Egyptian J. Nucl. Med., Vol. 30, No. 1, June 2025

Original Article, PET/CT

Role of ^{18}F-FDG PET/CT in Evaluating Therapeutic Response of Metastatic Colorectal Carcinoma: Metabolic (EORTC) Versus Morphologic (RECIST 1.1) Criteria

Mostafa N[1], Rayan A[1], Moustafa Sh[1], Mekawi M[1], Khallaf S[2], Tawakol A[3]

[1]Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Assiut University, [2]Department of Medical Oncology, South Egypt Cancer Institute, Assiut University, [3]Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Cairo University Egypt.

ABSTRACT:

Background: Colorectal cancer (CRC) is the third most common diagnosed cancer globally. Response Evaluation Criteria in Solid Tumors (RECIST) are the morphologic criteria extensively used in clinical practice to measure tumor response. However, they based on the size changes.^{18}F-FDG PET/CT is increasingly used to track tumor responses to anti-cancer therapy, which allows the evaluation of disease response irrespective of anatomical alterations. The FDG PET-based Research and Treatment of Cancer (EORTC) criteria are used to assess metabolic response to the anti-cancer therapy, we compared both criteria in the current work. **Patients and methods:** A total of 35 metastatic CRC (mCRC) patients were recruited in this prospective study. Baseline and post-therapy FDG PET/CT scans were conducted. PET/CT-derived parameters; SUVmax, TLG, and MTV were measured in each scan. The values of SUVmax of the target lesions (up to five lesions) were summed in both studies, and the assessment of the treatment response by EORTC and RECIST 1.1 criteria was carried out. The % changes in the SUVmax, TLG, and MTV of the hottest lesions between the baseline and follow-up scans were calculated. Also, the value of the PET/CT metrics in predicting disease control was determined. **Results:** We found a poor agreement rate

(48.6%) between EORTC and RECIST1.1 in response evaluation, a κ-coefficient = 0.053, while a significant good agreement (κ- coefficient = 0.719, $p < 0.01$) between both criteria was observed when the patients were divided into disease control and non-control groups. The %Δ SUVmax remained a significant independent predictor of disease control ($p= 0.029$). **Conclusions:** FDG PET/CT-based metabolic criteria are more accurate in assessing treatment response in patients with mCRC than CT-based morphologic criteria. The ΔSUVmax is the most significant predictor of disease control.

Keywords: FDG-PET/CT, EORTC, RECIST 1.1, Colorectal carcinoma, Response evaluation.

Corresponding author: Ahmed Tawakol **E-mail: dr.tawakol@gmail.com**

Submission date: 08/12/2024 **Acceptance date: 18/12/2024**

INTRODUCTION:

Colorectal (CRC) cancer is the third most frequent cancer diagnosed worldwide, accounting for 10% of new cases, and the second leading cause of cancer death, accounting for 9.4% of global cancer-related mortalities. [1] Approximately 15–30% of CRC patients presented with synchronous (simultaneously detected with the primary tumor) or metachronous (develop over the course of the disease) metastases. [2] The liver is the commonest site for metastasis. Up to 50% of metastatic CRC (mCRC) patients have synchronous colorectal liver metastases. [3] Assessing tumor response after treatment is one of the major challenges in the management of mCRC. [4] A variety of approaches for monitoring tumor response have been developed in an attempt to optimize cancer therapy and patient management. Typically, anatomic imaging is used to define accepted response criteria. The World Health Organization (WHO) criteria were suggested in 1976, followed by Response Evaluation Criteria in Solid Tumors (RECIST) in

2000. [5] In 2009, the updated RECIST 1.1 criteria were published to facilitate, optimize, and standardize tumor burden evaluations. [6] Nevertheless, with the advent of novel cytostatic rather than cytotoxic cancer therapies, the anatomic criteria appear to be insufficient for evaluating response. [5] In this scenario, ^{18}F- fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has been reported as a valuable tool for demonstrating metabolic response. [7] The majority of malignant tumors have elevated FDG uptake, which is generally associated with tumor cell viability and proliferation. Following successful therapy, the tumoral FDG uptake would rapidly decline, anticipating tumor size changes and reflecting tumor cell death rate. [8] Furthermore, the post-therapy change in metabolic activity could be quantified using PET-based semi-quantitative metrics. [9] Currently, two sets of internationally recognized PET-based criteria are available to assess metabolic alterations and therapeutic response following treatments. The European Organization for Research and Treatment of Cancer (EORTC) criteria is the first published PET-based scoring system for evaluating the metabolic response of solid tumors and is relied on baseline selected lesion-specific regions of interest (ROIs), which are monitored throughout the following follow-up scan. The selected lesions must have the highest FDG avidity. The metabolic response is assessed by calculating the percent change in the target lesion SUVmax between the baseline and follow-up scans. [8] The second is PET Response Criteria in Solid Tumors (PERCIST), in which the peak standardized uptake value adjusted for lean body mass (SUL peak) is used instead of SUVmax. [9] A meta-analysis encompassing 348 patients reported that both EORTC and PERCIST criteria had nearly perfect agreement in assessing tumor response, with a kappa of 0.946[10]. However, EORTC may be more practical for clinical use, as SUVmax remains the most commonly used metric to express metabolic tumor activity. [11]

Our study aims to compare FDG PET-based metabolic (EORTC) to CT-based morphologic criteria (RECIST 1.1), as well as to assess FDG PET/CT-based semi-quantitative indices, in evaluating treatment response in patients with mCRC.

