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Accuracy of 18F-FDG PET/CT in monitoring therapeutic response and detection of loco-regional recurrence and metastatic deposits of colorectal cancer in comparison to CT

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Abstract

Background: The study shows the role of PET/CT in monitoring response to therapy in colorectal cancer as well as detection of loco-regional recurrence and metastatic deposits hence guiding the clinician to the proper management strategy. Sixty patients (41 male and 19 female) were included in our study. All patients are pathologically proven colorectal cancer. They had undergone 18F-FDG PET/CT for follow up post-therapeutic (operative, and/or chemotherapy and/or radiotherapy) follow up for metastatic or recurrent colorectal cancer during the period from September 2015 to August 2017.

Results: Our study demonstrated that FDG PET/CT is highly sensitive and specific in assessing local recurrence and distant metastasis in patient with pathologically proved colorectal cancer, with sensitivity 95.45%, specificity 97.3%, and accuracy 96.7% in detection of local recurrence; and sensitivity, specificity, and accuracy of 100% in detection of hepatic metastasis as well as in detection of nodal metastasis.

Conclusion: FDG PET/CT is an accurate modality in the treatment plan of cancer colon in monitoring therapeutic response as well as defining their local extent and distant metastatic disease thus provides valuable information that is very helpful in the clinical decision-making process.

Keywords: FDG PET/CT, Monitoring response, CRC, Colorectal cancer

Background

Colorectal cancer (CRC) is among the most commonly diagnosed cancers worldwide. In 2012, there were 1,360,000 new cases of CRC [1], Globally, greater than 1 million people get colorectal cancer yearly resulting in about 0.5 million deaths. It represents a cancer entity that not only involves the elderly but also an increasing number of younger patients [2, 3]. Risk factors for CRC include dietary, hereditary, and environmental influences

[4], which lead to the gradual accumulation of genetic mutations and epigenetic alterations that drive the development of tumors over decades [5]. More than 80% of CRCs arise from adenomatous polyps but less than 1% of adenomatous polyps which are smaller than 1 cm ever become malignant [6]. Advances in our ability to detect developing CRC has begun to refine the prognostic information available and define patient groups that are likely to benefit from systemic treatment or targeted therapies [7].

Exact and complete staging is indispensable to offer a potentially curative therapy approach to patients. Contrast-enhanced CT of the chest, abdomen, and pelvis

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is the most commonly used for staging colorectal cancer. However, it offers only morphological data for the evaluation of tumor stage, and small involved lymph nodes could be missed [8].

Currently, computed tomography (CT) is used to detect recurrence; however, it has a high false-negative rate for extrahepatic intra-abdominal lesions (e.g., para-aortic nodes) and a high false-positive rate for pulmonary lesions [9, 10]. This disadvantage has led to the increased use of 18F-fluorodeoxyglucose (18F-FDG)-positron emission tomography (PET)/CT as an imaging modality, in both preoperative assessment and during follow-up. 18F-FDG PET has presented high accuracy in the detection of recurrent and metastatic CRC [11].

Integrated FDG-PET/CT imaging is introduced in clinical practice where it combines both anatomical and functional data and is proving itself to be the most accurate method in terms of tumor staging, restaging, and therapy response assessment [12].

FDG-PET/CT is generally not used for the diagnosis of colorectal cancer owing to its cost and radiation exposure. FDG-PET/CT provides an accurate preoperative whole-body tumor staging in a single session with correct evaluation of the local extent (T) of the tumor and of the regional lymph nodes (N) that is essential for the planning of optimal therapy considering the many therapeutic options available including radical or limited resection, palliative derivative surgery, local excision, laparoscopic surgical approach, preoperative neoadjuvant chemotherapy, and/or radiotherapy [13].

Recurrence of colorectal cancer occurs in one-third of the patients in the first 2 years after resection. It can recur loco-regionally or at distant sites. Timely diagnosis of recurrence is of paramount importance, as radical treatment of the localized disease can prolong survival. PET/CT is routinely used in restaging and surveillance of colorectal cancer, as it can demonstrate recurrent disease with good accuracy [2].

Aim of the work

The aim of this study is to show the role of PET/CT in monitoring the response to the therapy in colorectal cancer as well as the detection of loco-regional recurrence and metastatic deposits, hence guiding the clinician to the proper management strategy.

