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Research Article

Role of 18f-Fdg Pet/Ct in Detection of Colorectal Cancer Recurrence

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Abstract

Background: *Colorectal cancer (CRC) is the third most common cancer in the world. It is estimated that up to 40% of patients will present with recurrence after surgical resection of the primary tumor; often within the first few years after initial surgical resection.*

Objective: *The present study is aiming at emphasizing the role and value of 18FDG PET/CT in detection of colorectal cancer local, regional and/or distant metastatic disease recurrence as well as in follow up of patients with treated colorectal cancer.*

Patients and Methods: *This is a prospective study included 50 patients who were operated for colorectal neoplasm. The patients were investigated radiologically by means of 18F-FDG PET/CT for detection of recurrence.*

Results: *As regard site of recurrence, liver was the most common site for recurrence (34%), followed by peritoneum (24%), then lungs (16%). Multiple metastases were found in the liver, lungs, and – to less extent – bone. Local recurrence was found in 14/50 patients (28%) and regional lymph node recurrences was observed in 17 patients (34%). ROC curve analysis for PET/CT indicated that area under the curve was 0852, PPV was 86%, NPV was 47%, with 98% sensitivity, 92% specificity, and 96% accuracy (P <0.001).*

Conclusion: *It was concluded that 18F-FDG PET/CT is a good predictor of recurrence in colorectal cancer patients performed primary surgery. This imaging modality gives 98% sensitivity, 92% specificity, and 96% accuracy.*

Keywords: Colorectal cancer, PET/CT, recurrence.

Introduction

Colorectal cancer (CRC) is the third most common cancer in the world. It is estimated that up to 40% of patients will present with recurrence after surgical resection of the primary tumor; often within the first few years after initial surgical resection (1).

The current post-resection surveillance strategies involve physical examination, laboratory, endoscopy and imaging studies. Ultimately, the goal is to detect recurrent disease at the earliest possible instance, when it is potentially still curable with additional treatment (2).

Radiological imaging plays a major role for both early detection and differentiation of recurrent disease from benign findings, such as post-operative changes (3).

FDG PET/CT has been reported to have a very high sensitivity and specificity in the detection of CRC recurrence as it takes advantage the high rate of glycolysis in malignant tumor cells (PET), as well as precise anatomic correlation (CT) (4).

PET/CT has been shown to be superior to other conventional imaging modalities in evaluating for recurrence of CRC in patients with rising CEA and has been also useful in detecting recurrence in patients with normal or low CEA values but with suspicious clinical symptoms or radiological findings (5).

The present study is aiming at emphasizing the role and value of 18FDG PET/CT in detection of colorectal cancer local, regional and/or distant metastatic disease recurrence as well as in follow up of patients with treated colorectal cancer.

Patients and Methods

This is a prospective, non-controlled and non-randomized study, it is performed on 50 patients treated from CRC. The study was performed at the period of one year, from December, 2020 to December, 2021.

The Institutional Review Board (IRB) approval was obtained from Benha University for this study.

This study's inclusion criteria were: Adult patients of both sexes > 18 years who were under treatment of colorectal cancer and referred for follow-up after CRC treatment. Patients had other neoplasm than colorectal cancer and patients with blood glucose level > 150 mg/dl at the time of study as well as patients with known hypersensitivity to anyone of the radiological materials were excluded.

Methodology:

Complete personal and medical history were obtained, and general and local examinations were done for each participant.

Radiological evaluation:

1. Previous x-ray reports.

2. Previous radiological modalities such as ultrasonography (US), computed tomography (CT) or magnetic resonance imaging (MRI).

3. Previous radiotherapy.

4. PET/CT scan.

PET/CT scan protocol:

• Patients fasting for at least 6 hours before undergoing scanning.

• A standard dose of 1-1.5 mCi/kg of F-FDG was intravenously injected 45-60 min before imaging.

• Initially low dose CT was performed for attenuation correction.

