Original Paper, PET/CT.

Importance of ^{18}F-FDG-PET/CT in Detection of Early Colorectal Cancer Relapse and its Effect on Therapy Plan.

Talaat, O[1]. Mahmoud, E[2]. Hassan, M[3]. Ali, A[4] and Nasr, I[4].

[1]Oncology and Nuclear Medicine department, National Cancer Institute. [2]Radiodiagnosis Department, National Cancer Institute. [3]Surgical Oncology Department, National Cancer Institute, Cairo University. [4]Oncology and Nuclear Medicine Department, Faculty of Medicine, Zagazig University, Egypt.

ABSTRACT:

Introduction: Colorectal cancer (CRC) is the 7th commonest cancer in Egypt, representing 3.5% of male and 3% of female cancers. About 40% of patients with CRC develop early recurrence within the first two years after completion of their treatment. **Aim of the work:** To evaluate the importance of ^{18}F-FDG-PET/CT in detection of early relapse and to assess its effect on management in patients with CRC and equivocal CECT findings. **Patients and Methods:** Forty eight patients with treated colorectal cancer, under follow up were subjected to full clinical and laboratory assessment, CECT and PET/CT imaging plus histopathological examination of the biopsied sites of suspected recurrence.

Results: Among 48 patients with CRC, PET/CT and histopathology were concordant in 41 patients (31 patients positive & 10 patients negative) and discordant in 7 patients (6 false positive & one false negative). Overall SN, SP, PPV, NPV and accuracy of PET/CT were 96.9%, 62.5%, 83.8%, 90.9% and 75.6% respectively. PET/CT and CECT findings exhibit significant association in detection of local recurrence, hepatic lesions, loco-regional LNs and distant lesions (p value 0.001, 0.001, 0.004 and 0.003 respectively). PET/CT led to overall changes in the therapy plan for 26/48 patients (54.2%), 12/48 patients (25%) from negative to be positive for recurrence and recommended for therapy.

One patient (2.1%) from false positive to be negative and continue under follow up and 13/48 patients (27.1%) underwent modification in their plan either by addition or withdrawal of other therapy lines. 22/48 patients (45.8%) didn't show changes in their proposed plan. The changes in follow up, chemotherapy and radiofrequency strategies before and after PET/CT were significant (p value < 0.001, 0.004 & 0.038).

Conclusions:

PET/CT is efficient than CECT in detection of early CRC relapse. PET/CT has also a significant impact on directing management through improving the accuracy and decreasing the failure rate of the suggested therapy plan.

Key Words: Colorectal Cancer; follow up; ^{18}F-FDG-PET/CT; CECT.

Corresponding Author: Talaat, O. **E-mail**: mony.talaat@yahoo.com

INTRODUCTION:

Colorectal cancer (CRC) is one of the most commonly diagnosed cancer in males and the second most diagnosed cancer in females, accounting for over one million cases per year worldwide **(1)**.

Colorectal cancer is the 7th commonest cancer in Egypt, representing 3.5% of male cancers and 3.0% of female cancers. The estimated number of colon cancer patients (excluding rectal cancer) in 2015 was slightly more than three thousands **(2)**. Approximately up to 40% of patients with colorectal cancer suffer early recurrence within the first two years following curative surgical removal of the primary tumor. Early detection of recurrence is clinically important and can improve the prognosis and survival of patients with CRC **(3)**.

A progressive increase in circulating tumor marker levels may be the earliest indication and suggestive of recurrent cancer. Although widespread uses of CEA as a marker of early relapse, studies have shown opposing data, with a large number of false-positive results which may be found in some benign lesions, so it may lead to unnecessary surgery with associated morbidity. However, clinicians face a major challenge when the serum CEA is elevated but no evident relapse can be localized **(4)**.

The imaging modalities are important not only to recognize the tumor site at presentation but also to assess the tumor extent.

In current clinical practice, computed tomography (CT) is a routine modality for detecting the local recurrent disease.

However, it is often difficult to distinguish between pelvic recurrence and post-operative fibrosis [(5)]. Post-operative intensive follow-up is indicated to confirm the early detection of recurrences, improve patient outcomes and reduce mortality in patients with CRC [(6)].

Scott et al., reported that FDG-PET/CT has superior sensitivity compared to CT in the detection of colorectal liver metastases and in revealing extra-hepatic disease (especially metastases to peritoneum, mesentery, and lymph nodes) [(7)].

