ROLE OF POSITRON EMISSION TOMOGRAPHY / COMPUTED TOMOGRAPHY (PET/CT) IN ASSESSMENT OF COLORECTAL CANCER

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Abstract:

Background: Colorectal cancer is one of the third most common malignancies worldwide with more prevalence in middle age and male patients. PET/CT is one of the most important modalities in diagnosis, staging and follow up of the disease. It is highly sensitive in detection of response to surgery, chemotherapy or radiotherapy. It is also highly sensitive and specific in detection of local recurrence, lymph nodes or distant metastasis.

Aim: This study aims at highlighting the role of PET/CT in diagnosis and staging of colorectal cancer and to determine its value in monitoring response to treatment

Methods: Fifty patients of pathologically proved colorectal cancer were included in the study. All patients underwent PET/CT study followed by post contrast CT study of abdomen and pelvis. SUV was measured in colorectal masses, lymph nodes and metastasis by 2 independent observers.

Results: PET/CT accurately detected local colorectal tumour recurrence in (23) cases, nodal metastasis (in 13 cases) and distant organ metastasis (in 24 cases). There was an excellent inter-observer with high statistically significant value ($p< 0.001$) in detection of local CRC recurrence or distant metastasis. There is a complete matching between the two observers in detection of nodal metastases (Regional and distant).

Discussion: PET/CT is one of the most important diagnostic modalities in diagnosis and follow up of colorectal cancer cases. PET/CT is highly sensitive & specific in detection of local tumor recurrence, lymph nodes metastasis and distant metastasis.

Keywords: colorectal cancer, PET/CT, SUV, Nodal metastasis, Distant liver metastasis.

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Introduction:

Colorectal cancer (CRC) is the third most common cancer worldwide after lung and breast cancers. CRC affects men and women of all racial groups with slightly more prevalence among male group. Most CRC cases occurring more in the developed countries **(1).** The increasing incidence of CRC has been related to increased life expectancy, pollution as well as the increase in established risk factors such as smoking, obesity and sedentary lifestyles, inflammatory bowel disease in addition to some genetic factors **(2)**. The use of imaging in CRC has dramatically evolved over the last thirty years, establishing significant roles in surveillance, diagnosis, staging, treatment selection and follow up **(3).**

The widespread availability of Computed tomography (CT) scanners made it the standard imaging modality used in initial diagnosis, radiological staging of CRC, monitoring response to treatment and following up **(4).** CT scanning has many limitations as it only gives information about morphology and size of the lesion disregarding its cellular function information. Meanwhile, there is strong evidence suggests that tumour size does not always sufficiently correlate with clinical consequences. Magnetic resonance imaging (MRI) is a more useful technique and dynamic contrast-enhanced (DCE)-MRI and diffusion-weighted (DW)-MRI may be used to evaluate biological and functional effects of treatment. Hybrid PET/CT imaging combines metabolic and anatomical imaging to improve sensitivity and specificity of tumour detection **(3).**

Positron emission tomography (PET) is a non-invasive, 3-dimensional, metabolic imaging

technique using 18fluoro-2-deoxyglucose (FDG) which is a radio-active glucose analogue. The tumor cells have high affinity to utilize glucose. FDG undergo phosphorylation like glucose so trapped in metabolically active tumor **(5).** FDG uptake and accumulation is measured by standardized uptake value (SUV), so that PET gives functional information about tumor distribution and its metabolic activity **(6).** Hybrid PET/CT combines a PET scanner with a multi-detector helical CT then the resulting images are fused to provide accurate localization of FDG uptake providing more sensitive and specific imaging than either modality alone. Another advantage of PET/CT is the utilization of CT images for PET attenuation correction **(7)**. PET/CT is an essential imaging tool for colorectal cancer as PET is significantly beneficial than CT during tumor staging and is superior to CT in detection of liver metastasis **(8).** PET/CT is highly sensitive in detecting lesions this is attributed to the detection of FDG-avid normal-sized lymph nodes (usually <1 cm), detection of peritoneal lesions that usually non-detectable in CT scanning **(9).** Also, PET/CT helps in assessing early metabolic response to neo-adjuvant chemotherapy that may change the treatment plans **(10).** Moreover, PET/CT utility in post-surgical follow up helps in detection of residual activity suggesting recurrence. Early detection of disease with frequent follow-up is believed to have an important effect on outcome as early therapy for recurrent disease is more effective than delayed therapy **(11).**

Patients & methods

Patients:

This prospective study was conducted atii-PET/CT unit in Mansoura University Oncology Center during the period from April 2021 to March 2023. The study included fifty patients with pathologically proven colorectal cancer of different subtypes. All patients underwent colonoscopy and biopsy for pathological diagnosis confirmation. Forty-four (88%) patients underwent colorectal surgery and remaining 6 patients (12%) did not.