Methods

Study design

The study was conducted on 60 patients referred to the radiology unit with pathologically proven colorectal cancer for 18F-FDG PET/CT, during the period from September 2015 to August 2017.

Inclusion criteria

- Patients under follow-up post-therapeutic (operative, and/or chemotherapy and/or radiotherapy) for colorectal cancer.
- Patients under follow up for metastatic or recurrent colorectal cancer.

Exclusion criteria

- Patients with inadequate renal function above 1.9 serum creatinine.
- Uncontrolled diabetes mellitus.
- Pregnant females.

18F-FDG-PET/CT imaging protocol

Whole-body FDG PET/CT was performed with combined PET/CT scanners (Philips GEMINI TF TOF 64 & Philips GEMINI LXL 16).

Patient preparation and examination performance

- Two to 3 days before the exam, the patient was handled an instruction sheet that includes:
- Twenty-four hours before the study, avoid physical exercise, keep the body warm, and avoid exposure to cold places till the time of the exam
- Patients can drink water as usual but with no sugar.
- Patients should be kept on a low carbohydrate, low sugar, no caffeine diet.
- Diabetic patients should take their medications at the dawn of the day of the exam with light breakfast without honey or jam.
- Fasting for 6 h before the exam.
- Oral medications can be taken during fasting with water only.
- Patient must bring the most recent CT, MRI, or relevant films and the reports on the day of the scan.
- In the radiology unit, patients were rested in an isolated room where:
- History was taken including diagnosis, biopsy, pathology, operations, chemo or radiotherapy, other medications, diabetes or other chronic diseases, allergy, and current complaint.
- Body weight was measured.
- Blood glucose level was measured (should be ≤ 150 mg %).
- Patients were instructed to drink 5% Mannitol for bowel opacification.
- I.V cannula was inserted.
- Patients then received an intravenous injection of 3–3.7 MBq/kg body-weight dose of 18F-FDG.

- Sixty minutes later, an initial low dose CT attenuation correction study was done by acquiring CT images from the mid-thigh to the base of the skull this took about from 30 to 60 s.
- A whole-body emission PET scan for the same axial coverage was performed with a 2-min acquisition per each bed position (the overall time of the PET scan was about 15–30 min).
- This was followed by an injection of 70 ml nonionic contrast media followed by 25 ml saline.
- Then a contrast-enhanced CT study was done which took about 30–60 s.
- After the exam, the patient was asked not to be exposed to pregnant females and children for about 24 h.
- PET, CT, and fused PET/CT images were generated for review on a computer workstation.
- All co-registered images were viewed with dedicated software.

Identifications of the lesions

Lesions were identified by the presence of a metabolically active tumor tissue having high FDG accumulation and correlated this activity to its anatomical site in the combined PET/CT images.

Results

- Our statistical analysis was made to find out the role of PET/CT in assessing patients with colorectal as regards staging, restaging (detection of loco-regional recurrence and metastatic deposits), and monitoring therapeutic response “as demonstrated in four cases under follow up” (Figs. 1, 2, 3, and 4).
- Table 1 explained the distribution of the studied group as regard general data (gender and age).
- Regarding the percentage of patients who developed a local recurrence of the tumor after therapy, we found that 22 cases developed a local recurrence (36.7% of the total studied cases) and 38 cases did not develop a local recurrence (63.3% percentage of the total studied cases) according to our examination.
- In our study, the total numbers of the examined cases were 60 patients; true positive cases were 21 patients, true negative cases were 37 patients, one false-positive case and one false-negative case.
- The false-positive case showed positive long segment enhancing rectal mural thickening around the anastomotic site with high FDG uptake (high SUVmax) but later after the second biopsy, it was proved to be a negative case (colitis); the follow-up examination which was done 6 months later with no treatment or further management shows regressive course regarding the mural thickening and metabolic activity.
- The false-negative case showed low SUV-max at the collapsed rectosigmoid colon site and at the presacral soft tissue sheet; the known false-negative results of colorectal mucinous adenocarcinoma was worrisome for a biopsy which proved positive tumor recurrence and follow-up studies after chemotherapy shows regression in the uptake and the size.
- According to the previous data, we could calculate the sensitivity, specificity, and accuracy of PET/CT in detecting the local recurrence in post-therapeutic patients of colorectal cancer. Sensitivity is 95.45%, specificity is 97.36%, and accuracy is 96.7%.
- The number of patients who developed metastatic deposits were 40 cases (66.7%). While 20 patients did not develop metastatic deposits (33.3%).
- The number of patients with hepatic metastatic deposits were 12 cases (20%). While 48 patients did not develop hepatic metastatic deposits (80%).
- The number of patients with local nodal metastatic deposits were nine cases (15%). While 51 patients did not develop nodal metastatic deposits (85%).