Aim of the study: To evaluate the importance of ^{18}F-FDG PET/CT in detection of early relapse and to assess its ability to change management in patients with Colorectal Cancer and equivocal lesions identified by Contrast Enhanced Computed Tomography (CECT) with or without elevation in tumor markers.

PATIENTS AND METHODS:

This prospective study included 48 patients with treated colorectal cancer (CRC) at the National Cancer Institute (NCI) and Zagazig Universities hospitals in the period from July 2017 to March 2019.

The study protocol was agreed by the ethical committee of the board of Nuclear Medicine and Oncology Department at the National cancer Institute.

Inclusion criteria: CRC patients, above the age of 18 years of both sexes, who had equivocal/inconclusive CECT findings with or without elevation in tumor markers during follow up after curative surgical treatment and at least 3 months after the end of complementary therapy.

Exclusion Criteria: Patients less than 18 years old. Patients received chemotherapy or radiotherapy within 4 weeks before the PET/CT scan. Patients with history of second primary malignancy, uncontrolled diabetes and those with expected life less than 6 months. Pregnant females were also excluded.

Follow up protocol: Patients who met the eligibility criteria underwent full clinical examination, laboratory assessment (CBC, liver and kidney function tests), tumor markers measurement, CECT imaging and whole-body FDG-PET/CT scan. PET/CT and CECT studies were performed within one month. Histopathological examination of the biopsied suspected recurrent lesions was also performed.

All patients were followed up from 6-12 months after PET/CT imaging for evaluation of lesions behavior overtime. The decisions for therapy plan for each patient were based on clinical data, CECT and PET/CT findings as well as the results of pathological examination of the taken biopsies. Treatment decisions before and after PET/CT for each patient were taken separately for each patient by clinical oncology physician.

Malignant lesions include lesions documented pathologically or those progressed with time and/ or lesions that regressed or cured after specific therapy. Benign lesions include lesions documented pathologically or those whom regressed spontaneously or remain stationary without therapy.

Contrast-enhanced CT Scan (CECT): CT imaging was acquired by 64 multi-detectors CT scanner. Non-ionic iodinated contrast material (300 mgl/ml) was injected intravenous at dose rate of 1-2 ml/kg body weight. All CECT images were interpreted by expert radiologist.

^{18}F-FDG-PET/CT Scan: was performed at the Nuclear Medicine Unit of National Cancer institute (NCI). All patients enrolled in the study gave informed consent for study participation before imaging with full description of the procedures.

^{18}FDG-PET/CT scan was performed on an integrated PET/CT system with 16 slice CT (GE Medical Systems). All patients were asked to fast for six hours prior to scan. The patients were instructed to avoid any kind of strenuous activity prior to the examination following injection of the radioisotope to avoid physiologic muscle uptake of FDG. ^{18}F-FDG administered in a standard dose of 5.2 MBq/Kg, 60 min before scan through intravenous route. Patients were asked to rest in a quiet room. PET emission scan was performed over 5-7 for bed position each for 2 minutes with an axial field of view of approximately 21.6 cm per bed position and in-plane spatial resolution of 2 mm covering the same field of view as with CT. PET and CT images were first reconstructed and then reformatted into axial, coronal and sagittal images. For each of these sets of PET and CT images, corresponding "fusion" images, combining the two types of data, also were generated. PET image data sets were reconstructed using CT data for attenuation correction and co-registered images were displayed using special software. PET/CT scan was interpreted by an expert nuclear medicine physician.

Statistical analysis:

Data collected throughout history, basic clinical examination, laboratory investigations and outcome events were coded and analyzed by Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis according to type of data. Qualitative data represented as number and percentage, quantitative continues group represent by mean ± SD. The following tests were used to test differences for significance and association of qualitative variable by; Chi square test (X^2), Inter-rater agreement (Cohen's Kappa) for agreement. Criteria to qualify for strength of agreement were, K<0.2: poor; K 0.21 – 0.40: fair; K 0.41 – 0.60: moderate; K 0.61 – 0.80: good; K 0.81 – 1.00: very good. P value was set as < 0.05 was considered statistically significant.

RESULTS:

This study included 48 patients with colorectal cancer, under follow up after completion of their treatment with mean age 52.0 ± 12.1. Males and females have an equal number in the study population (24 patients each). The site of the primary tumor was more frequent in the right and recto-sigmoid colon (13 and 11 patients respectively) followed by the rectum (10 patients), left colon (7 patients) and sigmoid (4 patients). Patient characteristics and demographic data are given in ***Table (1)***.

