ROLE OF PET/CT IN ASSESSMENT OF TREATMENT RESPONSE IN METASTATIC COLORECTAL CARCINOMA

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Article History: Received: 10.06.2023 **Revised:** 19.07.2023 **Accepted:** 23.07.2023

Abstract

Background: Imaging with FDG in patients with colorectal cancer is accepted as an effective method that could lead to changes in patient treatment.

Aim: To evaluate the potential qualitative and quantitative role of 18F-FDG PET/CT in assessing response in patients with metastatic colorectal cancer mCRC.

Patients & Methods: This IRB approved study prospectively recruited 34 patients with metastatic colorectal cancer (mCRC), confirmed by unequivocal imaging evidence or histopathology. All patients underwent two 18F-FDG PET/CT studies according to a standardized protocol; baseline study that confirmed the presence of metastases and post-therapy study to evaluate response.

Results: Highly significant positive correlation was found between response categories from PET or final status with SUVmax metrics and also with follow up tumor markers after therapy; although the latter showed slightly less correlation co-efficient (0.734) compared to 0.864-0.939 for changes in SUVmax. ROC-curve analysis discriminated patients with CMR from patients with (PMR, SMD and PMD), with excellent and fair accuracy for PET/CT and tumor markers respectively; with highly significant difference between the 2 ROC curves ($p < 0.0001$).

Conclusion: 18F-FDG PET/CT is valuable tool for evaluation of response in patients with mCRC. Changes in SUVmax parameters correlate well with final disease categorization. Qualitative assessment could provide an accurate diagnosis for true disease status, both when disease detection or control are considered as endpoints. TM also could provide useful global information about disease control.

Key words: PET/CT, Colo-rectal cancer, Tumor markers, Response assessment, EORTC

DOI: 10.48047/ecb/2023.12.8.620

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INTRODUCTION

Globally, colorectal cancer (CRC) is the third most common cancer diagnosed, and is associated with high rates of incidence and mortality for both men and women [(1)].

In Egypt, CRC accounts for 6.5% of all cancers according to the National Cancer Institute, Cairo University [(2)].

Before a true cancer develops, there are often earlier changes in the lining of the colon or rectum. If diagnosed early, before it has metastasized, the disease is considered curable. If the cancer has already spread to distant organs, the long term survival is much lower. With the adoption of novel therapies and surgical resection of metastases, patients are expected to survive more than 20 months [(3)].

Radical resection and postoperative chemotherapy remain the major management options for colorectal cancer, but recurrence and/or metastasis occur in 30-50% of the patients after surgery [(4)].

Contrast-enhanced CT is currently the most established and important tool for restaging in patients with suspicion of colorectal cancer recurrence [(5)].

MRI is often used for detecting pelvic recurrence of colorectal cancer due to its excellent soft tissue resolution [(6)].

However, when used alone, these conventional imaging modalities are poor in visualizing small intra-abdominal disseminated lesions and lymph node metastases and for differentiating tumor recurrence from postoperative or post-therapy changes. Because tumor shrinkage is the final step in cascade of therapy-related changes, metabolic

changes can early predict treatment response [7].
Glucose analogue [18F] fluorodeoxyglucose positron emission tomography (FDG-PET) coupled with CT (18F-FDG-PET/CT) provides metabolic information and has been found to be accurate in the detection of colorectal cancer and its distant metastasis as well as assessment of response [7].

PATIENTS AND METHODS

Study design and data acquisition

This is a prospective study in which thirty-four patients with evidence of proven metastatic colo-rectal cancer were referred for ^{18}F-FDG PET/CT in Department of Nuclear Medicine in Maadi Armed Forces Medical Compound in the period from March 2015 to October 2017.

The protocol of the study was approved by the ethical committee in Oncology and NM department in faculty of Medicine Cairo University.

All clinical and histopathological information was extracted from the patients' clinical sheet in agreement with the referring physicians. This included the pathological data, evidence of metastasis and current reason for FDG-PET/CT referral.

