant metastasis during follow up. PET/CT results were compared to the results of conventional CT. The study was approved by the local scientific and ethical committee.

Patient preparation : Sixty seven patients (43 males and 24 females; age range 32 to 72 years, mean 55.7±9.2 years) with CRC underwent 18F-FDG PET/CT examination, the image data of diagnostic multi-slice CT scans of the abdomen/pelvis was acquired within 10 days prior to our study. Patients fasted for 6 hours before injection of 370-555 MBq (10-15 mCi) 18F-FDG via intravenous line. Diabetic patients were controlled prior to the study and blood glucose levels did not exceed 160 mg/dL. Patients were instructed to avoid any kind of strenuous activity prior to the examination and following injection of the radioisotope to avoid physiologic muscle

uptake of FDG and were asked to void prior to scanning.

Image acquisition:

Integrated 18F- FDG PET/CT Imaging: Whole body imaging was performed using a combined PET/CT scanner GEMINI TF; 64-slice PET/CT system; PHILIPS Medical Systems Nederland B.V.MDCT covered a region ranging from the meatus of the ear to the mid-thigh. The technical parameters of the 64-detector row helical CT scanner were a gantry rotation speed of 0.5 s and a table speed of 24 mm per gantry rotation. The PET component of the combined imaging system had an axial view of 16.2 cm per bed position) with an inter-slice spacing of 3.75 mm in one bed position and provided an image from the meatus of the ear to the mid-thigh. The trans-axial field of view & pixel size of the PET images reconstructed for fusion were 58.5 cm and 4.57 mm respectively, with a matrix size of 128×128. Scanning started 60-90 min after tracer injection (5–7 bed positions; acquisition time, 2-3 min/bed position adapted according to the patient's weight). Contrast agent was administered in the form of negative oral contrast (water with 5 % mannitol) 1 hour prior to study & Intravenous contrast (Non Ionic) injected at the time of imaging. Initially, patients were examined in the supine position with arms elevated, and CT scanning was started with the following parameters: 40 mAs; 130 kV; slice thickness, 2.5 mm; pitch, 1.5. The CT scans were acquired during breath holding within the normal expiration position and reached caudally to the mid thighs. PET over the same region was performed immediately after acquisition of the CT images. Patients were instructed to take normal breathing during the PET and hold breath during the CT part of the study. Attenuation correction of PET images was performed by using attenuation data from the low dose CT component of the examination; emission data were corrected for scatter, random events and dead-time losses by using the manufacturer's software. Images were reconstructed as 5-mm slices applying a standard iterative algorithm (ordered-subset expectation maximization).

Attenuation-corrected PET images, contrast-enhanced CT or non-contrast enhanced CT images and co-registered fused images were displayed together on the monitor. Non-attenuation corrected images are checked to avoid artifacts due to use of CT based attenuation correction.

Conventional CT images: CT images were viewed in coronal, axial and sagittal sections. Peritoneal implantation was diagnosed when nodular, plaque-like or infiltrative soft tissue lesions with abnormal enhancement were seen in the peritoneal fat or on the peritoneal surface. Lymph nodes (LNs) with a short-axis diameter greater than 1 cm were defined as malignant. Furthermore, the presence of a central un-enhancing area suggesting central necrosis was considered a sign of malignancy, and the presence of peripheral low attenuation suggesting a fatty hilum within a LN was considered a benign sign, regardless of node size.

Study interpretation: The PET, CT, and fused PET/CT Images were separately interpreted by 2 experienced nuclear medicine physicians and were compared to PET/CT images. Qualitative assessment for presence of hyper-metabolic lesions was evaluated on corrected PET images. Semi-quantitative evaluation was performed using the Standardized Uptake Value (SUV max), of all abnormal foci (Normal < 2.5). Comparison with other clinical and diagnostic methods including laboratory,

bone scan, diagnostic CT or MRI were done. Criteria used for the evidence of recurrence were histopathological confirmation of suspicious lesions, further clinical follow-up 6-12 months suggestive of disease recurrence, tumor markers and other independent imaging studies (such as CT, MRI, PET/CT, bone scan and ultrasound). Focal hyper-metabolic activity within the liver greater than adjacent normal liver was considered abnormal. Diffuse mild activity in the bowel was considered normal physiologic uptake, while focal uptake equal or higher than liver uptake is considered abnormal, lymph nodes with increased glucose uptake were considered positive for metastatic spread even if they were smaller than 1 cm in short-axis diameter. Conversely, lymph nodes with no detectable tracer uptake less than mediastinum uptake were considered negative for metastatic spread, even if they were larger than 1 cm in short-axis diameter.