Comparison between PET/CT and CT as regards local recurrence

- The results were compared according to detect the local recurrence results of PET/CT and CT in correlation with histopathology.
- CT revealed 19 true positive cases, 37 true negative cases, three false-positive cases, and only one false-negative case with 95% sensitivity, 92.5% specificity, and 93.3% accuracy accordingly in correlation with PET/CT and histopathological findings. Table 2 compares PET/CT and CT in correlation with histopathology regarding local recurrence. It is noticed that PET/CT is superior to CT regarding sensitivity, specificity and accuracy in correlation with histopathology.

Comparison between PET/CT and CT as regards hepatic metastasis

- CT revealed 12 true positive cases, 45 true negative cases, two false-positive cases, and only one false-negative case with 92% sensitivity, 95.7% specificity, and 95% accuracy accordingly in correlation with PET/CT and histopathological findings. Table 3 compares between PET/CT and CT in correlation with histopathology regarding hepatic metastasis.

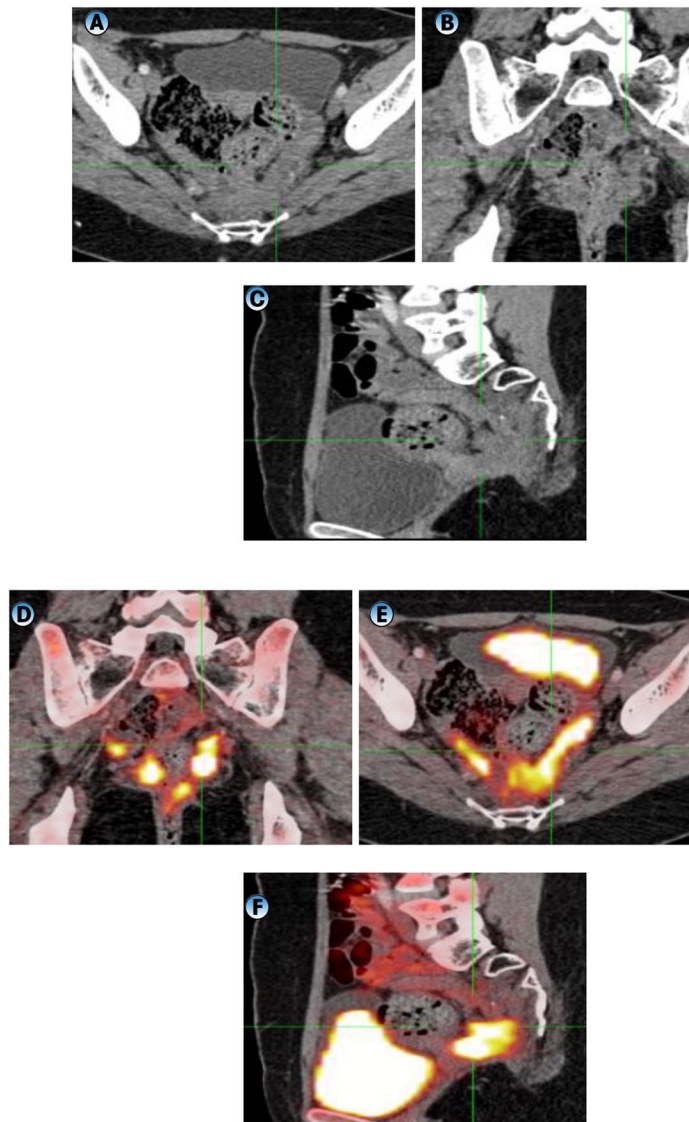


Fig. 1 A 36-year-old female patient with given history of treated cancer rectum 3 years ago (surgery, chemo and radiotherapy). Recent follow-up CT showed progression of pre-sacral soft tissue sheet and mild recto-sigmoid mural thickening, the patient came for PET/CT assessment. **a–c** Axial, coronal, and sagittal CT images of the pelvis showed pre-sacral soft tissue thickening extending to the terminal part of the colon which itself demonstrates circumferential thickening. **d–f** Axial, coronal, and sagittal fused PET/CT images of the pelvis. PET/CT showed increased FDG uptake with SUVmax 16.4 corresponding to this soft tissue thickening and proved to be local tumor recurrence