PATIENTS:

Inclusion criteria were Proven metastatic colo-rectal cancer evident by conventional methods, PET/CT, or histopathology. Baseline staging PET/CT and post-therapy PET/CT studies were done. A third FDG-PET/CT study was performed for few patients six months after complete therapy cessation for status evaluation and follow up. Baseline and post-therapy tumour markers assay was performed. Patients should have reasonable compliance and geographic proximity to allow adequate follow up. Life expectancy at least 6 months. Patients able to provide written informed consent before any study-specific procedure.

Exclusion Criteria: Patients with uncontrolled diabetes. Non metastatic patients. Life expectancy less than 6 months. Patients unable to provide consent.

Baseline work-up and Follow-up Protocol: Baseline assessment included complete medical history and physical examination. Radiological evaluation included computerized tomography (CT) scan of chest, abdomen and pelvis. Bone scan was performed at the baseline for patients with clinically suspicion of bone metastases or elevated tumor markers. Follow-up time after the post-therapy PET/CT was at least 6 months. PET/CT results were validated against the subsequent imaging studies or histopathological data whenever available. Our golden standard included clinical visits every month; tumour markers assay and conventional imaging also performed.

Technique of Whole-Body PET/CT Imaging with 18F-FDG:-

Physician Directive: Patients' full history were evaluated thoroughly for known allergy to the iodinated CT contrast prior to IV contrast injection. Dose modification for 18F-FDG according to patient's weight.

Patient Preparation: The patient was asked to fast for 6 hours prior to scan. Removal of any metallic items from the patient, including dentures, pants with zipper, bra, belts, bracelets, etc. The patient was asked to wear a staples gown. I.V. catheter was inserted in the patient's arm vein for administration of 18F-FDG. They were instructed to avoid caffeinated or alcoholic beverages but can have water during the uptake period. Patients were also instructed to avoid any kind of strenuous activity prior to the examination and following injection of the radioisotope to avoid physiologic muscle uptake of FDG. The patient was asked to void prior to scanning. Diabetic Patients: - Home blood glucose checks were performed few days before the PET exam to ensure adequate blood glucose levels (<200 mg/dl). In the current study, only six patients took oral treatment for diabetes and they were asked to discontinue metformin for 2 days before the study to minimize inadvertent gastrointestinal uptake. None of our patients was on insulin treatment.

Dosage Administration:

The average 18F-FDG dose was 0.1 mCi/kg for all patients and recorded. Imaging was performed 45 to 60 minutes after FDG administration, during this period patients were instructed to remain quiet in the relaxation room with minimal movement and talking until the completion of the PET/CT scan.

European Organization for Research and Treatment of Cancer (**EORTC)** response criteria were used for response evaluation, as follows: Complete Metabolic Response (CMR), Partial Metabolic Response (PMR), Stable Metabolic Disease (SD), and Progressive Metabolic Disease (PD).

STATISTICAL ANALYSIS:

Quantitative data were summarized and expressed as mean ± SD and median (range), whereas qualitative data were expressed as frequencies and percentages. Chi-square was used to find the association between different categorical variables. Correlation between different study characteristics was performed using Pearson's or Spearman's correlation test as appropriate. Differences of the mean values for continuous data were compared using Mann-Whitney or Kruskal Wallis test (for two or more independent groups, respectively). Bonferroni correction was used for multiple comparisons. True-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) readings were identified on the basis of subsequent clinical/imaging/histopathological validation. Diagnostic performance parameters were calculated in the form of sensitivity, specificity, accuracy, positive predictive value, and negative predictive value. The nonparametric McNemar test was used to evaluate the statistical significance of the differences

in sensitivity and specificity, whereas receiver-operating characteristic (ROC) analysis was used to compare the accuracy of PET/CT versus tumor markers. In all analyses, a two-sided $P < 0.05$ was considered significant.The analyses were carried out using the SPSS, 21.0 (SPSS Inc., Chicago, Illinois, USA), MedCalc 11.0 (MedCalc, Ostend, Belgium), and Microsoft Excel 2003 (Microsoft, Redmond, Washington, USA).