• PET scanning was done immediately after the CT from skull to knees.

• This was followed by diagnostic CT using IV contrast administration.

• All data were acquired with a combined PET/CT in-line system and processed by a dedicated work station.

18F-FDG PET/CT Procedure

Whole-body images were obtained by PET/CT (Discovery VCT, GE Healthcare) in accordance with institutional procedures. The mean dose was 379 MBq of 18F-FDG. Blood glucose levels were less 150 mg/L in all patients. The PET/CT scan was acquired approximately 60 min after tracer injection. Low-dose CT was acquired in all patients, and diagnostic CT with intravenous iodinated contrast was performed. Patients may receive 100 ml of Iomeron® 400 mg iodine/mL, if needed (1).

Due to inconsistent reporting of maximum standardized uptake values (SUVmax) in clinical study reports, all images were independently reviewed by two radiologists with solid experience with PET/CT. Any discrepancy in diagnosis among the readers was solved by consensus. The readers were aware of the clinical

history and laboratory results at referral but blinded to the original PET/CT report, clinical follow-up, and pathology reports (1).

Classification of lesions on PET/CT was based on combined parameters from both PET and CT. The readers did not report the diagnostic outcome for each modality separately.

Methods of Analysis

• All co-registered images were viewed with dedicated software through PET/CT work station.

• The Pre- and post-contrast CT images were assessed to detect any areas of suspected lesions.

• PET acquired images with also assessed for any areas of increased tracer fixation.

• Combined images were also be assessed for correlation of tracer fixation areas with the CT findings.

• SUVmax value was obtained for any abnormal area with increased tracer fixation as well as for the liver, spleen and/or mediastinum as an internal organ reference for validation quantitation.

• Full history; including patient histopathology, treatment data and previous studies were reviewed.

• PET/CT results were compared with histopathology and/or tumor markers to determine the diagnostic value of the PET/CT in detection of loco-regional or distant metastatic recurrence.

Statistical analysis

Statistical analyses were performed using SPSS v23 statistical software (SPSS, Inc, Chicago, Illinois). Descriptive statistics (means correlation standard deviations) were calculated for quantitative variables. Two-sided Chi-square, student-t and ANOVA test were used as appropriate for parametric data, and Mann-Whitney U and Kruskal Wallis tests were employed for non-parametric variables. The significance level was calculated and $P < 0.05$ was considered statistically significant, while $P > 0.05$ was considered statistically non-significant.

Results

The age of patients ranged from 23 to 77 years with mean ± SD of 54.0 ± 14.0 years. The study included 23 males (46%) and 27 females (54%) with a statistically non-significant (p = 0.053), table (1).

As regard treatment modality of the studied patients: previous surgery was performed for 48 patients (96%), chemotherapy was done for 44 patients (88%), radiotherapy was performed for 11 patients (22%), all of the radiotherapy patients received chemotherapy. Most of the vast majority of patients received more than treatment modality (table 2).

The biomarkers done for the patients; CEA was done to 37 patients and showed positive findings in 15 of them (30%), while CA19-9 was done to 30 patients and only 4 patients (8%) were positive of metastasis (table 3).

As regard site of recurrence, liver was the most common site for recurrence (34%), followed by peritoneum (24%), then lungs (16%). Multiple metastases were found in the liver, lungs, and – to less extent – bone. Local recurrence was found in 14/50 patients (28%) and regional lymph node recurrences was observed in 17 patients (34%), table (4).

The different diagnostic modalities used in this study; Biopsy and histopathology were done for 18 patients (36%), CT and PET/CT were done to all patients (100%), while MRI was performed in 2 patients (4%). Biopsy showed positive findings in 17 patients (34%), CT had positive findings of 12 patients (24%) and PET/CT showed positive findings in 29 patients (58%), while the 2 patients (4%) underwent MRI had positive findings. Compared with histopathology; PET/CT had the most relevant technique with statistically very highly significant difference (P <0.001), followed by CT with statistically significant difference (p <0.01), while MRI did not show significant difference (p > 0.05), table (5).