Comparison between PET/CT and CT as regards detection of local nodal metastasis

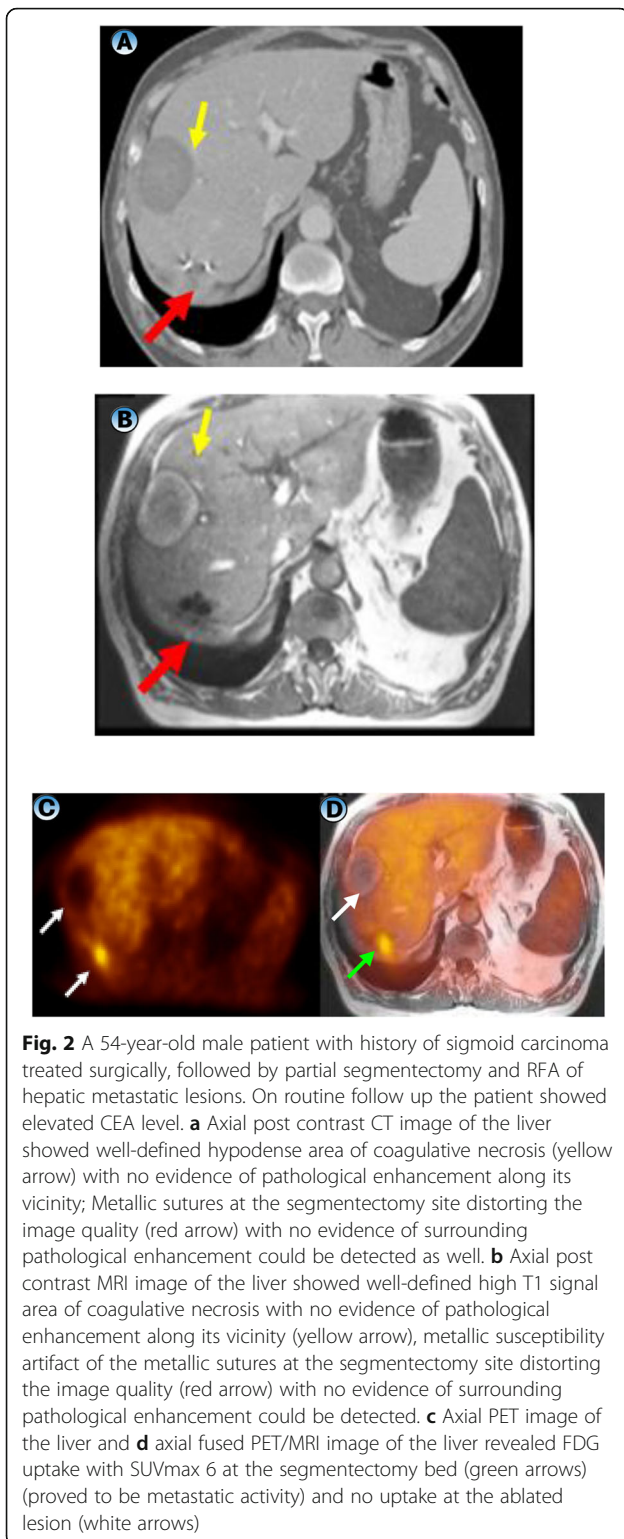
- CT revealed seven true positive cases, 49 true negative cases, two false-positive cases, and two false-negative cases with 77.8% sensitivity, 96% specificity, and 93.3% accuracy accordingly in correlation with PET/CT and histopathological findings. Table 4 compares PETCT and CT in correlation with histopathology regarding local nodal metastasis.

- It is noticed that PECT/CT is superior to CT regarding sensitivity, specificity, and accuracy in correlation with histopathology.