Their mean age (years) ± SD was 49.80±12.91 years. Forty-four patients have adenocarcinoma, and 6 patients have lymphoma (pathologically proven after colonoscopy and biopsy). There were 26 males & 24 females in our study. Twenty-nine (about 58 %) patients have cancer in the rectum and rectosigmoid regions in correlation with tumors at other sites. Our study includes 27 cases of free disease status (no residual or recurrent masses) and 23 cases of residual/recurrent (18 cases) or non-operable (5 cases) colorectal masses.

Methods:

Pre-procedure assessment in the form of : History taking including personal history (including age &iii-gender), present acute illness, previous surgical operations or any renal troubles, previous chemotherapy or radiotherapy. Laboratory investigations as renal function tests including serum creatinine level (better within 2 weeks), carcinoembryonic antigen (CEA) level, cancer antigen 19-9 (CA 19-9) level and biopsy from suspected lesions then histopathological assessment for all patients that revealed 44 adenocarcinoma cases and 6 lymphoma cases. Also, previous radiological examinations including CT, MRI, previous PET/CT and Barium study.

PET/CT Examination:

i- Patient preparation*:*

Patients were asked to fast 6 hours prior to scanning then measuring blood glucose level to assure it is ≤ 150mg/dl. (It is better for blood glucose to be less than 150 mg/dl for 3 days before the exam), height & weight of the patient and vital signs. Patients also asked to change clothes & remove any metal objects, drink plenty of water, evacuate bowel & urinary bladder, stay in warm area and stop sternous activity. All patients underwent scanning in supine position, head first. Low dose non enhanced CT scan was done first, then a whole-body PET study without patient movement from the brain to mid-thigh. It is followed by diagnostic enhanced post contrast whole body CT scan. The CT scan also starts from the brain to mid-thigh. PET/CT is performed on an integrated scanner (G.E discovery Vs CT; tube 16 slices CT) that combines both CT and PET capabilities in two sequential gantries, avoiding the need for patient motion between the CT and PET components of the study and thereby leading to accurate co-registration of the CT and PET data.

PET/CT technique: -

Patients fasted for at least 6 hours before the examination, and blood glucose levels were less than 150 mg/dL. A dose of (0.18–0.21mCi/kg, minimum 3mCi) FDG was injected intravenously. The patients rested in a quiet room. After the 45–60-minute uptake period, the patients underwent the PE-CT scan. A section thickness of 4 mm and a pitch of 1 were used. After CT acquisition, PET acquisition of the same axial range has begun with the patient in the same position on the table for 2–3 minutes per bed position. Total PET/CT scanning was taken time about 15-20 minutes. PET data were acquired by using a matrix of 128x128 pixels. CT-based attenuation correction of the emission images was used. After PET data acquisition was completed, the reconstructed attenuation corrected PET images, CT images, and fused images of matching pairs of PET and CT images were available for review in axial, coronal, and sagittal planes, as well as in maximum intensity projections and in three-dimensional cine mode.

Contrast-enhanced CT technique: -

Contrast-enhanced CT of the brain, chest, abdomen, and pelvis was performed by using a 16–detectors CT scanner. Patients were given 800–1000 mL of 2% oral contrast material was started 120 minutes before the examination. Intravenous bolus injection of a nonionic iodinated contrast material at a dose of 2-3mL/KG of body weight was performed just before initiation of scanning. Scans were acquired from the skull (head) to the above knee joint by using 2.5-mm-thick sections, and contiguous 5-mm axial image reconstruction. Scanning protocols with 120 kVp and effective tube current that varied from 60 to 140 mAs were used.
The patient stayed in the preparation room for the physician to confirm the accuracy of the exam then instructed to stay away from children and pregnant women for at least 24 hours. The patients were also instructed to change clothes after 24hours and drink a plenty of water and the clothes should be washed separately.