PATIENTS AND METHODS:

Our institution's ethics committee approved this prospective study, which enrolled 35 patients with histo-pathologically confirmed colorectal adenocarcinoma; all of them were ≥18 years old, had pathologically and/or radiologically identified synchronous or metachronous metastatic lesion(s) with at least one hypermetabolic lesion on the baseline PET/CT, had a life expectancy of more than 6 months, and underwent both pre-therapy (baseline) as well as end-of-therapy (follow-up) ^{18}F-FDG PET/CT studies. ^{18}F-FDG PET/CT was conducted within two weeks before initiating therapy and within one month (at least two weeks) after terminating therapy. Baseline and follow-up tumor marker; carcinoembryonic antigen (CEA) was obtained for all patients. Interval therapy included chemotherapy ± target therapy.

Patients with non-metastatic CRCs, CRCs other than adenocarcinoma, and those with a life expectancy of less than 6 months or severe comorbidities were excluded. All patients were instructed to fast (except for water) for 4–6 hours before the examination and to avoid strenuous activity for the preceding 24 hours. Prior to the ^{18}F-FDG injection, blood glucose levels were measured to make sure they were less than 200 mg/dL. in all participants, including diabetics. An intravenous dose of 0.1 mCi/kg of ^{18}F- FDG was given. Following ^{18}F-FDG administration (uptake time), all patients were told to remain supine or seated in a quiet room and to evacuate the urinary bladder shortly before starting PET/CT imaging, which began 45–60 minutes after tracer administration.

^{18}F-FDG PET/CT Imaging:

Imaging was obtained from the vertex to the mid-thigh using an integrated PET/CT system (Siemens Healthcare, Erlangen, Germany) with a 16-slice multi-detector CT scanner.

A non-contrast enhanced low-dose CT scan was acquired using these parameters: tube voltage of 130 kV, tube current of 125 mAs, rotation time of 0.6 seconds, pitch of 0.8,

and slice thickness of 5 mm. The CT scan was immediately followed by a PET scan. Approximately 6 bed positions were used, each with a 2-minute acquisition time. A time-off-light (TOF)+true X technique with four iterations, ten subsets, and a 5- mm Gaussian filter was used to reconstruct PET images. PET and CT images were then formatted and displayed in three different (axial, coronal, and sagittal) plans. Finally, the co-registration of PET and CT images was performed to create fused PET/CT images.

PET/CT Interpretation:

Volumes of interest (VOIs) were drawn over all hypermetabolic metastatic lesions in both PET/CT (baseline and follow-up) studies to obtain and record PET- semi- quantitative parameters (SUVmax, TLG, and MTV), and the lesions with the highest SUVmax were analyzed (target lesions). Nuclear medicine physicians with more than 15 years of experience interpreted the PET/CT images.

Metabolic response using EORTC criteria

As EORTC didn't give information about the exact number of target lesions to be assessed, up to five lesions in total were chosen. The same lesions were measured in the follow-up scan. In each scan, the targets' SUVmax measurements were added together to produce summed SUVmax. The difference between the baseline and post-therapy summed SUVmax was computed, divided by the baseline summed SUVmax values, and multiplied by 100. We reported the therapeutic response according to the EORTC criteria, which are divided into four categories as follows: [8]

Complete metabolic response (CMR): complete resolution of all FDG-avid metastatic lesions.

Partial metabolic response (PMR): a reduction of ≥ 25% in the summed SUVmax of the target lesions.

Progressive metabolic disease (PMD): an increase of at least 25% in the summed SUVmax of the target lesion, a significant

increase in the FDG uptake within the target lesion, or newly developed FDG-avid metastatic lesion (s).

Stable metabolic disease (SD): response between PMR and PMD.

Morphologic response using RECIST 1.1 criteria

On the baseline CT, up to five total target lesions were chosen (corresponding to the selected target lesions in PET/CT). The longest diameters of non-nodal (short-axis diameters of nodal) lesions were calculated and summed. The same target lesions were measured and summed in the post-therapy CT examination. Response was determined as the percentage difference in the summed diameters between the baseline and follow-up scans and interpreted as follows: [6]

Complete response (CR): disappearance of all lesions seen in the baseline study.

Partial response (PR): a reduction of ≥ 30% in the summed diameters of the target lesions in the absence of new lesions.

Progressive disease (PD): an increase of at least 20% in the summed diameters of the target lesions (an absolute increase of ≥ 5 mm) or newly developed lesion (s).

Stable disease (SD): neither PR nor PD.

Statistical analysis:

The data was analyzed using SPSS software version 22 (IBM Inc., Armonk, New York, NY, USA). Categorical data were described using frequency and percentage and compared using the Pearson chi-square test or Fisher exact test as appropriate. Continuous normally distributed data were described using mean ± standard deviation and compared using independent samples t-test. Continuous not normally distributed data were described using the median (range) and compared using the Mann-Whitney U-test. The agreement between EORTC and RECIST response criteria was determined using κ-statistic. The agreement was interpreted as poor (κ <0.20), fair (κ = 0.21 – 0.40), moderate (κ = 0.41–0.60), good (κ = 0.61 – 0.80),

and almost perfect (κ >0.80). Univariate and multivariate logistic regression analyses were conducted to identify predictors for disease control. The results were shown as odds ratio OR) with a 95% confidence interval (CI).