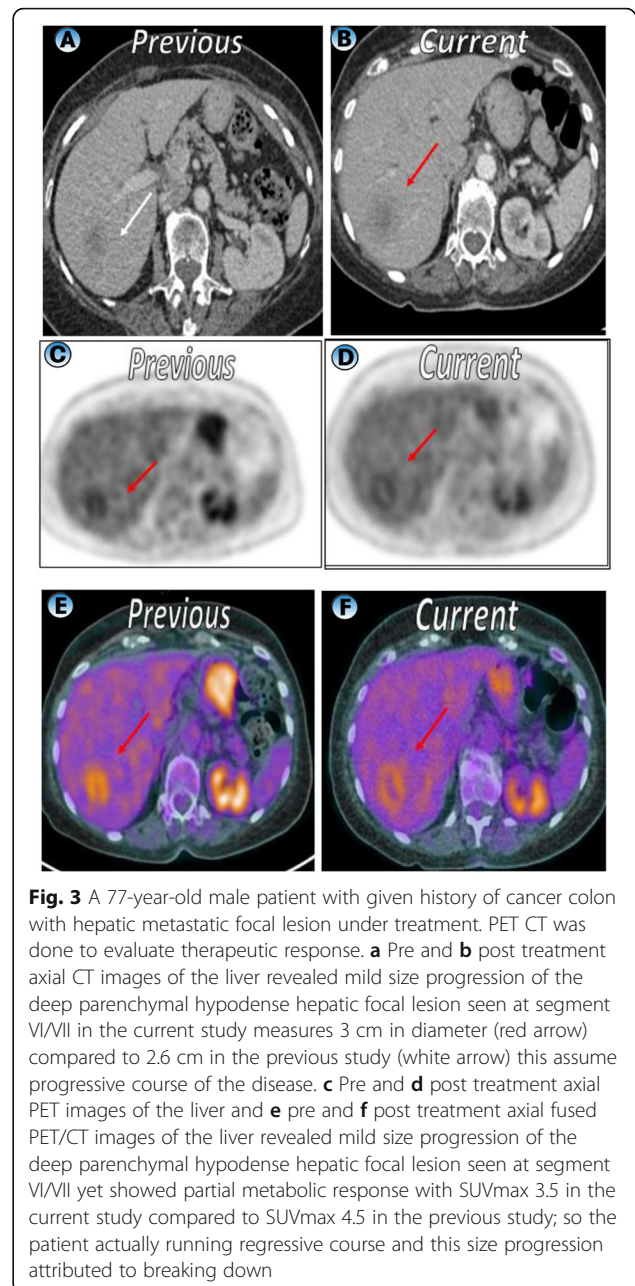
Discussion

Colorectal cancer is the third cause of cancer worldwide; it accounts for a large number of tumor-related deaths and recurrence occurs in about one-third of patients within the first 2 years after surgery [14].

Early detection of recurrent colorectal carcinoma has become more important in the past decade as the



treatment options for the localized disease have improved significantly. Therefore, detection of the tumor sites throughout the body is needed with high sensitivity and specificity [15].



Despite the fact that 70% of the patients have a chance of radical operation, 30–50% of them will develop metastasis or local recurrence within 2 years after the operation [16].

An effective imaging modality for restaging of patients with suspicion of recurrent disease is crucial as several studies have shown that surgery with curative intention may be possible even in patients with distant colorectal metastases [17].

Cross-sectional imaging modalities like computed tomography (CT) and magnetic resonance imaging (MRI) is usually the first tool for the evaluation of