Table 1: Demographic and Clinical Data of 48 Patients with Colorectal Cancer.

		N	%
Mean Age	**52.0 ± 12.1**	**----**	**----**
Sex	Male	24	50%
	Female	24	50%
Primary Site	Right colon	13	27.1%
	Left colon	7	14.6%
	Sigmoid colon	4	8.3%
	Recto-sigmoid	11	22.9%
	Rectum	10	20.8%
	Anorectal	3	6.3%
Biopsy site	Local	19	39.6%
	Regional LNs	6	12.5%
	Liver nodule	22	45.8%
	Bone	1	2.1%

Thirty two patients proved to have recurrent CRC by histopathological examination and the remaining 16 patients were recurrence free. PET/CT was concordant with histopathology in 41/48 patients (85.4%) (31 positive and 10 negative for CRC recurrence) and discordant in 7/48 patients (14.6%) (6 were false positive & one false negative). No significant difference could be found between them (*p* 0.21) ***(Table 2)***.

(Figure 1) showed local recurrence and ***(Figure 2)*** showed metastatic lesions.

Table 2: Agreement between PET/CT and Histopathological Results in 48 Patients with Colorectal Cancer.

		Pathological Diagnosis		**Total No**	**X2**	**kappa**	**P**
PET/CT Diagnosis		**Positive (No = 32)**	**Negative (No = 16)**				
	Positive	31 (64.6%)	6 (12.5%)	37 (77.1%)	1.6	0.2	0.21
	Negative	1.0 (2.1%)	10.0 (20.8%)	11.0 (22.9%)			
Total		32 (66.7%)	16 (33.3%)	48 (100%)			

The overall sensitivity (SN), specificity (SP), positive predictive value (PPV), negative predictive value (NPV) and accuracy were 96.9%, 62.5% and 83.8%, 90.9% and 75.6% respectively. We found 6 patients (12.5%) with false positive results, 3 patients of them had benign hepatic lesions (one focal nodular hyperplasia & 2 hepatic adenomas), 2 patients with post-operative inflammatory changes at the surgical bed and one patient with inflammatory loco-regional lymph node. Only one patient has false negative PET/CT result and proved pathologically to have low grade mucinous CRC recurrence.

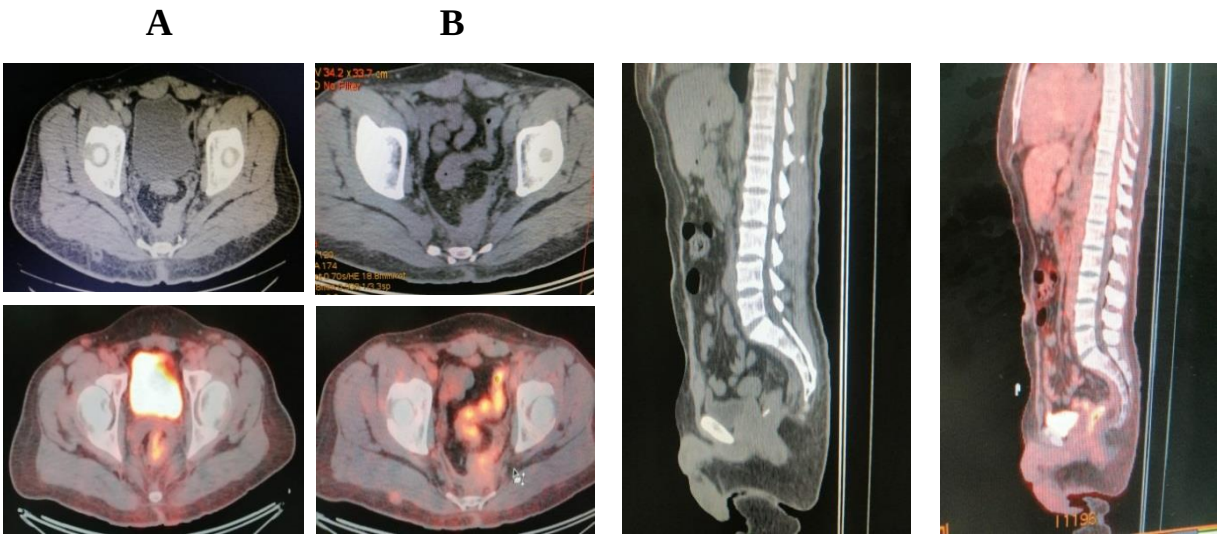

Fig. (1): 40 year old male patients with rectal cancer removed surgically and followed by chemo & RTH. A, B axial & E sagittal CT images shows soft tissue mass related to the posterior wall of the rectum measuring 35×48 mm. C, D axial & F sagittal PET/CT fused images confirm CT findings and revealed low grade metabolically active presacral mass not infiltrating the sacrum, denoting local recurrence with no other FGD avid lesions elsewhere.