RESULTS:

Clinico-pathologic characteristics:

A total of thirty-five patients with pathologically proven CRC and ^{18}F-FDG PET/CT-detected metastatic lesion (s) were recruited in this prospective study. The included patients were 22 males and 13 females with a mean age of 48.6±13 years (range: 20-80 years). Eighteen patients presented with metastases at the first presentation of the disease, whereas 17 patients presented with recurrent metastatic disease after treatment of the early primary tumor. Thirteen patients had rectosigmoid cancer (37.1%), a rectal/anorectal primary lesion was found in 10 cases (28.6%), followed by left-sided cancer colon (22.9%), and the lowest percent had right-sided cancer colon (11.4%). The majority of cases had non-mucinous adenocarcinoma (91.4%) and G2 primary tumor (82.9%). Nineteen patients (54.3%) had normal CEA and 16 had high-level CEA (45.7%). Twenty-seven (77.1%) patients received chemotherapy combined with target therapy, while the remaining 8 (22.9%) patients received only chemotherapy (**Table 1)**.

Table 1: Clinico-pathological characteristics of recruited patients

Characteristics	No.	%
Age (years):		
• < 50	21	60
• ≥ 50	14	40
Sex		
• Male	22	62.9
• Female	13	37.1
Primary Site		
• Recto sigmoid	13	37.1
• Rectal/anorectal	10	28.6
• Left colon	8	22.9
• Right colon	4	11.4
Type of metastases		
• Synchronous	18	51.4
• Metachronous	17	48.6
Pathological subtype		
• Non-mucinous adenocarcinoma	32	91.4
• Mucinous adenocarcinoma	3	8.6
Histologic grading		
• G1	2	5.7
• G2	29	82.9
• G3	4	11.4
KRAS status		
• Mutant	15	42.9
• Wild	16	45.7
• Unknown	4	11.4
Tumor marker (CEA, ng/ml)		
• Normal	19	54.3
• High	16	45.7
Type of therapy		
• Combined chemo-target therapy	27	77.1
• Chemotherapy	8	22.9

PET/CT distribution of metastatic lesions:

Peritoneal, regional nodal, hepatic, distant nodal, and pulmonary metastases were found in 15, 13, 11, 10, and 9 cases, respectively **(Table 2)**.

Table 2: PET/CT distribution of metastatic lesions in studied patients

Metastatic organs	No (%)
Peritoneum	15 (42.8)
Regional lymph nodes	13 (37.1)
Liver	11 (31.4)
Non-regional lymph nodes	10 (28.6)
Lung	9 (25.7)
*Others	6 (17.1)

* Other metastases included adnexal (2), urinary bladder (1), ureter (1), adrenal (1), and osseous (1)

Comparison between EORTC and RECIST criteria:

When we compared metabolic response using EORTC criteria to morphologic response using RECIST 1.1 criteria, we noted that 19 patients were evaluated as having PMD in respect to EORTC criteria, whereas SMD was observed in 7 patients and PMR was recorded in 5 patients. According to RECIST 1.1 criteria, PD was noted in 14 patients, whereas SD was seen in 13 patients, and 4 patients were evaluated as having PR. EORTC/RECIST inconsistency was found mainly in the categorization of stable disease; from 13 patients reported as demonstrating SD by RECIST, 3 patients upgraded to the category of PMR, while 4 patients were downgraded to the category of PMD by using EORTC ($p<0.01$). On the other hand, both criteria matched in assessing four cases as having complete remission **(Table 3)**. The agreement rate between EORTC and RECIST in response evaluation was only 48.6% (17/35) with a κ-coefficient of 0.053, indicating poor agreement. However, when the patients were reclassified into disease control (CR, PR, and SD) and non-control (PD) groups, EORTC and RECIST showed a significant good agreement (κ-coefficient = 0.719, $p < 0.01$).

Table 3: Treatment response of studied patients using EORTC versus RECIST 1.1 criteria

	EORTC-based Response				Total	P
RECIST 1.1-based Response	**CMR**	**SMD**	**PMD**	**PMR**		
CR	4	0	0	0	4	**<0.01**
SD	0	6	4	3	13	
PD	0	0	14	0	14	
PR	0	1	1	2	4	
Total	4	7	19	5	35	

Logistic regression analysis for predicting disease control:

In the univariate logistic regression analysis, synchronous metastases, normal baseline CEA, and the percentage difference in SUVmax (%ΔSUVmax) were significant independent predictors of disease control (p=0.014, 0.006, and 0.009, respectively).

While, in the multivariate analyses, only the %ΔSUVmax remained a significant independent predictor of disease control (p= 0.029) (**Table 4).**

Table 4: Univariate and multivariate logistic regression analyses for predicting disease control

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Sex						
• Male	0.972	0.246-3.849	0.968			
• Female*	1.00					
Age group						
• <50	1.980	0.494-7.939	0.335			
• ≥ 50*	1.00					
Primary tumor site						
• Rectal/anorectal	3.00	0.525-17.159	0.217			
• Rectosigmoid	1.714	0.339-8.676	0.515			
• Colon*	1.00					
Tumor histopathology						
• Mucinous	1.765	0.145-21.474	0.656			
• Non-mucinous*	1.00					
Number of distant metastatic organs						
• One organ	1.283	0.314-5.253	0.729			
• Multi-organs*	1.00					
Type of metastasis						
• Synchronous	6.500	1.467-28.804	**0.014**			
• Metachronous*	1.00					
Baseline tumor marker (CEA)						
• Normal	9.389	1.925-45.804	**0.006**			
• High*	1.00					
KRAS status						
• Mutant*	1.00					
• Wild	0.525	0.125-2.200	0.378			
• Unknow	0.875	0.096-7.952	0.906			
Target baseline SUV_{max}	0.988	0.941-1.038	0.640			
Target baseline MTV	0.997	0.989-1.006	0.574			
Target baseline TLG	0.999	0.977-1.001	0.371			
%Δ difference SUV_{max}	0.968	0.945-0.992	**0.009**	0.962	0.930-0.996	**0.029**
%Δ Percent difference MTV	0.985	0.968-1.002	0.076			
%Δ Percent difference TLG	0.986	0.971-1.002	0.096			