Data analysis:

True-positive lesion is defined as a focal active lesion seen on FDG PET/CT images and found to be positive for tumor tissue at histological examination or clinical/ radiological follow up.

False-positive lesion is defined as a focal active lesion seen on FDG PET/CT images and found to be negative in tumor tissue at histological examination or clinical /radiological follow up.

True-negative lesion is defined when no lesion was seen on FDG PET/CT images and the results at histological examination or clinical/radiological follow up were also negative.

False-negative lesion is defined as a lesion that was missed in FDG PET/CT–image analysis but was found to be positive for malignancy at histological examination or clinical/radiological follow up.

Diagnostic ability was determined on a patient basis and on a lesion site basis (loco-regional recurrence, hepatic or extra-hepatic metastases that include LNs, bone and other sites). The final diagnosis was obtained from the results of histo-pathological examination after surgery or biopsy, or follow-up after 6-12 months on the basis of clinical and imaging studies including ultrasound, CT, MRI, bone scan or PET/CT.

Statistical analysis

All data were collected, summarized, presented and analyzed by using appropriate statistical program SPSS version 20. The sensitivity and specificity of PET/CT and CT were calculated for the detection of loco-regional recurrence, metastatic nodal lesions, hepatic and extra-hepatic metastases. Accuracy was represented with the terms sensitivity and specificity using standard statistical formulae to compare PET/CT with CT results during follow up of patients.

RESULTS:

(Table 1): Patient characteristics in 67 patients with colorectal carcinoma.

Parameter	All patients No=67
Age range (years) (mean±SD)	32-72 55.7±9.2
Sex:	
Males	43 (64.2%)
female	24 (35.8%)
Primary site:	
Colon	36
Rectum	19
Sigmoid	5
Colorectal	4
Recto-segmoid	2
Ano-rectal	1
Carcino-embryonic antigen (CEA)	
Positive	18 (26.9%)
Negative	49 (73.1%)

Patient-based analysis:

In 56 out of 67 patients (83.5%), proved to have recurrence and/or distant metastasis was confirmed by histo-pathological examination after surgery or biopsy, or follow-up after at least 6-12 months. The remaining 11 patients (16.5%) were free of disease at the end of the study. 18F-FDG PET/CT was true positive in 53 out of 56 patients with sensitivity of (94.6%) with recurrence or metastases and while true negative in all 11 patients (100% specificity) without recurrence or metastases. was avidest the PPV, NPV and accuracy were. 95.5% and 86.6%. PET findings were false-negative in 3 patients with liver metastases detected by CT.

CT findings showed true positive results in 47 out of 56 patients with sensitively of (83.9%) and showed true negative results in all 11 patients (100% specificity). proved to be free of disease recurrence or metastases. False negative results were seen in 9 patients (4 with loco-regional lesions, 3 with hepatic lesions, 1 with iliopsoas muscle lesion and 1 with bone metastases); all detected by PET/CT **(Fig. 1).** (**Table 2**) shows the Diagnostic performance of PET/CT and CT in detection of recurrent and metastatic CRC showed higher sensitivity, negative predictive value and accuracy for PET/CT as compared to CT **(Table 2).**

(Table 2): Patient based analysis for detection of recurrent and metastatic CRC using 18F-FDG PET/CT and diagnostic CT.

Parameter	PET/CT	Diagnostic CT
Sensitivity %	94.6	83.9
Specificity %	100	100
PPV %	100	100
NPV %	78.6	55.0
Accuracy %	95.5	86.6

PPV = positive predictive value; NPV = negative predictive value.

(Table 3) Lesions based analysis in detection of loco-regional recurrence or metastatic lesions.