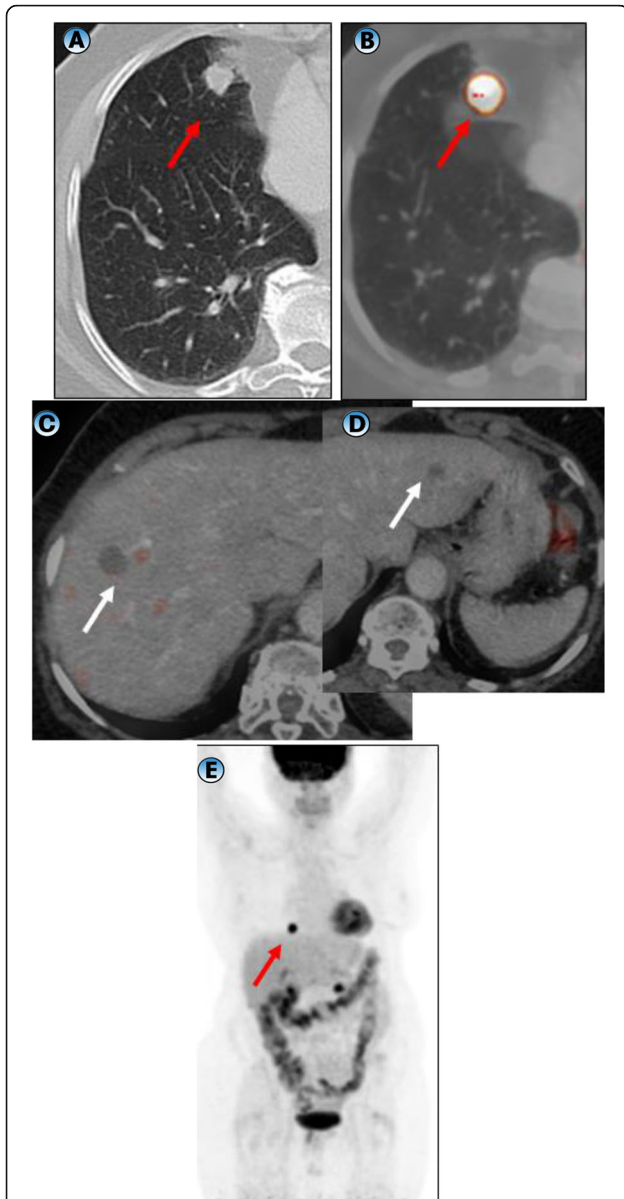


Fig. 4 Male patient 69 years old have colonic cancer underwent surgical resection and ended chemotherapy one month ago. Recent follow up CT showed right lung nodule and hepatic hypodense focal lesions. He was referred for further evaluation of the lesions. **a** Axial CT image of the right lung base showed solitary right middle lung lobe medial segment sub pleural pulmonary nodule with speculated outline and measures 1.3 cm in diameter (red arrow). **b** Axial fused PET/CT image revealed avid FDG uptake by the solitary right lung nodule with SUVmax 8.6 (red arrow). **c, d** Axial fused PET/CT image of the liver revealed no abnormal FDG uptake by hepatic bi-lobar hypodense focal lesions at segments II and VIII (white arrows) in keeping with benign etiology. **e** Whole body MIP PET image revealed avid FDG uptake by the solitary right lung nodule (red arrow) with no abnormal uptake elsewhere

suspected cases of rectal cancer that not only help in detection but also in local staging as well as in delineating the distant spread of cancer [18].

Table 1 Distribution of the studied group as regard general data

Gender and age	Number	Percentage %
Gender		
• Male	41	68.3%
• Female	19	31.7%
Age	53.81 ± 29	

High-resolution MRI of the pelvis with distension of rectum by positive contrast agent is an investigation of choice for local staging of rectal cancer due to its superior soft-tissue contrast resolution. MRI is superior to CT in local staging except in T1 and T2 stage where both have comparable accuracies [19].

An emphasis on the postoperative follow-up is the local recurrence and distant metastasis which could not be detected by traditional imaging techniques such as CT, MRI, and ultrasonography until the lesion reaches a considerable size. Monitoring by tumor markers was not always accurate and could not provide an orientation indication of the possible lesion [20].

¹⁸F-FDG PET enables detection of the increased glucose metabolic rate that is characteristic of most of the malignant cells. It has been demonstrated to be useful for the initial diagnosis, staging, detection of recurrence, and for the evaluation of chemotherapeutic or radiation therapeutic responses [21].

O'Connor et al. [22] stated that recurrence occurs in one-third of the patients within the first 2 years after resection and local recurrence is common in patients with rectal cancer ranging from 7 to 33%; we nearly agree with that as we diagnosed local recurrence in 36.7% of the total studied cases which is much less than Mittal et al. [23] who reported that PET/CT showed recurrences in 71% of post-operative CRC patients.

Ozkan et al. [7] and Lee et al. [24] evaluated a group of CRC patients using PET/CT in the detection of disease recurrence in postoperative patients and both studies agreed with our study in high sensitivity (97% and 95% respectively) yet disagree as regarding specificity (61% and 76% respectively) as our study has much higher specificity in the detection of the local recurrence.