ROC curve analysis for PET/CT indicated that area under the curve was 0852, PPV was 86%, NPV was 47%, with 98% sensitivity, 92% specificity, and 96% accuracy (P <0.001), fig. (1).

The PET/CT interpretation showed that 20 patients (40%) had one lesion, 4 (8%) had two lesions and 26 (52%) had multiple lesions. The findings were 39 (76%) were true positive cases, 8 (16%) were true negative, 2 (4%) were false positive, only one patient (2%) was false negative. The mean SUVmax min was 4.9 ± 4.7, while SUVmax max was 13 ± 8.3 (table 6).

Table (1): Age and sex distribution of the study groups

	Mean ± SD	**Range**	**Significance**	
Age (years)	54.0 ± 14.0	23 – 77		
Gender	**Number (N)**	**Percent (%)**	**χ^2-test**	**P value**
Males	23	46.0	0.354	0.053
Females	27	54.0		

χ^2 = Chi square test, P >0.05 = non-significant.

Table (2): Treatment modalities of the studied patients.

Treatment	**Yes**		**No**	
	No.	**%**	**No.**	**%**
Previous surgery	48	96.0	2	4.0
Chemotherapy	44	88.0	6	12.0
Radiotherapy	11	22.0	39	78.0
Chemotherapy + radiotherapy	11	22.0	39	78.0

Table (3): Incidence of tumor biomarkers of the studied patients

Biomarker finding	**CEA**		**CA19-9**	
	No.	**%**	**No.**	**%**
Positive	15	30.0	4	8.0
Negative	22	44.0	26	52.0
Not done	13	26.0	20	40.0
Total	50	100	50	100

Table (4): Incidence of recurrence by PET/CT of colorectal cancer patients.

Metastatic site of recurrence	**Yes**		**No**	
	No.	**%**	**No.**	**%**
Liver	17	34.0	33	66.0
Lungs	8	16.0	42	84.0
Liver + lungs	4	8.0	46	92.0
Lungs + bone	1	2.0	49	98.0
Liver + lungs + bone	1	2.0	49	98.0
Lungs + abdominal lymph nodes	2	4.0	48	96.0
Peritoneum	12	24.0	38	76.0
Other	19	38.0	31	62.0
Local recurrence	14	28.0	36	72.0
Regional nodal recurrence	17	34.0	33	66.0

Table (5): Follow-up diagnostic techniques for the study patients.

Technique	Number		+ve Finding		-ve Finding	
	No.	%	No.	%	No.	%
Histopathology	18	36	17	34.0	1	2
CT	50	100	12	24.0	38	76.0
MRI	2	4.0	2	4.0	0	0.0
PET/CT	50	100	29	58.0	21	42.0