Image interpretation:

Cross linking of axial, coronal & sagittal reformats for PET, CT & combined images. Attenuation correction by using CT **(**it is essentially "subtracts counts" from areas that are attenuated much less than all other tissues (e.g. lungs and body surfaces) for better localization of areas of interest that show increased tracer uptake. Assessing tumour recurrence or response to treatment, regional or distant suspicious lymph nodes, distant metastasis in different body regions.

Assessment of FDG uptake by 2 independent radiologists separately, each one maximum SUV (standard uptake values) by manually inserting region of interest (ROI) in the most active part of the colorectal mass, lymph nodes or distant metastatic lesions.

Statistical analysis and data interpretation:

- Data collected from all steps above will be computed and statistically analyzed using suitable statistical software program and suitable statistical tests**.** Data analysis was performed by SPSS software, version 25 (SPSS Inc., PASW statistics for windows version 25. Chicago: SPSS Inc.). Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) for non-normally distributed data and mean± Standard deviation for normally distributed data after testing normality using Kolmogrov-Smirnov test. Significance of the obtained results was judged at the (0.05) level. Mann Whitney U test was used to compare between 2 studied groups for non-normally distributed data. Bland -Altman analysis and interclass correlation were used to assess agreement for continuous data and Kappa agreement for qualitative data.

Results:

Our study included 50 patients, 26 males and 24 females, their age range in between 20 and more than 60 years. About half of cases in our study, their mean age ranges from 40 to 60 years old (about 25 cases). All patients had sever abdominal pain, some of them presented by anemia, bleeding per rectum and intestinal obstruction. All cases were diagnosed by colonoscopy & histopathological correlation that revealed 44 adenocarcinoma cases and 6 lymphoma cases. The most common affected colonic segments were rectum. Rectosigmoid and sigmoid colon (58 %, 29 cases). Also, in our study 46 patients received chemotherapy and 19 patients received radiotherapy (**Table 1**).
In our study, timing of performing PET/CT scan was variable due to many subjective factors including adequate patient preparation, availability of tracer material as well as some financial limitations. Thirty-nine patients having adenocarcinoma underwent surgical resection, then post-operative PET/CT assessment was done to detect residual/ recurrent masses and or any possible metastatic deposits. The other 5 adenocarcinoma patients showed metastatic deposits by initial PET/CT scanning and were under chemotherapy treatment when three of them developed acute intestinal obstruction and underwent palliative surgical relief without complete malignant mass removal due to extensive serosal and local infiltration. Follow-up PET/CT evaluation was required after palliative surgery for assessment of disease state and treatment planning. Two patients were accidently diagnosed having colonic lymphoma after developing acute intestinal obstruction with surgical resection and re-anastomosis. PET/CT was then done post-operative for regional and systemic disease evaluation. Other non-operated four patients with colonic lymphoma performed PET/CT scanning before starting of chemo/radiotherapy to provide baseline examination for staging and treatment follow up.

Twenty-three cases of all included 50 cases showed local mass recurrence and 27 cases show free operative bed. 13 cases showed nodal metastasis, 2 regional metastasis & 11 distant nodal metastasis. 24 cases showed distant organ metastasis, the liver is the most common organ to be affected. This revealed high sensitivity of PET/CT in detection of local recurrence, nodal and distant organ metastasis (**Table 2**).
There was no statistically significant difference the CA 19-9 level between the cases with and without local lesions (p= 0.008), cases with and without lymph nodes metastases (p= 0.705) and cases with and without lymph distant metastases (p= 0.272) (**Table 3**). There was no statistically significant difference in the CEA level between the cases with and without local lesions (p= 0.922), cases with and without lymph nodes metastases (p= 0.897). However, the CEA level was statistically significantly higher in the cases with distant

metastases compared to the case without distant metastases (p= 0.005) (**Table 4**).

The agreement coefficient between observer 1 and observer 2 in detection of local site lesions was 0.960. The degree of agreement was excellent with high statistically significant value (p< 0.001). The agreement coefficient between observer 1 and observer 2 in detection of site of distant metastases was 0.931. The degree of agreement was excellent with high statistically significant value (p< 0.001). It also shows there is a complete matching between the two observers in detection of nodal metastases (Regional and distant) (**Table 5**).