OR, odds ratio; CI, confidence interval; %Δ: percent difference between baseline and follow-up PET/CT based indices

* Reference group

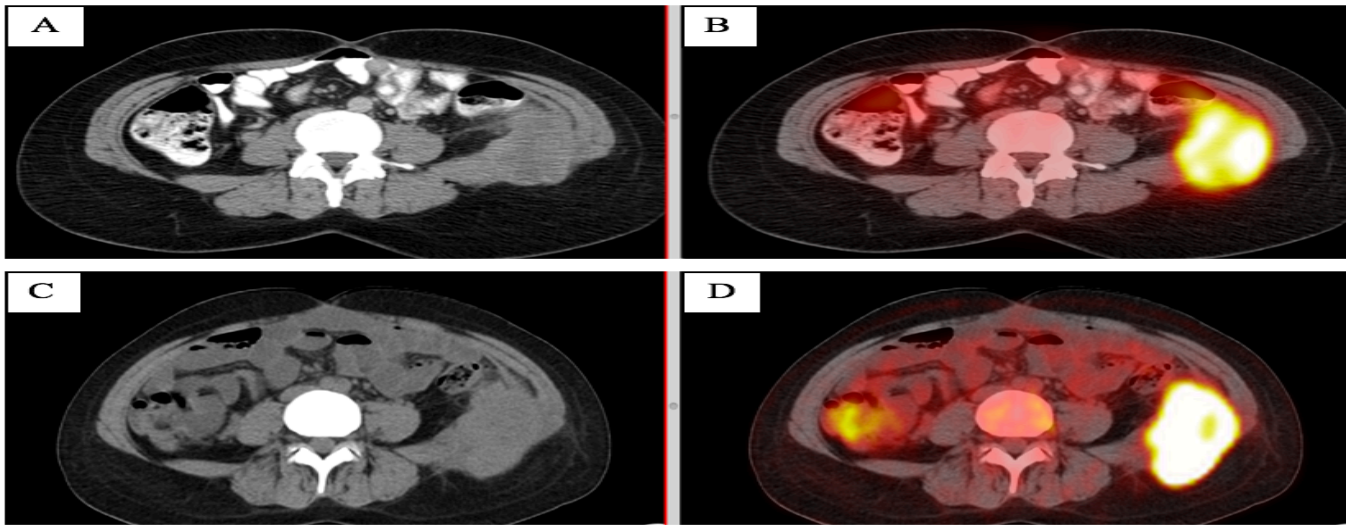

Figure (1): A 32-year-old female patient with left-sided colorectal adenocarcinoma underwent left hemicolectomy. After treating the primary lesion, she developed a metachronous metastatic left ilio-lumbar lobulated soft tissue mass lesion implanted at the surgical incisional scar, which invaded the underlying muscles, as illustrated in the baseline CT image (A). The baseline ^{18}F-FDG PET/CT scan (B) showed corresponding intense FDG uptake. The follow-up CT (C) following chemo and target therapy indicated stable disease (SD), while follow-up PET/CT (D) showed progressive metabolic disease (PMD).