RESULTS

Table (1): Demographic and clinical data among 34 CRC patients:

Variables		Range	N (%)
Age (years)		32 – 78	57.14 ± 12.43 *
Sex		Male	20 (59%)
		Female	14 (41%)
Pathology		Adenocarcinoma	34 (100%)
Primary tumor site	Ascending		14 (41.2%)
	Transverse		0 (0%)
	Descending		5 (14.7%)
	Sigmoid		6 (17.6%)
	Recto-Sigmoid		3 (8.8%)
	Rectal		6 (17.6%)

Table 1 showed that the mean age of all patients was 57.14 ± 12.43 years. The majority of patients (59%) were males.

Table (2): Details of PET/CT metastatic findings among 34 CRC patients:

Variables		Frequency (%)
Number of metastatic sites		56 (100%)
Metastatic site distribution	Lymph Nodes (LN)	15 (27%)
	Liver	18 (32%)
	Lung	12 (21%)
	Peritoneal	6 (11%)
	Adrenal	2 (4%)
	Bone	1 (2%)
	Vaginal wall	1 (2%)
	Spleen	1 (2%)

Table 2 showed the number of total metastatic sites was (56). Most patients (32%) had liver metastasis, then (27%) for LN lesions, then (21%) for lung; while (21%) for the remaining sites. One patient had 4 metastatic sites (liver, lung, lymph nodes and bone), three had 3 metastatic sites: liver is common metastatic site for all of them (lung + adrenal, lung + LN and LN + peritoneum). Fourteen patients had 2 metastatic sites and 17 has only one site of metastase.

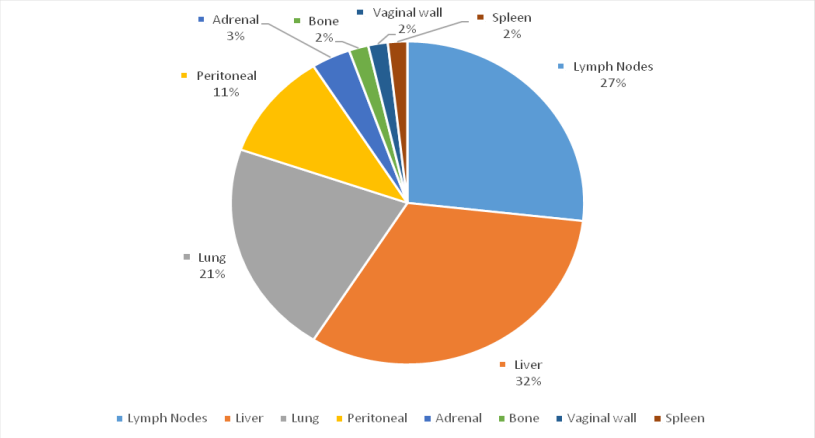

Figure (1): Metastatic site distribution among 34 CRC patients.

Table (3): Comparison between patients with 4 types of metabolic response as regards some avidity variables using ANOVA test:

Variable	CMR (N= 7)	PMR (N= 11)	SMD (N= 3)	PMD (N= 13)	ANOVA test	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	F-ratio	p value
SUVmax percentage change (the worst site)	-86 ± 3.05	-49.72 ± 21.26	2.33 ± 3.21	397.61 ± 476.61	6.070	0.002**
Sum of SUVmax percentage change (all sites)	-107.71 ± 38.54	-73.27 ± 49.79	2.33 ± 3.21	411 ± 495.61	6.452	0.002**
Average of SUVmax percentage change (all sites)	-84.28 ± 2.98	-44.45 ± 14.41	2.33 ± 3.21	197.46 ± 241.36	7.31	0.001**