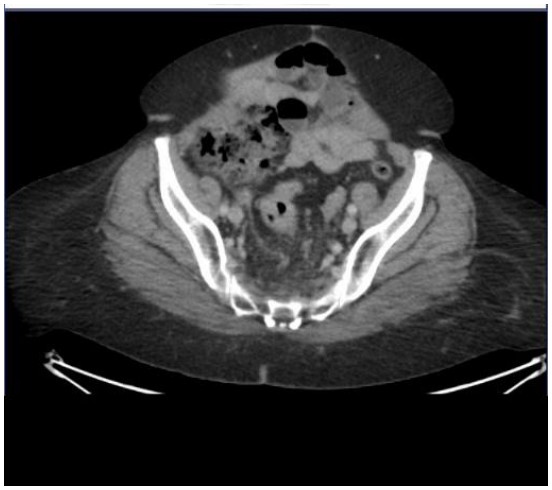


Figure A

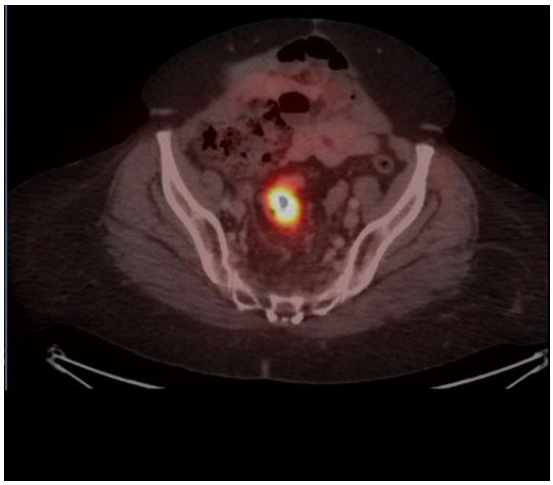


Figure B

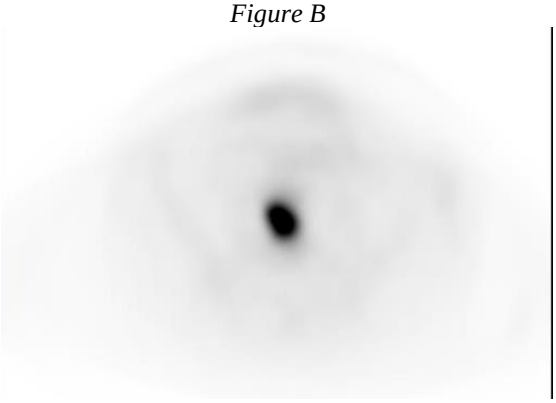
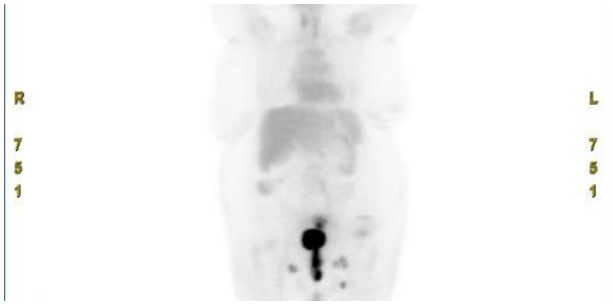


Figure C

Figure 1: 64-year-old, female patient, case of sigmoid cancer, presented with IO then underwent transverse colostomy (without tumor resection), received chemotherapy. Axial CT (A) and axial PET/CT (B) images revealed metabolically active rectosigmoid circumferential wall thickening invades the surrounding serosa. Axial MIP images (C) revealed absence if distant metastasis or nodal metastasis.



