SMJ- Sohag Medical Journal, Vol. 29 No (2) 2025

Print ISSN1687-8353 Online ISSN2682-4159

Original Article

Prognostic Value of Metabolic Tumor Volume and Total Lesion Glycolysis Measured by Positron Emission Tomography for liver metastases in Colorectal Cancer

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Abstract

Introduction: The liver is considered the most common site for hematogenous spreading in colorectal cancer (CRC). PET/CT has a great value for the detection, staging, restaging and follow up treatment response of colorectal cancer patients.

Aim of the current study is to determine prognostic value of measuring PET parameters, Standard Uptake Value (SUV) total lesion glycolysis (TLG) and metabolic tumor volume (MTV) of liver metastatic lesions in colorectal patient s.

Methods: Two consecutive PET/CT scans belong to 50 patients with pathologically proven colon cancer and liver metastasis are reviewed for SUV max, MTV, TLG of the liver metastatic lesions, MTV difference and TLG difference were calculated. Patients are classified into 4 groups according to the results of 2nd PET/CT: Group 1: complete remission, Group 2: partial remission, Group 3: stable disease& Group 4: progressed disease, One way ANOVA, ROC curve analysis and Cox regression model were done.

Results: there is significant difference between the 4 groups for both SUV max and MTV with P value< 0.05 while for TLG, P value was 0.08, the best Cut off point for SUV max 7.9 with sensitivity 61% and specificity 59%, for MTV 16.21 with sensitivity 52% and specificity 63%& for TLG 77.5 with sensitivity 55% and specificity 62%. TLG difference has significant prognostic value.

Conclusion: quantitative PET parameters as MTV, TLG, percent MTV and TLG difference can provide additional diagnostic and prognostic value in patients with colorectal patients with liver metastases .

Key wards: Colorectal cancer-liver metastasis- PET/CT- SUV max- MTV- TLG.

DOI : 10.21608/SMJ.2025.382412.1564 **Received:** May 07 , 2025 **Accepted:** June 02 , 2025

Published: June 25 , 2025

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Citation: **Wafaa Abd-Elhamied . et al**., Prognostic Value of Metabolic Tumor Volume and Total Lesion Glycolysis Measured by Positron Emission Tomography for liver metastases in Colorectal Cancer **SMJ,**2025 Vol. 29 No (2) 2025 142- 149

Introduction

Colon cancer is one of the most frequent malignancy worldwide with the incidence and mortality rates vary markedly around the world. The CRC is more common among men than women and 3–4 times more common in developed than in developing countries.(1)

The median age of CRC is 70 in men and 72 in females, although there is a wide range in age. (2) Women are more likely to develop cancers in the proximal colon, whereas in men cancers are more common in the distal colon region. In addition, with advancing age, a greater proportion of colorectal tumors are located in the proximal colon, with a reduced proportion of rectal tumors.(3)

There is increasing evidence for the prognostic value of quantitative parameters obtained from initial staging using 18FDG PET/CT in patients with many solid tumors. To date, the SUV max has been the most widely studied parameter. More recent studies include the volume-based metabolic assessments such as MTV and TLG .(4)

Unlike SUVs, PET/CT metabolic parameters (represented by MTV and TLG) obtained by measuring high metabolic activity areas of tumors can provide volume and metabolic information for highly metabolized tumor cells and are independent prognostic factors with important predictive value for disease-free survival time of CRC patients and using these parameters, a more accurate preoperative diagnosis of the CRC can be performed. (5)

Patients and methods:

This study was done in Nuclear Medicine unit in National cancer institute .

Ethical Approval: The Institutional Review Board, Faculty of Medicine permitted this work .

Inclusion criteria included 50 patients; had either pathologically proven colon or colorectal cancer with liver metastasis. Patients who are excluded from the study include those with colorectal cancer without liver metastasis, having double primary, liver metastasis secondary to any other primary and those below 16 years old were excluded from the study.

PET/CT imaging protocol:

Patients were fasting for 6 hours before the ^{18}F FDG PET/CT scan in order to minimize the blood insulin levels and glucose utilization of normal tissue. Blood glucose levels of all patients were less than 190 mg/dl at the time of the scan.

Patients were injected with 370–555 MBq of 18F FDG, depending on body weight. Imaging time was 45-90 after IV injection of 18F FDG. Whole-body PET emission scans were obtained from the base of the skull to the mid-thigh, followed by low dose CT imaging without the patient having to change positions. Low-dose CT images were used for attenuation correction of the PET data. PET images were reconstructed using CT-based attenuation correction by an ordered subset expectation maximization iterative reconstruction algorithm

1. Data reading & Image analysis:

Data were displayed, measured and registered by using a using a G.E health care workstation where both qualitative and quantitative assessment were done and a visually abnormal focus of FDG uptake was identified and lesion size, SUV max & TLG of each liver metastatic lesion were calculated in the all colorectal liver metastatic lesions. SUV max is the single voxel within the entire tumor with the highest SUV value. MTV corresponds to the metabolically active areas of uptake within the tumor. MTV is also defined as the number of voxels within the VOI, which had a greater uptake than the chosen background threshold which is a relative threshold of 40 % of the SUV max of the tumor areas. TLG is calculated as MTV multiplied by the mean SUV (TLG = MTV × mean SUV). As this parameter incorporates both the MTV and SUV, it represents both the degree of FDG uptake and the size of tumor.