Table 3 showed that different SUVmax metrics were compared against 18F-FDG PET/CT metabolic response impression. Statistically-significant difference was found between PMD and the rest of the categories

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Table (4): Overall 1st PET impression metabolic response compared to final outcomes using Chi square test:

Final Status →		CMR (N= 7)	PMR (N= 8)	SMD (N= 7)	PMD (N= 12)	p value
1st PET metabolic response	CMR (N=7)	7	0	0	0	< 0.0001**
	PMR (N=11)	0	8	3	0	
	SMD (N=3)	0	0	3	0	
	PMD (N=13)	0	0	1	12	

Table 4 showed that Comparative study between the 4 groups revealed highly significant difference as regards final true outcome compared to 1st metabolic impression in PET/CT ($p < 0.01$).

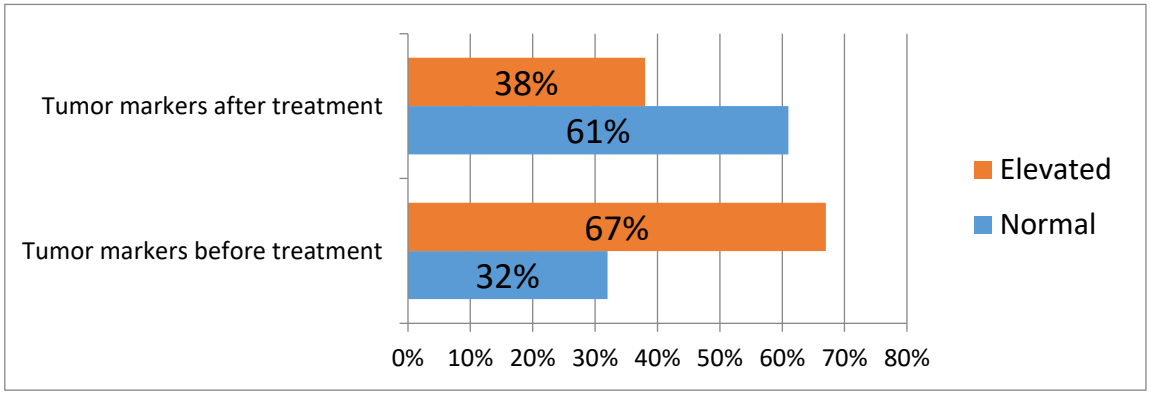

Figure (2): Tumor marker levels among 34 CRC patients before and after therapy.

Table (5): Comparison of SUV max metrics between patients with normal and elevated follow up tumor markers:

Variable	Normal (N= 21)	Elevated (N= 13)	Mann-Whitney U test
	Median (IQR)	Median (IQR)	p value
SUVmax percentage change (the worst site)	-51 (-83.75 to -19.25)	99 (17.25 to 487.5)	= 0.00012**
Sum of SUVmax percentage change (all sites)	-83 (-98 to -19.25)	133 (-4.5 to 528)	= 0.00016**
Average of SUVmax percentage change (all sites)	-51 (-83 to -19.25)	67 (-4.5 to 154.75)	= 0.000278**

Table 5 showed that the 34 CRC patients were classified according to the level of follow up tumor marker into 2 groups with normal (n = 21) and elevated (n = 13) levels. Normal tumor markers group showed highly significant decrease in FDG avidity compared with elevated tumor markers group ($p < 0.01$).

Table (6): Comparison between baseline and follow up tumor markers using McNemar's test:

Variable	Normal	Elevated	p value
Tumor markers before (N= 34)	11	23	= 0.0129**
Tumor markers after (N= 34)	21	13	
Percentage difference	+ 67.6%	- 32.4%	

Table 6 showed that Comparative study between baseline and follow up tumor markers revealed a marked decrease in tumor markers (- 38.2%) after therapy; while there was marked increase (+ 67.6%) before therapy; with highly significant difference.