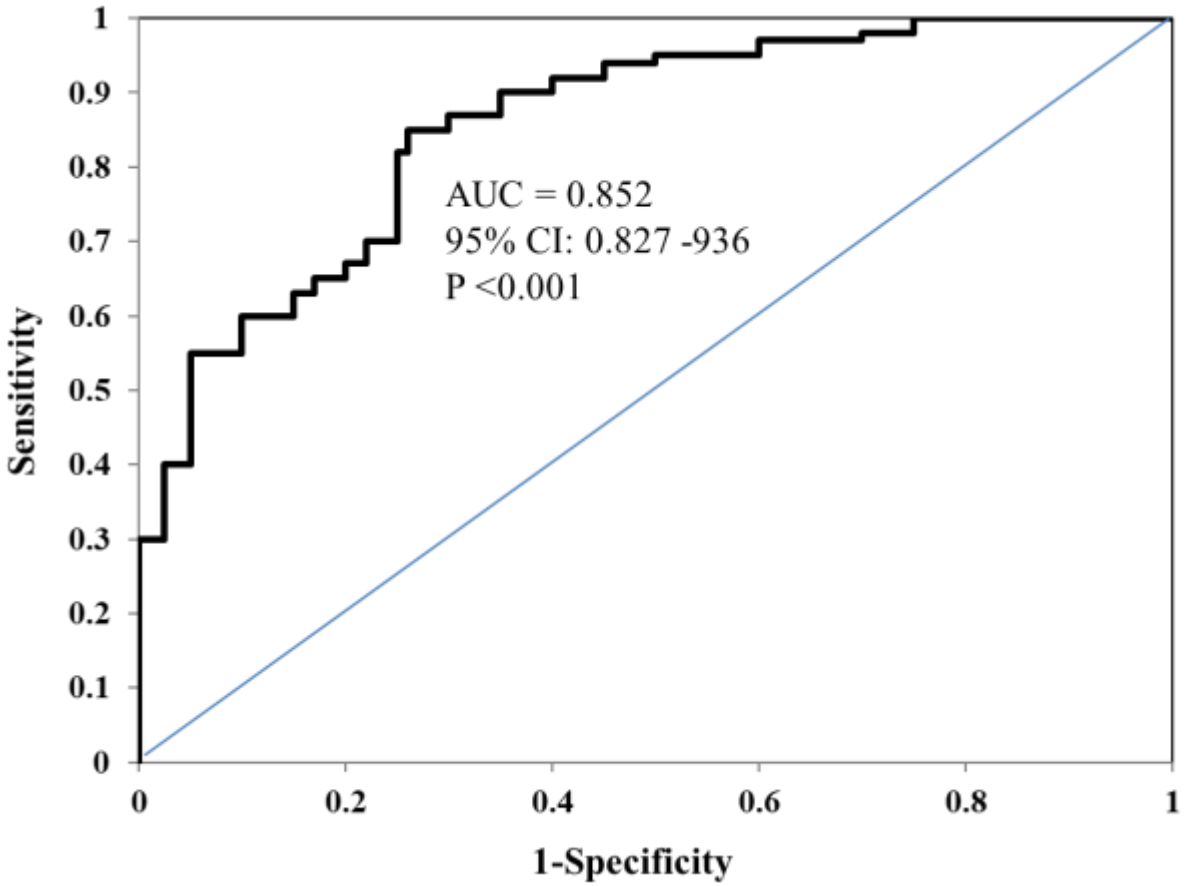

Fig. (1): Roc curve analysis for PET/CT according to the following:

AUC	PPV	NPV	Sensitivity	Specificity	Accuracy	P value
0.852	86%	47%	98%	92%	96%	<0.001

ROC: Receiver operating characteristic curve. AUC: Area under the curve.
PPV: Positive predictive value. NPV: Negative predictive value. CI: confidence interval

Table (6): PET/CT interpretation.

PET/CT interpretation	No.	%
Number of lesions		
• One	20	40.0
• Two	4	8.0
• Multiple	26	52.0
Findings		
• True positive	39	76.0
• True negative	8	16.0
• False positive	2	4.0
• False negative	1	2.0
Total	50	100
SUVmax	**Range**	**Mean ±SD**
• Minimum	2 – 26	4.9 ± 4.7
• Maximum	2 – 35	13.0 ± 8.3

Discussion

Our study was designed to address the diagnostic accuracy of 18F-FDG PET/CT in the recurrence of CRC. The most common indication for PET/CT is rising tumor biomarkers; CEA & CA19-9 (32%), followed by CT findings (24%), and follow-up (24%), then US findings (10%) and clinical findings (8%).

CEA sensitivity in detecting the recurrence of CRC of 48.1% is considered low. It may partly be attributed to normal CEA levels in the presence of recurrence that may be found after chemotherapy when apoptosis and cell death of malignant cells happen. It may also be the case in poorly differentiated CRCs. However, when 18F-FDG PET/CT results (positive vs. negative) were associated with CEA (normal vs. elevated), a statistically significant association was found to exist (p=0.033) (6).