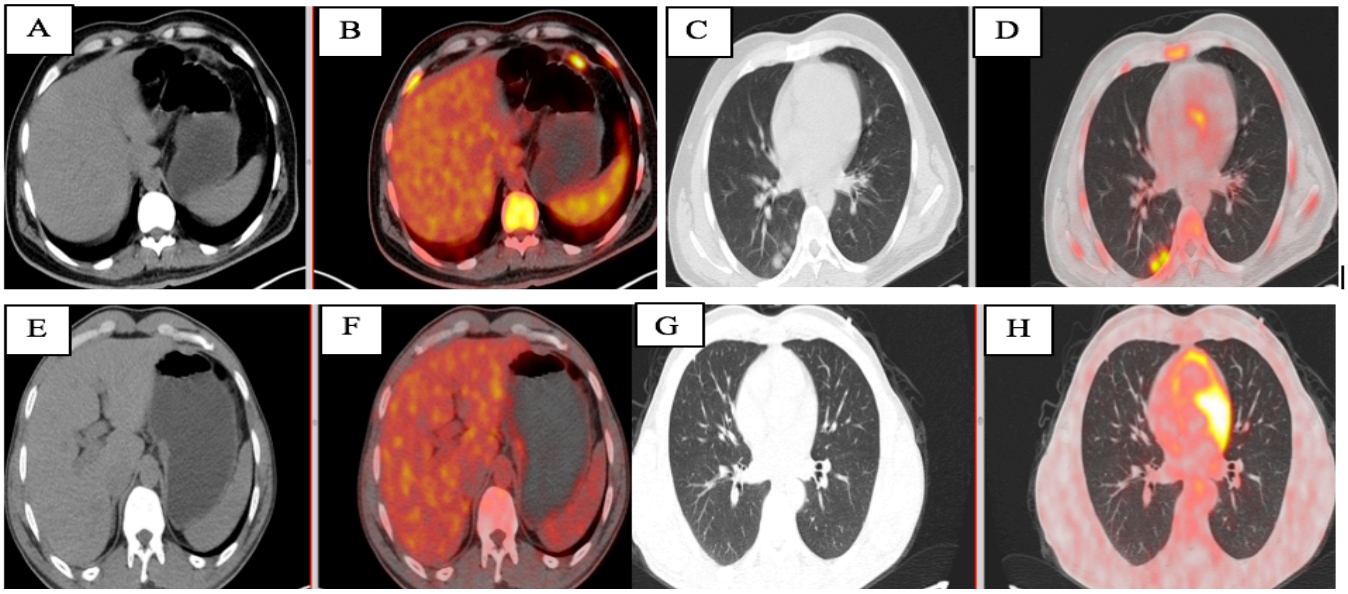

Figure (2): A 28-year-old male patient with sigmoid adenocarcinoma underwent sigmoidectomy. The baseline CT (A&C) and ^{18}F-PET/CT (B&D) images showed synchronous peritoneal and pulmonary deposits. Both follow-up CT (E&G) and PET/CT (F&H) images following chemo and target therapy demonstrated complete remission (CR).

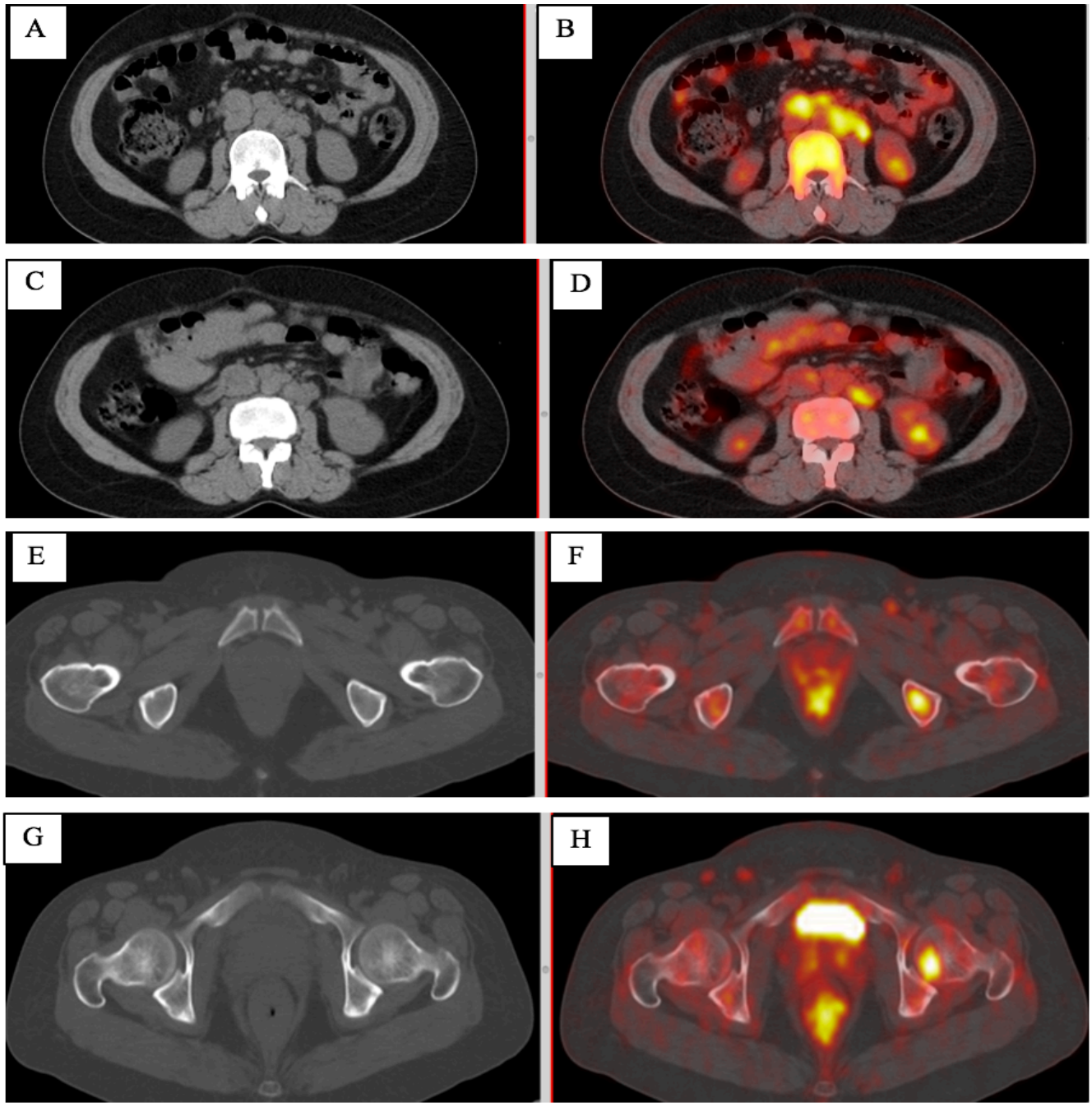

Figure (3): A 34-year-old female patient with anorectal adenocarcinoma had synchronous metabolically active metastatic abdomino-pelvic lymph nodes, as shown in the baseline CT (A) and ^{18}F-PET/CT (B). The follow-up CT (C) following chemo and target therapy demonstrated >30% decrease in the summed short-axis diameters of the target nodal lesions denoting a partial response (PR); however, follow-up PET/CT (F&H) demonstrated newly developed hypermetabolic bone marrow metastatic lesions (ischium & left femoral head), indicative of progressive disease (PMD), whereas no remarkable changes were seen on CT images (E&G).