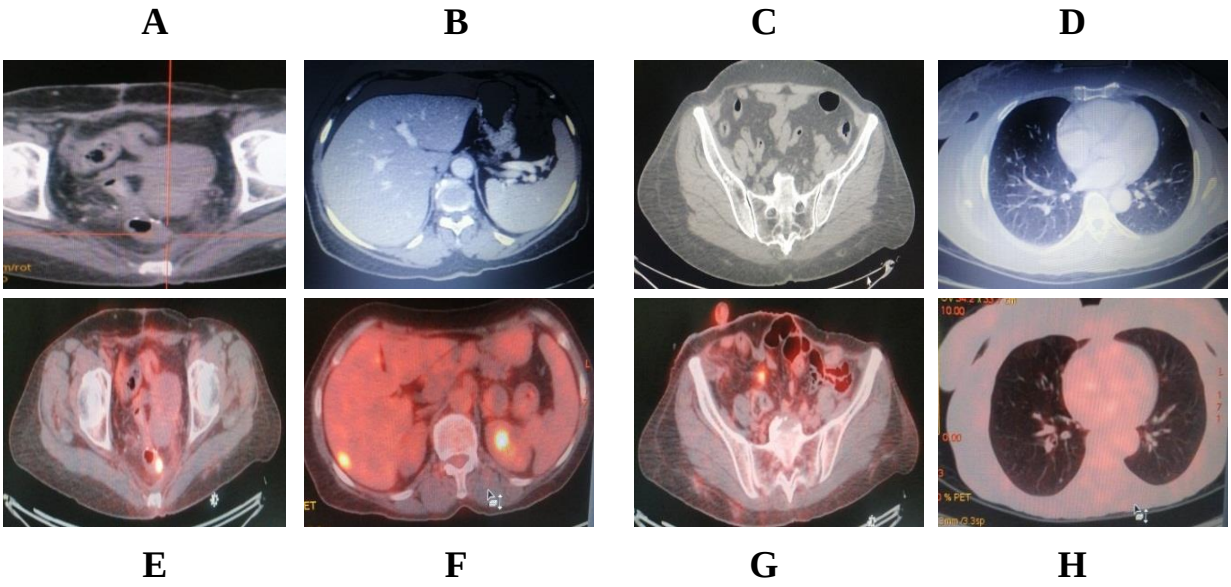

Fig (2): 52 year old female with rectal cancer, treated surgically and followed by chemo & RTH. CT axial images (A): showed local thickening at the left postro-lateral aspect of the rectum measuring 1.8 cm. B & C images didn't show any significant structural abnormality while (D) image displayed small sub-centimetric lung nodule. PET/CT axial images (E): displayed metabolically active FDG avid lesion at the left aspect of the rectum, (F): Small FDG avid peripheral right lobe hepatic focal lesion, (G): Active pelvic peritoneal nodule. (H): Low grade FDG avid small pulmonary nodule.

Table 3: Patient-based analysis of PET/CT in 48 Patients with Colorectal Cancer.

	No	Percentage (%)
True Positive	31	64.6%
False Positive	6	12.5%
True Negative	10.0	20.8%
False Negative	1.0	2.1%
Sensitivity	----	96.9%
Specifity	----	62.5%
Positive Peredective Value	----	83.8%
Negative Peredective Value	----	90.9%
Accuracy	----	75.6%

Concordance between CECT and PET/CT findings were found in 44/48 patients (91.7%) in detection of local recurrence (19 patients had positive local recurrence and 25 patients were negative) with significant p value 0.001. Also, there is agreement between both modalities in detection of hepatic lesions, loco regional lymph nodes involvement and other distant lesions. All had statistically significant association (P value 0.001, 0.004 and 0.003 respectively). The data concerning the peritoneal lesions is discordant with p value 0.31 ***(Table 4)***.