Site of recurrence	No	PET/CT	Diagnostic CT
Loco-regional	25	25 (100%)	14 (56%)
Liver	26	22 (84.6%)	21 (80.7%)
Lymph nodes	42	32 (76%)	23 (55%)
Extra-hepatic	14	14 (100%)	8 (57%)

Lesion-based analysis. On lesion based analysis, recurrent or metastatic lesions were classified into three major categories; loco-regional (local recurrence and LN lesions), hepatic and extra-hepatic lesions **(Table 3).** The last category is subdivided into pulmonary, peritoneal, abdominal wall, and bone metastases. 18F-FDG PET/CT was superior to CT in detection of local recurrence in all 25 local recurrent lesions (100%) compared to only 14 out of 25 lesions (56%) detected by CT. surgical decision was conducted in 15 patients. **(Fig 1) represents a case with true positive PET/CT for local recurrence and para-aortic LNs metastases.**

Twenty six metastatic liver lesions proved to be positive at final diagnosis were present in 12 patients. PET/CT and CT accurately detected 22 lesion (84.6%) and 21 lesions (80.7%) respectively. PET-CT was able to detect additional 5 hepatic lesions not detected by CT, while CT detected 4 lesions that were missed by PET-CT.

Final positive lesions were seen in 42 LNs in 19 patients. PET/CT detected 32 LNs (76%), While the missed 10 LNs were missed by PET/CT (two iliac LNs and one LN in each of the left axillary, pretracheal, omental, left para-aortic, retrocaval, pretracheal, subcarinal and inguinal regions). On the other hand, CT detected 23 positive LNs (55%), the missed 19 LNs were located in (hilar, paracaval, paratracheal, supraclavicular, obturator, mesentric, pelvic and iliac regions). All The 9 missed lesions by CT were detected by PET/CT. PET/CT detected 14 extra-hepatic lesions including (3 peritoneal lesions, 2 pulmonary lesions, one uterine invasion, one abdominal wall nodule at site of operation scar, one Iliopsoas muscle metastasis and 6 osseous bone lesions). Diagnostic CT detected only 8 lesions of them. **Fig. 2** shows extrahepatic lung metastases from rectal cancer.