Table (7): Tumor markers status after therapy compared to final outcome using Chi square test:

Final Status →	CMR (N= 7)	PMR (N= 8)	SMD (N= 7)	PMD (N= 12)	p value

Tumor marker after therapy	Normal (N=21)	7	8	4	2	< 0.0001**
	Elevated (N=13)	0	0	3	10	

Table 7 showed that tumor markers level was significantly associated with the final response status. However, 6 patients with SD (n = 4) or PD (n = 2) were having normal tumor markers.

Table (8): Correlations of PET avidity changes and tumor marker status against qualitative PET impression response and final outcomes among 34 CRC patients using Spearman's correlation test:

Variable	Metabolic Response		Final status	
	rho	p-value	rho	p-value
SUVmax percentage change (the worst site)	0.935	< 0.0001**	0.939	< 0.0001**
Sum of SUVmax percentage change (all sites)	0.869	< 0.0001**	0.864	< 0.0001**
Average of SUVmax percentage change (all sites)	0.938	< 0.0001**	0.936	< 0.0001**
Tumor markers (after therapy)	0.640	< 0.0001**	0.734	< 0.0001**

Table 8 showed that highly significant positive correlation was found between response categories from PET or final status with SUVmax metrics and also with follow up tumor markers after therapy; although the latter showed slightly less correlation co-efficient (0.734) compared to 0.864-0.939 for changes in SUVmax
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Table (9): Roc-curves of PET/CT and tumor marker for disease detection to discriminate patients with CR from patients with (PR, SD and PD):

(+ve) from (–ve) cases	Sensitivity	Specificity	Accuracy
PET (Disease detection)	100 %	100 %	100 %
Tumor markers (Disease detection)	48 %	100 %	74 %
p- for difference	P = 0.0001	-	P < 0.0001

Table 9 showed that ROC-curve analysis discriminated patients with CMR from patients with (PMR, SMD and PMD), with excellent and fair accuracy for PET/CT and tumor markers respectively; with highly significant difference between the 2 ROC curves (p < 0.0001)