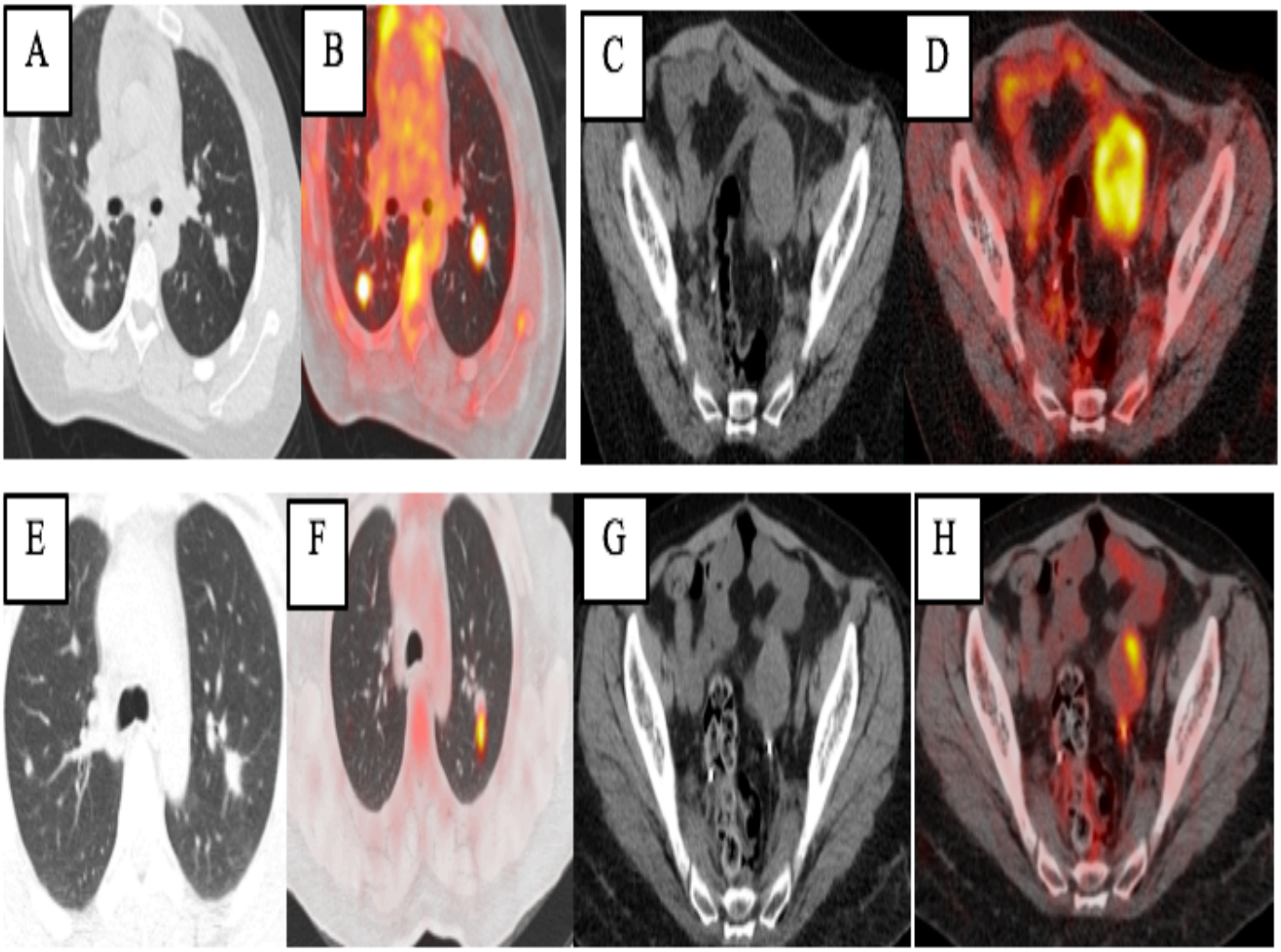

Figure (4): A 27-year-old female patient with rectal adenocarcinoma underwent resection re- anastomosis. After treating the primary lesion, she developed metachronous metastatic left adnexal, ureteric, and bilateral pulmonary deposits, as illustrated in the baseline CT image (A&C). The baseline ^{18}F-FDG PET/CT scan (B&D) showed correspondingly intense FDG uptake. The follow-up CT (E&G) after chemo and target therapy revealed an 18.7% decrease in the summed longest diameters of the target lesions suggesting stable disease (SD), while PET/CT (F&H) demonstrated > 25% decrease in the summed SUVmax of the target lesions indicative of a partial metabolic response (PMR).