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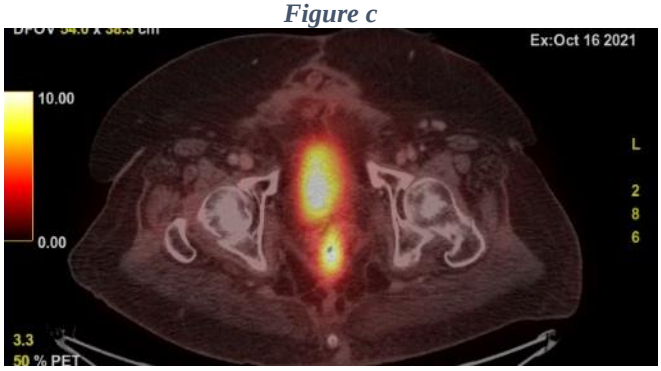

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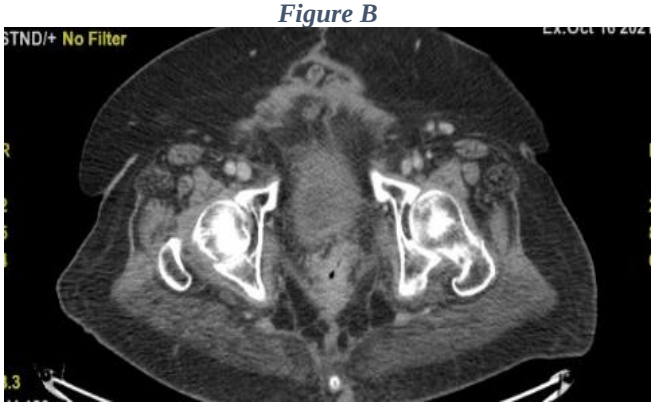

Figure A

Figure 2: 72-year-old, female patient, case of recurrent lower third rectal cancer received chemotherapy1st PET/CT revealed metabolically active anorectal residual soft tissue mass. Axial CT (A) and axial PET/CT (B) images also revealed residual lower third rectal cancer. Coronal MIP image (C) revealed the anorectal mass, no distant metastases.

Figure 3: 49 years old, male patient, with low rectal carcinoma. He was underwent hartmann colostomy procedure with receiving radiotherapy and chemotherapy. Axial CT (A) and axial PET/CT (B) images revealed metabolically active thickening at the anastomotic site. Axial CT (C) axial PET/CT (D) images revealed multiple metabolically active hepatic metastatic deposits. Axial CT (E) and axial PET/CT (F) revealed metabolically active peritoneal deposits.