2. Statistical analysis:

Data analysis was performed using SPSS software , One-way ANOVA Test was done to find significant difference between the 4 groups in relation to values of TLG in the first PET/CT images and the test showed that there is significant difference for both SUVmax and MTV with P value< 0.05 while for TLG, P value was 0.08Receiver-operating characteristic (ROC) analyses were performed to determinate best cut off point of MTV, TLG, percent MTV difference and percent TLG difference and to evaluate the ability of each PET parameter, their pre and post treatment values and percentage reduction, to

differentiate between responder and poor responders. The P values ≤ 0.05 were regarded as significant. The best cutoff values of PET parameters determined from ROC curves with significant P values were used in a univariate logistic regression analysis to validate their ability to predict therapy response. Cox regression model was performed

Results

A total of 50 consecutive patients of colon cancer with liver metastases (29 males and 21 females) were included in the study. The age of patients ranged from 29 to 76 years, with a median and mean age of 59.3 and 8.1 years, respectively. 32 patients (64%) had initial surgery, as illustrated at **table (1).**

Table 1: Demographic and clinical data of patient population:

Age (years)	
mean	59.3±8.1
range	29-76
Sex	
Male	29 (58%)
Female	21 (42%)
Primary	
Colon	40 (80%)
Rectum	9 (18%)
Rectosigmoid	1 (2%)
Therapy	
Surgery	32 (64%)
Chemotherapy	33 (66%)
Target therapy	9 (18%)
Radiotherapy	1 (2%)
radiofrequency	1 (2%)

The patients are classified into 4 groups: Group 1: 7 patient with complete remission, Group 2: 13 with partial remission, Group 3: 7 with stable disease & 23 patients included in Group 4: with progressed disease.

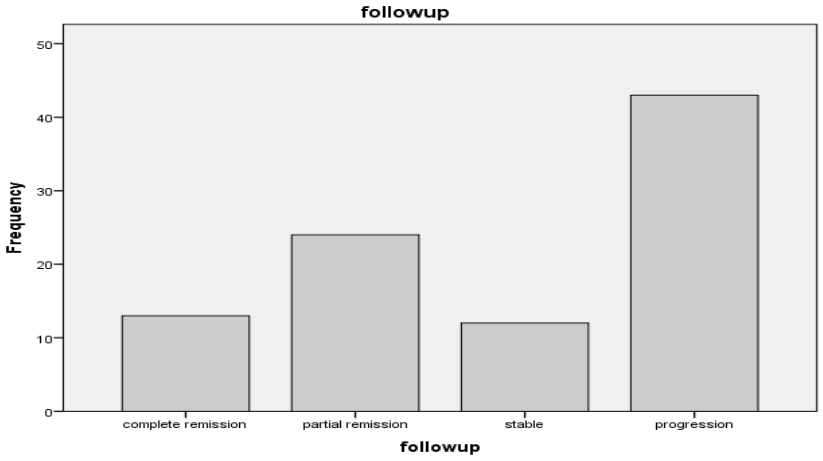


Figure 1: Bar chart for 4 groups of patients according to their follow up PET/CT

Analysis of liver lesions:

In 50 patients with colorectal cancer, a total of 93 liver lesions are analyzed in both pre therapy (1st) and post therapy (2nd) FDG PET/CT studies , where different semi quantitative PET parameters as SUV max , TLG, MTV and lesion size in CT part of PET/CT Table (2).

Table 3 illustrate the average (median) of the different parameters as compared between the 4 classified groups according to their therapy response

Table 2: descriptive analysis for PET parameters (SUVmax, MTV, TLG) and size in CT for liver metastatic lesions in the 1st and 2nd PET/CT scans

	1st PET/CT scan	2nd PET/CT scan
SUVmax		
Minimum	2.98	2.01
Maximum	24.2	27.91
Mean	9.76	8.81
Lesion size in CT (cm)		
Minimum	0.8	0.4
Maximum	18	14.4
Mean	4.1	4.5
Total lesion glycolysis (TLG)	7.62	2.76
Minimum	5407.3	5369
Maximum	371.4	503
Mean		
Metabolic tumor volume (MTV)		
Minimum	1.9	0.91
Maximum	487.54	914
Mean	58	75.9

One-way ANOVA Test was done to find significant difference between the 4 groups in relation to values of MTV and TLG in the first PET/CT images and the test showed that there is significant difference for both SUVmax and MTV with P value< 0.05 while for TLG, P value was 0.08.

Post hoc test showed that there is significant difference for SUVmax values between partial remission group and the other 3 groups also there is significant difference for MTV values between complete remission and progression groups also between complete remission and stable disease. For TLG values there is significant difference between progression and partial remission groups.