DISCUSSION:

Despite recent advances in cancer research, CRC remains the second leading cause of death in both men and women globally. [1] CRC metastases represent a major obstacle to curative therapy, contributing significantly to CRC-related mortality. [12] It is well known that the liver is the most common site for metastasis in patients with CRC, followed by the lung, with the peritoneum ranking third. [13] In contrast, our results revealed that peritoneal metastases were the most frequent, accounting for 42.8% of our mCRC patients. The high prevalence of young age (<50 years) and lymph node involvement among our patients, which are established risk factors for synchronous peritoneal metastases in CRC, may explain the contradictory findings. [14], [15] Usually, the morphological size criteria of tumor lesions as determined by CT or magnetic resonance imaging is used to assess the therapeutic response in mCRC. However, emerging evidence demonstrates that tumor size does not accurately predict clinical outcomes for treatments based on alternative mechanisms, such as targeted therapy and immunotherapies. [16] FDG-PET/CT proved to be effective in determining responses to chemo and targeted treatment. [17]

In the present study, we compared two different therapy response criteria, FDG PET-based EORTC and CT-based RECIST 1.1, for the evaluation of therapeutic response in patients with mCRC.

Stable disease category of CT-based RECIST criteria is a fundamental issue that can potentially be addressed by FDG PET-based criteria, as long as FDG uptake is determined by tumor cell metabolic activity, which has been reported to correlate with tumor cell proliferation in many tumor varieties. Tumor growth suppression is more likely to cause a reduction in tumor FDG uptake than stationary FDG uptake. As a result, FDG PET is more suitable than CT for identifying true disease stabilization.[18] We found that response discordance between EORTC and RECIST criteria appears predominantly in patients with stable disease on RECIST; EORTC reclassified 7/13 with SD into three

patients as having PMR and four patients as showing PMD. **Skougaard et al.** compared PET/CT-based and CT-based criteria for assessing therapeutic response in patients with mCRC and reported that 20/39 patients with SD were reclassified as having PMR and 4/39 as having PMD. [19] **Aras et al.** observed that seven patients had stable disease based on anatomic criteria while exhibiting partial responses based on metabolic criteria. The authors emphasized that, whilst anatomic imaging modalities demonstrate a reduction in the tumor size considerably later after starting therapy, the metabolic response occurs much earlier. [20] Notably, in comparison to our findings, the aforementioned two studies demonstrated that a considerable portion of patients shifted from the SD category to the PMR category when response assessment based on FGD-PET/CT. This disparity is presumably due to the different treatment lines used in both studies, as well as the diversity of the cancer patients included in the latter.[19],[20] On the other hand, despite a partial response recorded in one patient using RECIST criteria, it was declared stable according to EORTC criteria. The patient's follow-up confirmed the disease's stability.

In spite of the poor agreement between EORCT and RECIST criteria in evaluating therapy response, we observed a significant good agreement between both criteria when we classified the patients into disease control and non-disease control categories, which is consistent with the findings of **Bang et al.,** who noticed an increased agreement rate (from 38% to 78%) between RECIST and PERCIST criteria when this categorization was applied. [21]

Monitoring treatment response in cancer patients is crucial for identifying responders and non-responders. In clinical practice, patients demonstrating disease progression following anti-cancer treatment typically require a shift in therapeutic strategy. If the metabolic criteria had been applied instead of morphologic criteria, the treatment outcomes would have changed in about 10% of the patients. [10] According to this hypothesis, four (11.4%) patients in our research who were considered to have SD using RECIST were reclassified as having progressive disease by EORTC, necessitating a change in treatment line. This highlights the clinical significance of metabolic response criteria for making treatment decisions. The current study found that %Δ SUVmax was a significant

predictor of disease control, while %ΔMTV and %ΔTLG were ineffective. **Melton et al.,** in a study discussing the efficacy of FDG PET/CT for evaluating the response of rectal cancer to neoadjuvant treatment, found that %ΔMTV and %ΔTLG were not useful predictors of response, but %ΔSUVmax was useful. [22] **Burger and colleagues** demonstrated a significant link between ΔSUV and pathologic response to neoadjuvant therapy in CRC patients with hepatic metastases. [23]

We observed that whereas normal-level pretreatment CEA and synchronous metastasis were significant predictors of disease control in the univariate analysis, they lost their relevance in the multivariate analysis**. Eker et al.** revealed similar findings with CEA and concluded that CA 19-9 is superior to CEA in predicting outcomes in mCRC patients. [24]

Some articles demonstrated identical prognosis for patients with synchronous and metachronous mCRC [25], [26] , while others claimed a slightly more favorable prognosis for those with metachronous mCRC. [27], [28]

This disagreement might be due to racial variations, different definitions of synchronous and metachronous metastases, and environmental variables. The current study's small sample size, as well as the prevalence of left-sided vs right-sided cancer colon among our patients with synchronous metastases, may explain this finding.

Our study has some limitations: an intravenous contrast agent was not routinely used for PET/CT examination at our department, which might lead to an inaccurate assessment of tumor diameter; a relatively small sample size; and insufficient survival data to correlate with overall survival. However, the current manuscript's findings could be interpreted as preliminary results and should be verified by larger prospective studies.

CONCLUSIONS:

The current manuscript revealed that FDG PET/CT-based metabolic criteria are more accurate in assessing treatment response in patients with mCRC than CT-based morphologic criteria, particularly in the setting of stable disease. Our data demonstrated that both criteria agreed well in discriminating between controlled disease and disease progression. Predictive indicators for tumor response to therapy provide more effective treatment options. We suggest that ΔSUVmax is the most significant predictor of disease control.