Ronald et al. [25] and Whiteford et al. [26] both stated that mucinous colorectal carcinoma has low uptakes

Table 2 Comparison between sensitivity, specificity, and accuracy of PET/CT and CT regarding local recurrence

	PET/CT	CT
Sensitivity	95.45%	95%
Specificity	97.36%	92.50%
Accuracy	96.7%	93.3%

Table 3 Comparison between sensitivity, specificity, and accuracy of PET/CT and CT regarding detection of hepatic metastasis

	PET/CT	CT
Sensitivity	100%	92.3%
Specificity	100%	95.7%
Accuracy	100%	95%

than non-mucinous carcinoma on FDG-PET imaging and that the sensitivity of FDG-PET for mucinous adenocarcinoma is significantly lower than that for non-mucinous carcinomas which are totally aligning with our study.

Borasio et al. [27] showed that two-quarters of false-negative cases were mucinous adenocarcinoma and it demonstrated that mucinous carcinoma was the main factor responsible for false-negative scans. We disagree with that as we only diagnosed one false-negative case out of the 60 studied cases yet this may be attributed to our small sample size.

Yan Zhang et al. [28] stated that PET/CT showed better sensitivity and specificity (87–100% and 90–98%, respectively) for the detection of hepatic and extra-hepatic metastasis. Our study nearly agrees with that as sensitivity and specificity for the detection of hepatic and extra-hepatic metastasis is (100–96.7% and 100–98% respectively). These results are also comparable with Kazuhiro Kitajima et al. [29] who stated that FDG-PET and PET/CT have high accuracy for the detection and the staging of liver lesions in CRC patients pooled sensitivity and specificity of 93%.

O'Connor et al. [22] reported that enlarged and non-enlarged FDG avid lymph nodes can be identified in the mesentery on PET-CT, indicating the presence of regional lymph node metastases; this is encountered on re-staging patients with CRC. We agree with that as our study showed that PET/CT sensitivity and specificity in detecting regional lymph node are 100%; this not going with Sung Hoon Kim et al. [30] who demonstrated that nodal [18F] FDG uptake findings were highly specific for LN metastases status, but it had a relatively low sensitivity; this low sensitivity in this study was attributed to the fact that the later study excluded the patients who had received neoadjuvant treatment and they stated that I if

Table 4 Comparison between sensitivity, specificity, and accuracy of PET/CT and CT regarding local nodal metastasis detection

	PET/CT	CT
Sensitivity	100%	77.8%
Specificity	100%	96.08%
Accuracy	100%	93.33%

these advanced rectal cancer patients who underwent neoadjuvant chemotherapy were included in the present study, the LN detectability of [18F]FDG PET/CT may be improved because the majority of these patients have shown high nodal [18F]FDG uptake.

Conclusion

Our study revealed that FDG PET/CT has high sensitivity, accuracy, and specificity in the detection of loco-regional recurrence of CRC as well as detection of and metastatic deposits.

Our data suggests that PET/CT is an excellent option to replace CT in the follow-up of CRC patients.

PET/CT imaging provides a whole-body overview at one examination and it has become an efficient and accurate non-invasive examination technique in the post-operative follow-up of colorectal carcinoma as well as being a cost-effective way to differentiate the resectable from the non-resectable disease.

Limitations

In the current study, we had some limitations; first is the financial element as well as the availability of the machines are the main limitation of the study as positron emitted tomography-computed tomography (PET CT) is still of high cost and PET CT machines are not available in most of centers and hospitals; second is the potential of PET-CT for false-positive results due to the presence of inflammatory reaction; the potential of PET/CT for false-negative results is another limitation as adjuvant chemotherapy may interfere with FDG uptake. PET/CT has limitations in distinguishing the wall layers of the colon. High radiation dose is also another disadvantage of PET/CT study.

Abbreviations

CRC: Colorectal cancer; FDG: Fluoro-deoxy-glucose; PET CT: Positron emitted tomography-computed tomography; SUVmax: Standardized uptake value

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Not applicable.

Authors' contributions

WH made the design of the work and drafted the manuscript. GN revision of data, acquisition, and analysis of data. MA participated in the design of the study and interpretation of data. All authors have read and approved the manuscript.

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Availability of data and materials

The data used and/or analyzed during the current study are available with the corresponding author on reasonable request.

Ethics approval and consent to participate

The study done after approval of ethical board of Ain Shams university (the reference number is not appropriate) and an informed written consent was taken from each participant in the study.

Consent for publication

Written consent for publication was taken from all participants.

Competing interests

The authors declare that they have no competing interests.

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