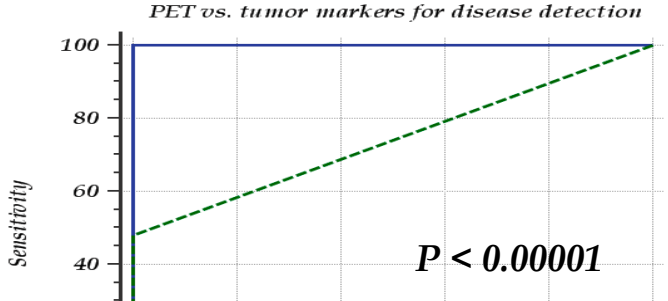


Figure (3): ROC-curve analysis for disease detection

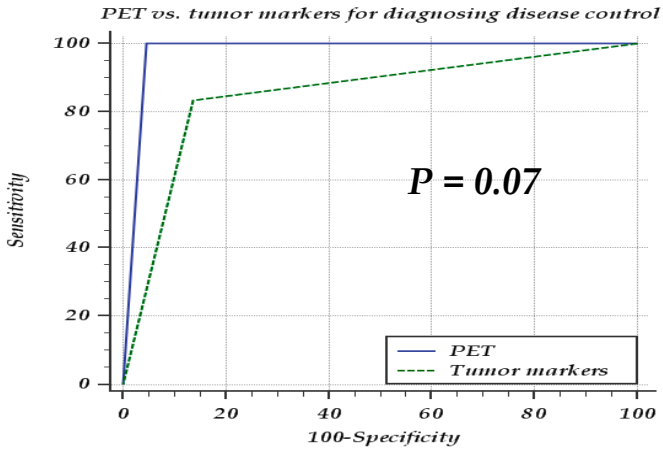
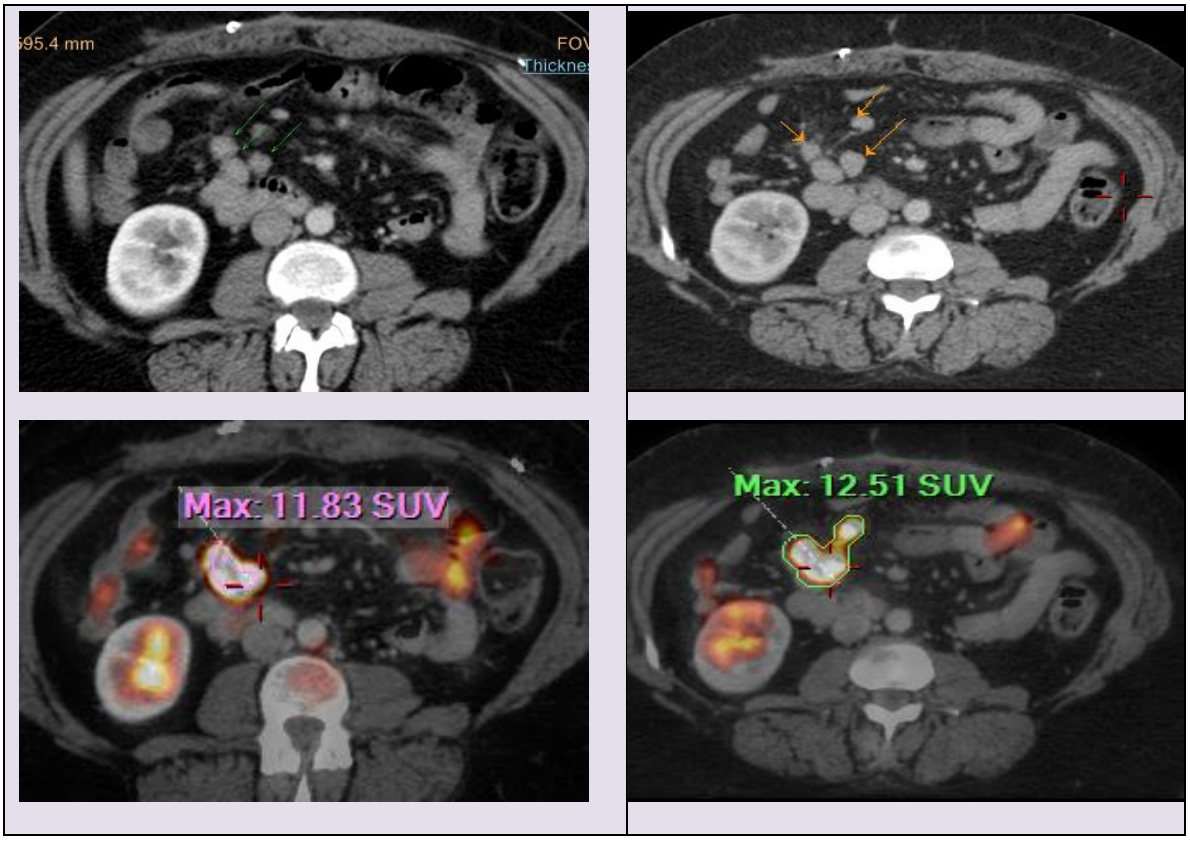


Figure (4): ROC-curve analysis for disease control.

Case No.3

A 50-year- old female patient, presented with history of cancer colon surgically resected on 11-2016. The first PET/CT in "January 2017" revealed hypermetabolic mesenteric lymphadenopathy, for which chemotherapy was received, she referred for follow up PET/CT examination in "July 2017". **PET/CT** in "January 2017" showed hypermetabolic mesenteric lymph nodes with SUV max= 12. **PET/CT** in "July 2017" showed stationary course of the previous hypermetabolic mesenteric lymph nodes with SUV max= 12.5. Tumor markers levels were normal before and after treatment.