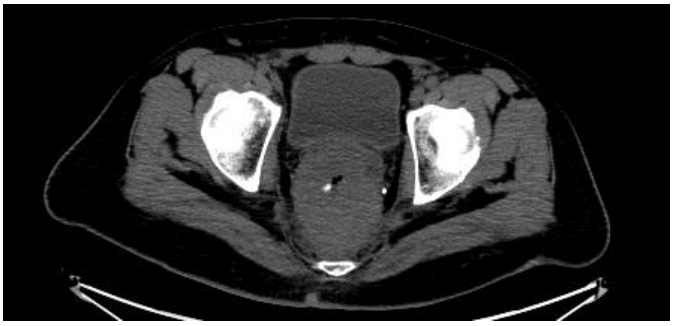

Figure A

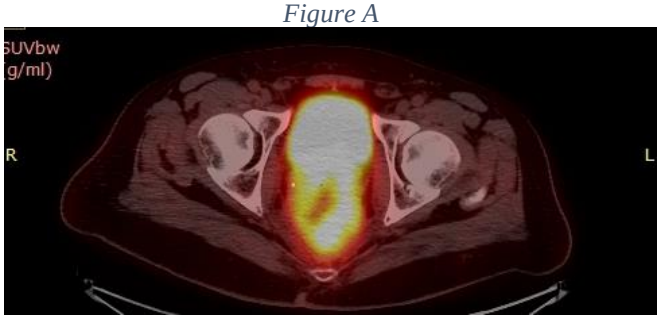

Figure B

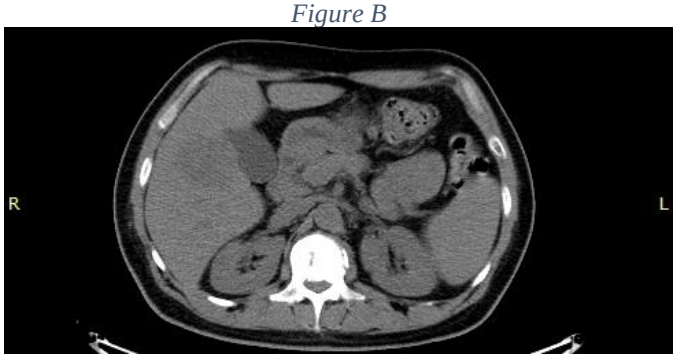

Figure C

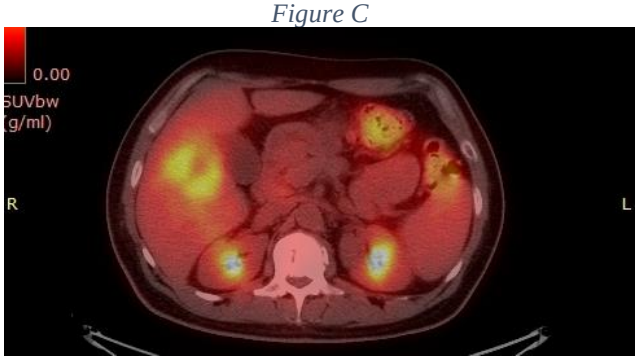

Figure D

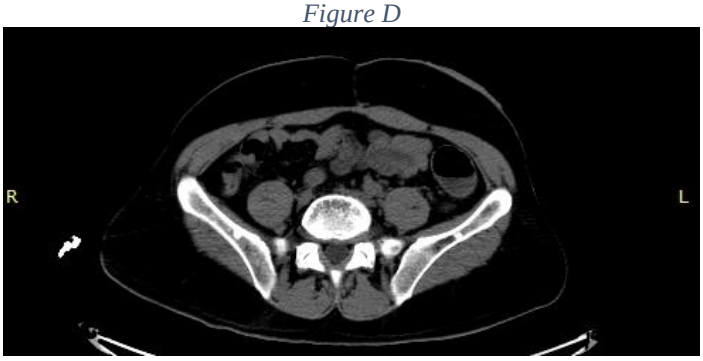

Figure E

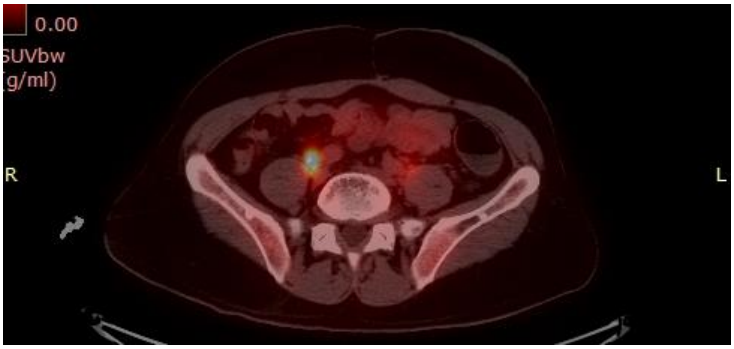

Figure F

Table (1): Descriptive statistics of the studied cases

Clinical characterization of the patient	**N=50**	**%**
Age/years	49.80±12.91 (22.0-73.0)	
- 20-29	2	4
- 30-39	10	20
- 40-49	15	30
- 50-59	10	20
- > 60	13	26
……in between 40-60 years	25	50
Sex		
Male	26	52.0
Female/	24	48.0
Final diagnosis of CRC in 50 patients		
Adenocarcinoma	44	88
Lymphoma	6	12
Total	50	100
Site of cancer (confirmed by colonoscopy)		
Rectum	13	26.0
Sigmoid	10	20.0
Rectosigmoid	6	12.0
Descending colon (LT. side)	1	2.0
Transverse colon	1	2.0
Ascending colon (RT. side)	9	18.0
Caecum	7	14.0
Total colon	3	6.0
prev. chemotherapy		
No	4	8.0
Yes	46	92.0
Prev. Radio		
No	31	62.0
Yes	19	38.0

Table (2): PET/CT radiological findings in our study (disease status):

Radiological findings	N=50	**%**
Free colonic operative bed	27	54.0
Local (regional) CRC mass	23	46.0
Nodal metastasis	13	26.0
Distant organ metastasis	24	48.0
Liver	10	20.0
Lung	6	12.0
Omental nodules	8	16.0
Bone	4	8.0

Table (3): Analysis of the results of CA19-9 according to the findings of observer one