Table 4: Agreement between CT diagnosis and PET/CT findings in 48 Patients with Colorectal Cancer.

		PET/CT Findings		Total No	X2	kappa	P
CT Findings		**Local Lesions**					
Local Lesions		**Positive**	**Negative**		34.18	0.83	0.001**
	Positive	19 (39.6%)	0.0 (0.0%)	19 (39.6%)			
	Negative	4.0 (8.3%)	25 (52.1%)	29 (60.4%)			
Loco-regional LNs		**Loco-Regional LNs**			8.07	0.58	0.004*
		Positive	**Negative**				
	Positive	13 (27.1%)	5.0 (10.4%)	18 (37.5%)			
	Negative	9.0 (18.7%)	21 (43.8%)	30 (62.5%)			
Liver Lesions		**Liver Lesions**			33.5	0.83	<0.001**
		Positive	**Negative**				
	Positive	23 (47.9%)	1 (2.1%)	24 (50%)			
	Negative	3.0 (6.2%)	21(43.8%)	24 (50%)			
Other Distant Lesion		**Other Distant Lesions**			8.51	0.62	0.003*
		Positive	**Negative**				
	Positive	11 (22.9%)	5.0 (10.4%)	16 (33.3%)			
	Negative	8.0 (16.7%)	24(50%)	32 (66.7%)			
Peritoneal Lesions		**Peritoneal Lesions**			0.99	0.21	0.31
		Positive	**Negative**				
	Positive	1 (2.1%)	3 (6.3%)	4 (8.4%)			
	Negative	4 (8.3 %)	40 (83.3%)	44 (91.6%)			

^{18}F-FDG PET/CT findings and changes in therapy plan: We compared the treatment decisions of the suspected therapy plan for all patients before and after PET/CT that showed: curative surgical intervention was decided for 17 patients before PET/CT imaging and increased to 18 patients after PET/CT, while palliative chemotherapy and palliative radiotherapy were increased from 13 to 25 for the former and from one to two patients for the later.

On contrary, the number of patients planned to continue under follow up only without any additional therapy were reduced from 13 before PET/CT to two patients after PET/CT imaging.

Radiofrequency was decided for 3 patients with solitary hepatic focal lesions with mean size less than 3 cm, but PET/CT changed this decision, as two of them had additional metastatic sites detected by PET/CT and the third had focal nodular hyperplasia which proved by pathology.

Only one patient stayed on combined palliative chemo & radiotherapy before and after PET/CT. As regarding the changes in management, ^{18}F-FDG PET/CT led to changes in therapy plan for 13/48 patients (27.1%), as the plan was changed for 12/48 patients (25%) from negative to be positive for recurrence and received therapy, one patient (2.1%) from false positive to be negative and continue under follows up without therapy.

Another 13 patients (27.1%) underwent modification in their therapy plan either by addition or withdrawal of other therapy lines. The remaining 22 patients (25.8%) didn't show changes in their proposed therapy plan. The changes in the follow up only (No therapy), chemotherapy and radiofrequency strategies before and after PET/CT were statistically significant, with p values <0.001, 0.004 and 0.038 respectively ***(Tables 5&6)***.

Table (5): Role of PET/CT in change Management of 48 Patients with Colorectal Cancer.

	Decision Before PET/CT		**Decision After PET/CT**		**P value**
	No.	**%**	**No.**	**%**	
Follow-up only (No therapy)	13	27.1%	2.0	4.2%	<0.001**
Palliative Chemo	13	27.1%	25	52.1%	0.004*
Palliative Radio Therapy	1.0	2.1%	2.0	4.2%	0.42
Palliative Chemo & Radio Therapy	1.0	2.1%	1.0	2.1%	1.0
Curative Surgery	17	35.4%	18	37.4%	0.81
Radiofrequency	3.0	6.2%	0.0	0.0%	0.038*
Total No.	48	100%	48	100%	

Table (6): Management Change in 48 Patients with Colorectal Cancer.

	No.	Percent %
No Change in Therapy Plan	22	45.8%
Change from F/U only to Therapy	12	25.0%
Change from Therapy to F/U only	1.0	2.1%
Modification in Therapy type	13	27.1%
Total No.	48	100.0%

DISCUSSION:

Colorectal cancer (CRC) is one of the most popular types of cancer in both sexes [(8)]. About 40% of patients develop local and distant recurrences during follow-up, after curative resection of the primary tumor [(9)]. ^{18}F-FDG PET/CT has an essential role in the detection of CRC relapse either local or distant and can differentiate between malignant and benign lesions [(10)].