A meta-analysis published by Huebner et al. included 11 studies and 577 patients showed that FDG-PET had 97 % sensitivity and 76 % for detecting recurrent colorectal cancer (7). However, they reported that prevalence of PET-positive cases in rectal cancer patients was higher with an increase in carcinoembryonic antigen (CEA) levels (41 % PET positivity for CEA level of 5–10 vs 83 % with CEA level >50).

Therefore, a rising CEA level, equivocal findings on other imaging, should be considered an indication for PET/CT in patients with known or suspected recurrent colorectal cancer (8). It has been shown that PET/CT detects colonic abnormalities larger than 13 mm in diameter with 90 % accuracy; however, the specificity for differentiating hyperplastic benign polyps from primary colorectal cancers is reported to be 43 % and thus the application of this technique is uncertain (9).

Regarding site of tumor, the most common primary site in the studied patients was the colon which was found in 29 patients (58%), followed by rectum in 10 patients (20%), sigmoid in 9 patients (18%) and only 2 cases of anorectal tumors (4%).

Pugh et al. (10) conducted a randomized controlled trial on patients following surgery for CRC and found that 17% experienced recurrence. The researchers found that incidence of recurrence varied according to location of primary tumor; 14% for the right colon, 16% for the left colon, and 21% for the rectum. The research work has concluded that pulmonary recurrence was most commonly associated with the rectal tumors and multi-site recurrence appeared more frequently with right-sided CRC (11). Similarly, in a retrospective study by Augestad et al. (12) that aimed to determine pattern of metastatic disease after curative surgery for CRC, the authors have reported recurrence incidence of 11.2%, 12.8%, 22.2%, 24.2% for right colon, left colon, high rectum, and low rectum, respectively.

Although a majority of patients experienced disease recurrence, most first recurrences were isolated to one organ site, primarily the lung or the liver and the majority of recurrences happened more than 1 year following liver resection, results that are similar to prior published literature (13-15).

As regard treatment modality of the studied patients: previous surgery was performed for 48 patients (96%), chemotherapy was done for 44 patients (88%), radiotherapy was performed for 11 patients (22%), all of the radiotherapy patients received chemotherapy. Most of the vast majority of patients received more than treatment modality.

Patients with stage 1 colon cancer have high cure rate with surgery alone and do not require adjuvant therapy. On the other hand, patients with node positive colon cancer following surgery are at high risk of recurrence. Adjuvant chemotherapy for patients with high-risk stage II and III colon cancer has substantially evolved over the past 2 decades (16). The patients with stage II are considered to be at high risk of recurrence if pathology demonstrates at least one of the following characteristics: lymph nodes sampling <12; poorly differentiated tumor (except in MSI-high cancers); vascular or lymphatic or perineural invasion; tumor

presentation with obstruction or tumor perforation and pT4 stage (17,18).

The usefulness of CEA and CA19-9 in screening, follow-up after diagnosis, and monitoring treatment has been explored in CRC patients since their discovery (19). They used CEA and CA19-9 combination for prediction of CRC recurrence. Until now, guidelines recommended only the use of CEA for determining prognosis, surveillance after a curative resection, and monitoring treatment. CA19-9 is still not recommended as a useful marker in CRC patients (18,20).

As regard site of recurrence, liver was the most common site for recurrence (34%), followed by peritoneum (24%), then lungs (16%). Multiple metastases were found in the liver, lungs, and – to less extent – bone. Local recurrence was found in 14/50 patients (28%) and regional lymph node recurrences was observed in 17 patients (34%).

Similarly, Manfredi et al. (21) reported pattern of distant recurrence of CRC after curative surgery involves liver (45%), lung (10%), brain (2%), bone (2%), and other sites in 4%.