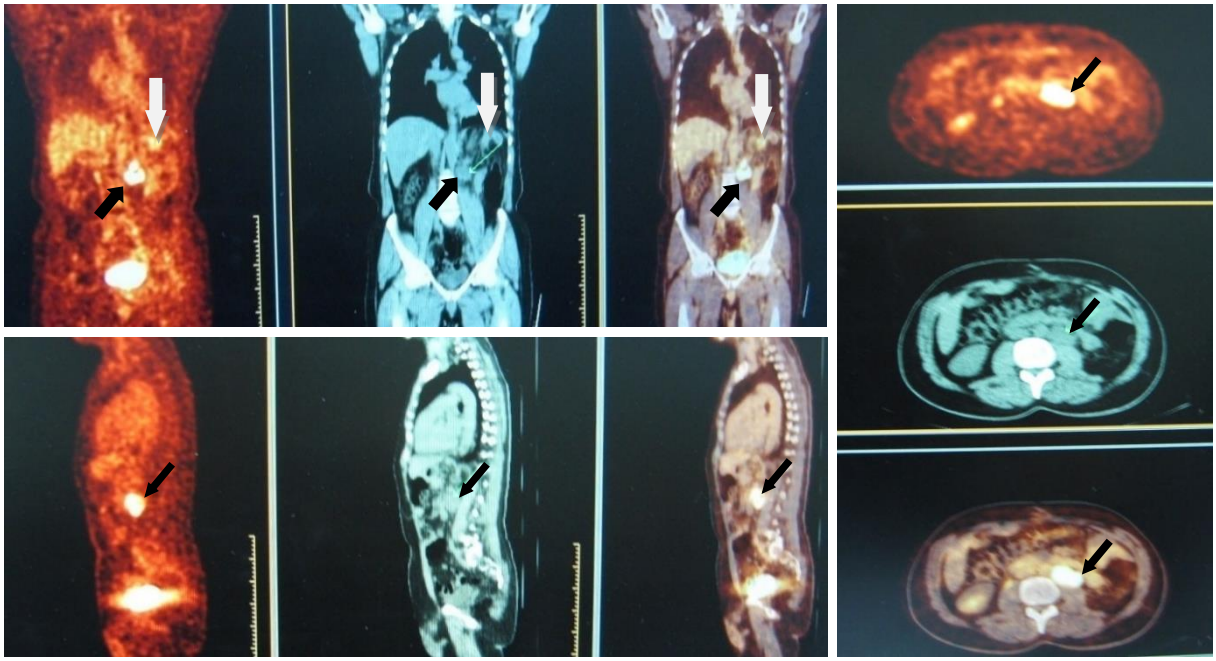

Fig 1. 54 year old male with recurrent colonic adenocarcinoma in the splenic flexure. Transaxial, coronal and sagittal images show FDG PET/CT uptake in the operative bed denoting local recurrence (white arrows) and left para-aortic LNs metastases (black arrows). CT findings were false-negative for local recurrence lesion.

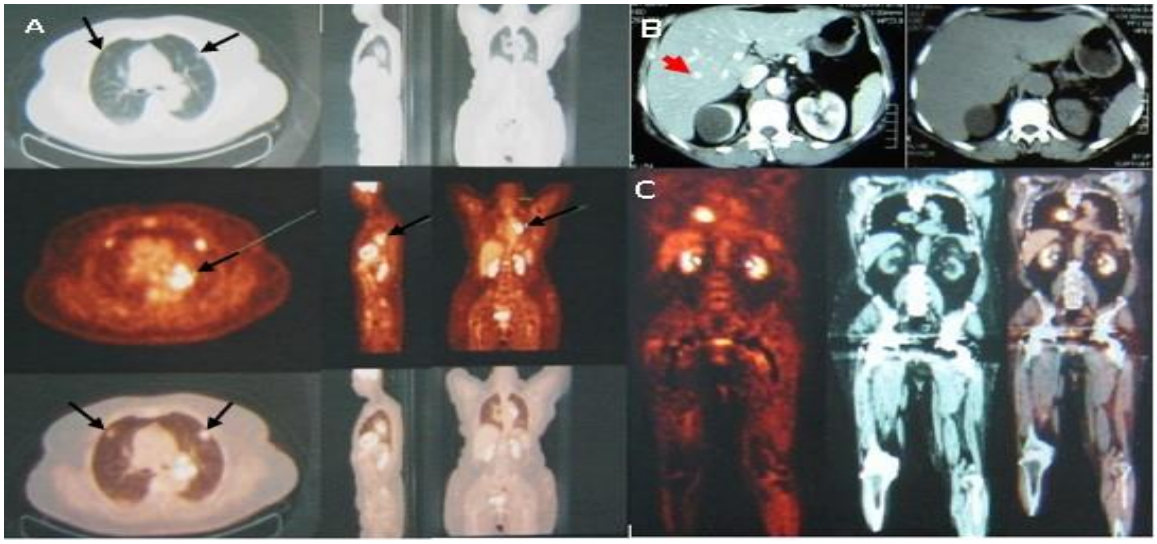

Fig 2. A- Base-line 60 year old female with rectal carcinoma, 18F-FDG PET/CT scan A- Transaxial, sagittal and coronal (from LT to RT) images show FDG uptake in multiple bilateral lung metastases (black arrows). B- Contrast enhanced CT shows equivocal liver lesion as hyperdense nodule in segment VIII of liver in arterial phase (LT, red arrow), while venous phase (RT) is free. C- Follow-up PET/CT after 6 months confirmed lung metastases while hepatic lesion shows no FDG uptake and proved to be focal nodular hyperplasia.

Follow up carcino-embryonic antigen level was elevated in only 18 patients (26.9%). PET/CT showed recurrent disease in the all 18 patients, 5 patients out of them were negative by CT. Collectively, 18F-FDG PET/CT changed the treatment modality in 28 out of our total 67 patients (41.7%) in which PET/CT was being able to detect recurrent and/or metastatic lesions during their regular follow up that were not detected by diagnostic CT.

DISCUSSION:

Local and distant recurrences of CRC occur in 30–50% of patients during follow-up after primary surgery [(10)]. Accurate detection of recurrent CRC remains a clinical challenge. 18-F-fluorodeoxyglucose PET/CT -positron emission tomography allows direct evaluation of cellular metabolism [(11)].

PET/CT is not routinely done for patients with CRC during their follow up unless there was an equivocal lesion seen on conventional imaging modalities. Thus the aim so, we aimed at this study is to reconsider the necessary introduction of PET/CT as a crucial part in routine follow up of these patients.