Early diagnosis of recurrent malignancies is vital for planning future therapeutic strategies [(11)]. PET/CT has an undisputed role in the evaluation of recurrent CRC with elevated CEA (carcinoembryonic antigen) and often with equivocal/negative CT findings [(12)].

In our study, 32/48 patients proved to have CRC recurrence, among them PET/CT detected 31/48 patients (64.6%). This is also in line with other studies published by ***Hussein., and Ince et al.,*** they found CRC relapse in 74/96 patients 77.1% and 30–50% respectively [(13, 14)].

As regarding the diagnostic performance of PET/CT, there was high sensitivity (96.9%) and relative satisfactory specificity of 62.5% with of PPV, NPV and accuracy of 83.8%, 90.9% and 75.6% respectively. The reduced specificity of PET/CT in our data is attributed to the relatively low number of negative cases in our sample.

Also, ***Laurens and Oyen*** postulated that ^{18}F-FDG-PET/CT is very sensitive, but less specific for detection of recurrence in CRC [(15)].

Furthermore, *Lu et al,.* in a meta-analysis study included 510 patients with suspected CRC recurrence,**.,** found that PET/CT had sensitivity of 94.1%, specificity of 77.2% and accuracy of 88.6% for diagnosis of CRC relapse [(12)].

***Sanli* et al.,** stated that FDG-PET/CT has high results in the diagnosis of CRC recurrence with SN, SP, PPV, NPV and accuracy of 98.2, 84.1, 94.4, 94.6 and 94.4 %, respectively [(16)].

Similarly, ***Shamim et al.*** stated that the SN, SP, PPV, NPV and accuracy of FDG-PET/CT in detecting CRC recurrence were 87%, 90%, 93%, 80% and 88% respectively [(17)].

We found significant association between PET/CT and CECT in detection of local recurrence, hepatic metastases, lymph nodes involvement and distant lesions, p value was 0.001, 0.001, 0.004 and 0.003 respectively.

Also, ***Kruse et al.,*** reported satisfactory sensitivity and accuracy of ^{18}F-FDG PET/CT in the detection of recurrent CRC with better sensitivity and specificity (87%-100% & 90%-98%, respectively) for detection of hepatic and extra-hepatic metastasis than CT [(18)].

***Also, Zhang* et al.,** reported that PET/CT has superior sensitivity compared to CT in the detection of colorectal metastases, either hepatic or extra-hepatic (especially metastases to peritoneum, lymph nodes and distant sites). ^{18}F-FDG PET/CT has an excellent diagnostic performance in the detection of CRC recurrence and metastasis. Its sensitivity and accuracy were significantly superior to those of CECT [(19)].

Concerning the impact of PET/CT on management, we recorded overall changes in the therapy plan for 26/48 patients (54.2%), 12/48 patients (25%) were changed from negative to positive for CRC recurrence and recommended for therapy, one patient (2.1%) proved to be false positive and suggested to continue under follow up. The therapy plan was modified in 13/48 patients (27.1%) either by addition or removal of other therapy lines. While 22/48 patients didn't showed changes in their therapy plan.

Also **Zidan et al.,** found that PET/CT had changed patient management in 38/42 patients (90%) who were referred to do PET/CT due to a clinical or radiological suspicion of recurrence after surgical removal of their primary tumor [(20)].

Furthermore, ***Gordin et al and Filippi et al.,*** stated that PET/CT altered therapy plan in more than 50% of the study population [(21, 22)].

In addition, *Tural et al.* retrospectively evaluated the impact of PET/CT on the management plan in 122 patients with suspected CRC recurrence; the authors verified that PET/CT changed the treatment plan to curative intent in 37% patients [(23)].

The National Oncologic PET Registry has proved that physicians often change their proposed management depending on PET scan results in 36.5% of patients [24].

To conclude, we agree with many earlier authors that PET/CT imaging has the chance to be better imaging modality in evaluation of CRC recurrence, attributed to its power to identify and localizes the disease in one setting in addition to its ability to guide the therapeutic management.

CONCLUSIONS:

PET/CT is a more potent and efficient imaging modality than CECT in detection of early CRC relapse. PET/CT also has a significant impact on directing management through improving the accuracy and decreasing the failure rate of the suggested therapy plan.

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