Follow up PET/CT examination revealed stationary course of the hypermetabolic mesenteric lymph nodes with no newly developed metastatic deposits, reflecting: **stationary disease.**

Discussion

In this study, we investigated the potential role of FDG PET/CT and tumor markers in patients with metastatic colorectal disease. The mean age of all patients was 57.14 ± 12.43 years. The majority of patients (59%) were males, which comes in line with the age groups reported by **Cusack** et al as age incidence between 45-50 years **[8].**

Regarding primary tumor site, this study showed that most patients (41%) had their tumor located at the ascending colon; sigmoid and rectal were 17% each; while 14% had descending colon tumor, this result was not quite well matching with results of **Cusack** et al that showed in his study the incidence of local recurrence in ascending colon was 9 % and rectum was 30 %, in sigmoid was 28 % and in descending it was 9 %**. [8],** no specific reason was established to this discordance, however the possibility of the racial reason or dietary habits should be considered **[8].**

The most common sites of metastases included the liver, lung and brain **[105].** According to the study done by **Khatri** et al, liver metastases was found in 35-55 %, where as in our study it was nearly the same results as it was about 32 % of cases found with liver metastases **[9].**

Also, **Davey** et al showed pulmonary metastases in 10-25 % of cases, while in the current work it was found that pulmonary metastases represent 21 % of the cases **[10].**

Koppe et al agreed with **Yang** et al that peritoneal deposit could occur in 10- 30 % of cases, we also in our study relatively agreed with that as we found that peritoneal deposits represent 11 % of cases **[11],[12].**

In this study, each patient underwent at least two PET/CT studies: baseline scan, which documented the presence of metastatic colorectal disease and follow-up study to assess treatment response after cessation of specific therapies.

We found that half of the patients (53%) had complete or partial metabolic response to therapy; while about one third had progressive metabolic disease. That comes in line with the work performed by **Walker** et al, they showed that the positive yield of FDG-PET in this situation ranges between 38 and 77%. **[13].**

In our study the 34 CRC patients were classified according to the level of follow up tumor marker into 2 groups with normal (n = 21) and elevated (n = 13) levels.

A marked decrease in tumor markers (- 38.2%) after therapy was found; while there was marked increase (+ 67.6%) before therapy; with highly significant difference (= 0.008), as shown by a comparative study in our work between baseline and follow up tumor markers. Normal tumor markers group showed highly significant decrease in FDG avidity compared with elevated tumor markers group (p <

0.01).

Also, our study showed a highly significant positive correlation between different response categories (as assessed from PET or according to the final true status) with SUVmax metrics and also with follow up tumor markers after therapy.

A number of studies have suggested that levels of the circulating tumor markers such as CA 15-3 or CA 27.29 are related to tumor burden **(14).**

In a study conducted by **Sanli** et al, a comparison of PET/CT performance in patients with normal and elevated CEA levels was performed on a pool of 235 patients **(14).** CRC recurrence was detected in 64.4% of patients with CEA levels <5 ng/ml (sensitivity and specificity of 100 and 84%, respectively) and 88% of patients with levels >5 ng/ml (sensitivity and specificity of 97.1 and 95.7%, respectively) **(15)**

In a study conducted by **Caglar** and his colleagues they showed the value of serum tumor marker assay and their correlation with semiquantitative FDG PET parameters, they reported a sensitivity and specificity for serum CEA measurement in detecting recurrent CRC of 74% and 86%, respectively, compared to 48% and 100% in our study, which could be related to the timing of tumor marker assay in relation to the given therapy (early after therapy or after therapy completion) **(16).**

In the current study two analyses were performed. First, for disease detection, CMR was considered negative and the rest of categories were considered positive for disease, second, for disease control evaluation, categories with CMR, PMR or SMD were considered negative while PMD was considered positive, with a PET sensitivity and accuracy of 100% in contrast to a sensitivity of 48 % and accuracy of 74 % for tumor markers.

Conclusion

semiquantitative assessment of 18F-FDG PET/CT studies in patients with metastatic colo-rectal cancer, could correlate with true disease status and generate superior yet complementary information compared to tumor markers.

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