Variables	CA 19-9	Test of significance	P value
Local recurrence			
No (n= 27)	15 (1-1200)	z = - 1.708	0.088
Yes (n= 23)	5.27 (0.90-392)		
LNs Metastasis			
No (n= 37)	8.65 (0.90 - 392)	z = - 0.378	0.705
Yes (n= 13)	6.8 (0.2 - 1200)		
Metastases			
No (n= 26)	6.9 (0.9 - 1200)	z = - 1.099	0.272
Yes (n= 24)	(1 - 392)		

Table (4): Analysis of the results of CEA according to the findings of observer one

Variables	CEA	Test of significance	P value
Local recurrence			
No (n= 27)	4 (0.50 - 105)	z = - 0.098	0.922
Yes (n= 23)	4.8 (0.6 - 125)		
LNs Metastasis			
No (n= 37)	4.5 (0.50 -125)	z = - 0.129	0.897
Yes (n= 13)	4 (0.6 - 37.3)		
Metastases			
No (n= 26)	2.9 (0.50- 43.1)	z = - 2.745	0.005*
Yes (n= 24)	9 (1.8 - 125)		

Table (5): Agreement between observer 1 and observer 2 in detection of tumours.

Variables	Observer 1 N = 50		Observer 2 N = 50		Test of significance
	Number	Percent	Number	Percent	
Local tumour site					
No lesions	27	54 %	26	52%	κ= 0.960 P < 0.001*
Lesions	23	46 %	24	48%	
Regional LN metastases					
No lesions	48	96%	48	96%	κ= 1 P < 0.001*
Lesions	2	4%	2	4%	
Distant LN metastases					
No lesions	39	78%	39	78%	κ= 1 P < 0.001*
Lesions	11	22%	11	22%	
Sites of distant metastases					
No metastases	26	52%	27	54%	κ= 0.931

Single site	19	38%	17	34%	P < 0.001*
Two sites	3	6%	4	8%	
Three sites	2	4%	2	4%	

Discussion:

Our study revealed that PET/CT accurately detected local colorectal recurrency, nodal metastasis and distant organ metastasis. There was an excellent inter-observer in detection of local CRC recurrence or distant metastasis. That was in agreement with Hetta, W., et al who revealed that 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 **(12).**

The age of half of the included cases ranges in between 40-60 years old and the mean age is about 50 years with slight male predominance about 52%. Increasing age and male sex were significantly associated with increased risk of colorectal cancer. Similar results were conducted in the study by Low et al., used colonoscopy screening of 68,067 person of which 651 were diagnosed by colorectal cancer with mean age about 43.2 years and male predominance 82.3%. **(13)**.

We found that the rectum and rectosigmoid regions are the most commonly affected regions (58 % of all cases). This matches with MH, H., et al., 2021 results that proved a recto-sigmoid location is the most common site for colonic tumors accounting for 60% in his study which included fifty tissue blocks (16 females and 34 males) of patient groups with CRC **(14)**.

O'Connor et al. stated that accurate preoperative TNM staging is essential to estimate prognosis and institute appropriate therapy in CRC. Many imaging modalities can be performed including endorectal ultrasound, CT, MRI and FDG PET/CT. The limited spatial resolution of PET/CT makes it unsuitable for precise regional T staging which require accurate detection of depth of invasion. Hence, the local staging depends mainly on pathological and surgical information **(9)**. In our study, PET/CT is highly effective in evaluation of post-operative recurrence due to its high biological activity & high glucose uptake and hence increased radioactive tracer (FDG) uptake. It is also effective in evaluation of non-operable masses for follow up of activity and response to chemotherapy &/ or radiotherapy. Our study includes 50 cases in which about 23 cases of colorectal cancer shows FDG activity (either post-operative recurrent activity, non-operable cases with post therapy follow up). Our results were in agreement with Shamim, S.A et al 2010 study that stated that PET/CT showed high sensitivity, specificity, and accuracy for the detection of recurrent disease in patients, who were earlier treated for CRC **(15).** Our study also agrees with Yu, T. et al 2015 study that concluded 18F-FDG PET/CT has good diagnostic performance in detecting local recurrence in patients with CRC **(16).**

In our study, there was excellent inter-observer agreement of both reviewers for evaluation of operative bed residual or recurrent masses activity or follow up of residual non-operable masses.