The recurrence pattern for colon cancer showed that liver was involved significantly more in the early-recurrence group, while lung metastasis was recorded significantly more in the late recurrence group. In patients with rectal cancer, locoregional recurrence was significantly higher in the late-recurrence group. Interestingly, there was no difference in recurrence time in terms of hepatic and lung metastases for patients with rectal cancer (11).

The different diagnostic modalities used in this study; Biopsy and histopathology were done for 18 patients (36%), CT and PET/CT were done to all patients (100%), while MRI was performed in 2 patients (4%). Biopsy showed positive findings in 17 patients (34%), CT had positive findings of 12 patients (24%) and PET/CT showed positive findings in 29 patients (58%), while the 2 patients (4%) underwent MRI had positive findings. Compared with histopathology; PET/CT had the most relevant technique with statistically very highly significant difference ($P < 0.001$), followed by CT with statistically significant difference ($p < 0.01$), while MRI did not show significant difference ($p > 0.05$). So, PET/CT showed to be the best for diagnosis of recurrence.

Imaging plays a crucial role in the diagnosis, staging assessment for specific therapy and follow-up of patients with colon and rectal cancer with the main function of defining the locoregional extent, identifying synchronous lesions and distant metastases (22). Computed tomography-colonography (CT or CTC) can contribute to the CRC diagnosis (23,24), as a potential alternative to the endoscopy. However, CTC does

not offer the opportunity of taking biopsies or immediate polypectomy and the patient needs to return for a colonoscopy, in case of detected lesions (22).

CT has a sensitivity of 74–84% and a specificity of 95–96% in detection of CRC liver metastases (25). However, CT has shown to be poor in identifying nodal disease (26), with specificity for lymph node staging of 55% and sensitivity of 76% (27).

The PET/CT interpretation showed that 20 patients (40%) had one lesion, 4 (8%) had two lesions and 26 (52%) had multiple lesions. The findings were 39 (76%) were true positive cases, 8 (16%) were true negative, 2 (4%) were false positive, only one patient (2%) was false negative. The mean SUVmax min was 4.9 ± 4.7, while SUVmax max was 13 ± 8.3.

Standard incorporation of SUVmax as the metabolic parameter in the PET/CT reports increases the specificity. Adding another metabolic parameter was proven to further increase specificity (28). Attempts have been made in oncological imaging to further increase the specificity by introducing many quantitative PET/CT parameters that characterize the tissues in what is called ‘multiparametric approach’ (29). Such parameters reflect, for example, tumor vascularity or tissue heterogeneity, and present one of the future directions of PET/CT development (6).

Milardović et al. (6) studied the correlation of CEA and SUVmax, a non-significant low positive rank correlation (ρ=0.164, p=0.38; n=31) was found. This result could be attributed to complex and differing factors causing each. Serum CEA level is thought to be influenced by a tumor location, invasiveness of a tumor and tumor burden making more differentiated and left-sided CRCs to cause higher CEA levels. Research of Ozkan et al (30) showed no correlation between patients’ serum CEA and lesions’ SUVmax to exist.

The power of the study is that it gives hint about the important role of 18F-FDG PET/CT in prediction of recurrence and its important role in diagnosis and management of CRC, however, some limitations were noticed. First, the relatively low sample size of patients that interferes with the accuracy of statistical data. Second, is the lack of recurrence timing in this thesis as mentioned in previous literatures and differentiated into early (<1 year) and late (>1 year), so the importance of detection biomarkers like 18F-FDG PET/CT. Early recurrence does not reflect a worse prognosis as compared with late recurrence in CRC. Finally, lack of tumor staging in this research and its effect on recurrence.

Conclusion

From this study, it was concluded that 18F-FDG PET/CT is a good predictor of recurrence in colorectal cancer patients performed primary surgery. This imaging modality gives 98% sensitivity, 92% specificity, and 96% accuracy.

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