REFRENCES:

1. **Sung H, Ferlay J, Siegel RL, et al.** Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin.; 71(3):209–49, **2021**.
2. **Väyrynen V, Wirta E V, Seppälä T, et al.** Incidence and management of patients with colorectal cancer and synchronous and metachronous colorectal metastases: a population-based study. BJS open.; 4(4):685–92, **2020**.
3. **Mitchell D, Puckett Y, Nguyen QN.** Literature review of current management of colorectal liver metastasis. Cureus.;11(1), **2019**.
4. **Monteil J, Mahmoudi N, Leobon S, et al.** Chemotherapy response evaluation in metastatic colorectal cancer with FDG PET/CT and CT scans. Anticancer Res.;29(7):2563–8, **2009**.
5. **Miceli A, Jonghi-Lavarini L, Santo G, et al.** [18F] FDG PET/CT criteria for treatment response assessment: EORTC and beyond. Clin Transl Imaging.;11(5):421–37, **2023**.
6. **Eisenhauer EA, Therasse P, Bogaerts et al.** New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer.; 45(2):228–47, **2009**.
7. **Van den Abbeele AD.** The lessons of GIST—PET and PET/CT: a new paradigm for imaging. Oncologist.;13(S2):8–13, **2008**.
8. **Young H, Baum R, Cremerius U, et al.** Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. Eur J Cancer.;35(13):1773–82, **1999**.
9. **Wahl RL, Jacene H, Kasamon Y, et al.** From RECIST to PERCIST: evolvingconsiderations for PET response criteria in solid tumors. J Nucl Med.;50(Suppl 1):122S-150S, **2009**.
10. **Kim JH.** Comparison of the EORTC criteria and PERCIST in solid tumors: a pooled analysis and review. Oncotarget.;7(36):58105, **2016**.

11. **Lodge MA, Wahl RL.** Practical PERCIST: a simplified guide to PET response criteria in solid tumors 1.0. Radiology.;280(2):576, **2016**.
12. **Yu X, Zhu L, Liu J, et al.** Emerging role of immunotherapy for colorectal cancer with liver metastasis. Onco Targets Ther.;11645–58, **2020**.
13. **Hess KR, Varadhachary GR, Taylor SH, et al.** Metastatic patterns in adenocarcinoma. Cancer.;106(7):1624–33, **2006**.
14. **Enblad M, Graf W, Birgisson H, et al.** Risk factors for appendiceal and colorectal peritoneal metastases. Eur J Surg Oncol.;44(7):997–1005, **2018**.
15. **Zhang Y, Qin X, Luo R, et al.** Risk factors for synchronous peritoneal metastases in colorectal cancer: a systematic review and meta-analysis. Front Oncol.;12:885504, **2022**.
16. **Van Cutsem E, Verheul HMW, Flamen P, et al**. Imaging in colorectal cancer: progress and challenges for the clinicians. Cancers (Basel).;8(9):81, **2016**.
17. **Skougaard K, Nielsen D, Jensen BV, et al.** Comparison of EORTC criteria and PERCIST for PET/CT response evaluation of patients with metastatic colorectal cancer treated with irinotecan and cetuximab. J Nucl Med.;54(7):1026–31, **2013**.
18. **Pinker K, Riedl C, Weber WA, et al.** Evaluating tumor response with FDG PET: updates on PERCIST, comparison with EORTC criteria and clues to future developments. Eur J Nucl Med Mol Imaging.;44:55–66, **2017**.
19. **Skougaard K, Johannesen HH, Nielsen D, et al.** CT versus FDG-PET/CT response evaluation in patients with metastatic colorectal cancer treated with irinotecan and cetuximab. Cancer Med.;3(5):1294–301, **2014**.
20. **Aras M, Erdil TY, Dane F, et al.** Comparison of WHO, RECIST 1.1, EORTC, and PERCIST criteria in the evaluation of treatment response in malignant solid tumors. Nucl Med Commun.;37(1):9–15, **2016**.
21. **Bang J-I, Lim Y, Paeng JC, et al.** Comparison of quantitative

methods on FDG PET/CT for treatment response evaluation of metastatic colorectal cancer. Nucl Med Mol Imaging (2010).;51:147–53, **2017**.

22. **Melton GB, Lavely WC, Jacene HA, et al.** Efficacy of preoperative combined 18-fluorodeoxyglucose positron emission tomography and computed tomography for assessing primary rectal cancer response to neoadjuvant therapy. J Gastrointest Surg.;11:961–9,**2007**.
23. **Burger IA, Schwarz EI, Samarin A, et al.** Correlation between therapy response assessment using FDG PET/CT and histopathologic tumor regression grade in hepatic metastasis of colorectal carcinoma after neoadjuvant therapy. Ann Nucl Med.;27:177–83, **2013**.
24. **Eker B, Ozaslan E, Karaca H, et al.** Factors affecting prognosis in metastatic colorectal cancer patients. Asian Pacific J Cancer Prev.;16(7):3015–21, **2015**.
25. **Slesser AAP, Georgiou P, Brown G, et al.** The tumour biology of synchronous and metachronous colorectal liver metastases: a systematic review. Clin Exp Metastasis.;30:457–70, **2013**.
26. **Jeong S, Heo JS, Park JY, et al.** Surgical resection of synchronous and metachronous lung and liver metastases of colorectal cancers. Ann Surg Treat Res.;92(2):82–9, **2017**.
27. **Colloca GA, Venturino A, Guarneri D, et al.** Different variables predict the outcome of patients with synchronous versus metachronous metastases of colorectal cancer. Clin Transl Oncol.;22(8):1399–406, **2020**.
28. **Reboux N, Jooste V, Goungounga J, et al.** Incidence and survival in synchronous and metachronous liver metastases from colorectal cancer.JAMA Netw Open.;5(10):e2236666–e2236666,**2022**.