Lymph node metastasis is one of the most vital prognostic factors for patients with CRC. Moreover, survival is directly related to the presence of residual / newly developed local or distant metastatic LNs after primary surgery. Accurate diagnosis of LN metastasis at early stage may improve diagnosis and prompt the initiation of second-line treatment **(17).** Our study shows early detection of regional and distant metastatic L.Ns that improve planning of treatment with few limited role in detection of regional metastatic lymph nodes (due to limited spatial resolution) that noted in only 2 cases in our study in comparison with better detection of distant metastatic lymph nodes that noted in 11 cases in our study. That was in agreement with the previously mentioned study by O'Connor et al., 2011. **(9)** Our study in agreement with the study stated 18F-FDG PET/CT demonstrates a low sensitivity and high specificity for detecting the metastasis of LNs in patients with newly diagnosed CRC **(17)**. Also, 18F-FDG PET/CT is only useful for the confirmation of LN metastasis (when positive) in patients with CRC and this agree with local lymph nodes metastatic detection in our study **(17)**. In our study, there was excellent inter-observer agreement of both reviewers for evaluation of regional or distant metastatic L.Ns.

PET/CT has an effective role in detection of distant metastasis in multiple organs including liver, omental nodules, lung and bone. Our study revealed effective detection of distant organ metastasis in 24 cases of 50 cases (48%) and most common metastasis found in the liver and this agree with that represent 20 % of all study cases and 41.6 % of the metastatic cases. Our study revealed that FDG PET/CT has high sensitivity, accuracy, and specificity in the detection of distant metastatic deposits. Our data suggests that PET/CT is an excellent option to replace CT in the follow-up of CRC patients and this was in agreement with previously reported study by **Hetta, W., et al, 2020**. **(12)** In our study, there was excellent inter-observer

agreement of both reviewers for evaluation and detection of distant metastasis in multiple organs.

Our study shows that there was no statistically significant difference in the CA 19-9 level between the cases with and without local lesions. It also shows no statistically significance in cases with and without lymph nodes metastases and cases with and without lymph distant metastases. This agree with the study that was done by **Wu, T., et al., 2020** who revealed that the sensitivity of a single index in laboratory investigations is relatively low in detection of recurrence after operations. **(18)** It also revealed that the sensitivity of detection of recurrence can be improved by combination of multiple laboratory investigations as CEA, CA 19-9 & CA 72-4 (that is not available in our laboratory investigations in our study cases). **(18)**

Our study also shows no statistically significant difference in the CEA level between the cases with and without local lesions, cases with and without lymph nodes metastases. **Zaręba, K. P., et al, 2021** stated that the elevation of CA 19-9 and CEA tumor markers significantly correlates with the presence of metastasis to distant lymph nodes. The location of the primary tumor determines the formation of metastases in distant lymph nodes **(19).** The previous study disagrees with our previous results as regard no definite correlation in between elevation of CEA and nodal metastasis (regional or distant) **(19).** However, our results confirm that the CEA level was statistically significantly higher in the cases with distant metastases compared to the case without distant metastases, that was in concordance with the **Luo, T., et al, 2021,** that suggested high correlation in between increased CEA level and incidence of distant metastasis in different organs **(20)**.

Conclusion

PET/CT is highly sensitive in diagnosis of CRC and detection of tumour recurrence It is also low sensitive but highly specific in detection of regional metastatic LNs and highly sensitive & specific in detection of distant metastatic L.Ns. It is also highly sensitive in detection of metastasis to distant organs as liver (which is considered the most common site), peritoneal nodules, lung and bone. There was an excellent interobserver agreement in detection of local CRC mass recurrence and nodal & distant metastasis.

Abbreviations:

18F-FDG: 18F-2-fluoro-2-deoxy-D-glucose
CRC: Colorectal cancer
FDG-PET/CT: 18 F-fluorodeoxy glucose positron emission tomography/computed tomography
LNs: lymph nodes
MDCT: Multidetector computed tomography
PET-CT: Positron emission tomography-computed tomography
ROI: Region of interest
SPSS: Statistical package for social science
CEA: carcinoembryonic antigen
CA 19-9: Cancer antigen 19-9

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