The final diagnosis of recurrence and/or metastases based on patient analysis was evident in 83.5% in our patients with a sensitivity, specificity and accuracy of 94.6%, 100%, and 95.5% for FDG-PET/CT versus 83.9 %, 100% and 86.6% for CT scan, respectively. These findings match the results of several studies; **Kalu et al**. compared the results of PET/CT and CT scan in 69 patients for assessment of recurrence or metastatic lesions, they reported a sensitivity, specificity, and accuracy for malignant findings of 98%, 94% and 97% for FDG-PET/CT compared with 85%, 91% and 89% for CT scan, respectively [(11)].

Also, **Hirakawa et al.** reported the sensitivity and specificity of PET/CT for detecting colorectal recurrent lesions were 96% and 98% respectively. They concluded that tumors ≤10 mm were significant factors for false-negative PET/CT [(12)].

In the current study, FDG-PET/CT affect the clinical management in 28/67 patients (41.8%) by guiding further management. Surgical decision was conducted in 15 patients of them based on PET/CT results. Similary, **Kalu et al**. found that FDG-PET/CT influenced surgical decisions in 23.6% of their 69 patients with proven recurrent CRC [(11)].

Detection of liver metastases in 12 patients in the present study showed nearly similar sensitivity results using, 18F-FDG PET/CT and diagnostic CT in detection of (84.6%) and (80.7%) of metastatic lesions. Based on lesion based analysis, similarly respectively. PET-CT was able to detect 5 hepatic lesions not seen by CT, while CT detected 4 lesions that were missed by PET/CT. This─could be explained by whether CT was done with contrast or not, degree of differentiations and size of hepatic lesions. On the other hand, **Kitajima et al**, in their study of liver metastases of colorectal origin, found that the diagnostic sensitivity and specificity for both CT, PET/contrast-enhanced CT was 93.3% and 98.6 % respectively [(13)].

For detection of lymph node involvement, PET/CT had relatively 76% sensitivity ~~low~~ which is (76%) but still higher than that of conventional CT (55%). The reasons for

low sensitivity might be due to small sized lesions that were difficult to distinguish and localize especially in the abdomen and pelvis, where physiologic uptake in the gut may mask them. **Kitajima et al**. mentioned that the sensitivity and specificity for detection of recurrent LNs lesions differ with the use of contrast enhancement material with PET/CT that improves sensitivity for abdominal and pelvic LNs (88.9% vs 94.4% for abdominal LNs and 85.7% vs 92.9% for Pelvic LNs). **(13).**

In the current study, PET/CT detected further extra-hepatic lesions not identified by CT in 5 patients. Similar to our results, **Israel and Kuten** found that PET/CT had a superior rate of detection of extra-hepatic dissemination, with a sensitivity of 89%, compared with 64% sensitivity for CT **(14).** **Ozkan et al**. concluded that PET/CT is a safe imaging method that can be used in the determination of CRC recurrence in patients with elevated CEA levels, regardless of the CEA level **(15).** In this study, Follow up PET/CT showed additional recurrent disease in 18 patients with elevated CEA, 5 of them were negative by CT. Several studies support our findings, **Metser et al** performed a retrospective study on 50 patients with CRC and elevated CEA and they found that PET-CT was more sensitive than contrast-enhanced 64-slice MDCT in identifying sites of recurrent and metastatic disease (was 97.3% versus 70.3%) with similar specificities for both modalities (94.4%) **(16). Chen et al.** also found that recurrence and/or metastasis was detected in 91.7% (22/24) of patients with elevated serum CEA levels by 18F-DG PET/CT imaging, but his study included all cases of elevated CEA not only those with negative CT and positive PET/CT **(10)**.

CONCLUSIONS:

18F-FDG PET/CT is superior to diagnostic conventional CT, in both lesion-by-lesion and patient based analysis in detection of recurrent and metastatic lesions in colorectal cancer patients. 18F-FDG PET/CT changed the treatment strategy in a significant number of patients which helped in providing the best management that will guarantee better survival for CRC patients. Consequently, the use of 18F-FDG PET/CT in the regular follow up of CRC patients is worth considering.

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