Table 3: Descriptive analysis for average PET parameters (SUVmax, MTV & TLG) for liver metastatic lesions in different 4 patients groups

	SUVmax		MTV		TLG	
	SUV1	SUV2	MTV1	MTV2	TLG1	TLG2
Complete remission	8.6062	2.4715	127.9192	45.9346	612.9446	99.4492
Partial remission	10.2867	5.0175	54.2000	49.3775	477.1463	254.9188
Stable	9.1092	7.9933	88.1442	84.3983	481.7883	682.2567
Progression	9.9449	12.8807	31.1642	95.6574	210.4172	710.2433

ROC curve analysis

Receiver operating curve (ROC curve) was done for PET parameters (SUV max, TLG, MTV, percent TLG difference and percent MTV difference) to determine optimum cut off point (here the lesions were classified into two groups: progressed group and progression free group) for PET parameters Figure (2) described the different ROC curve analysis and shows that according to SUV max values in the 1st PET/CT, the optimal cutoff point was 7.9 with a sensitivity of 61% and specificity of 59%. According to MTV values in the 1st PET/CT, the optimal cutoff point was 16.21 with a sensitivity of 52% and specificity of 63%. According to TLG values in the 1st PET/CT, the optimal cutoff point was 77.5 with a sensitivity of 55% and specificity of 62%. According to the TLG percent difference between 1st and 2nd PET/CT scans, the optimal cutoff point was 30% sensitivity 89% and specificity 71%. Figure (2)

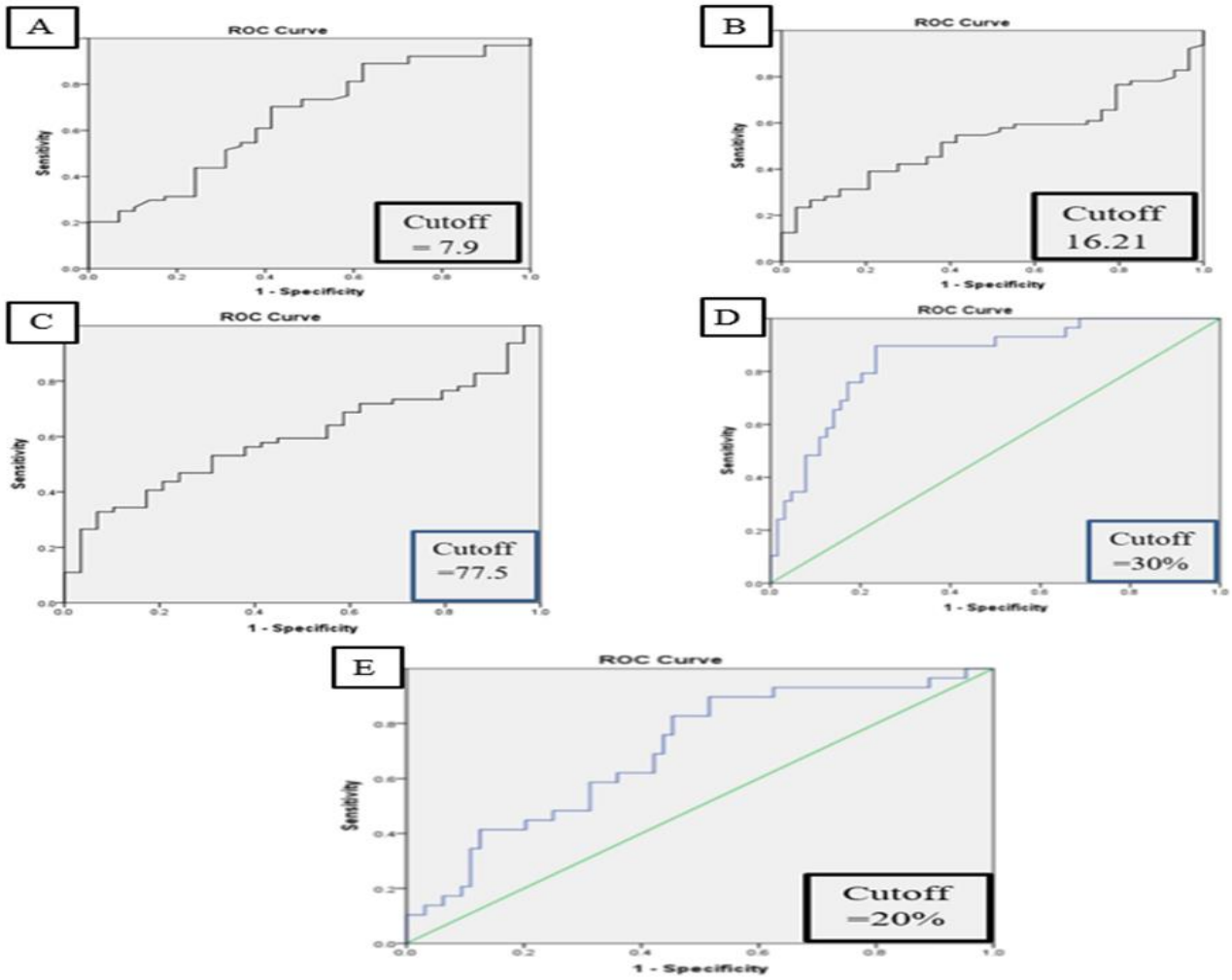


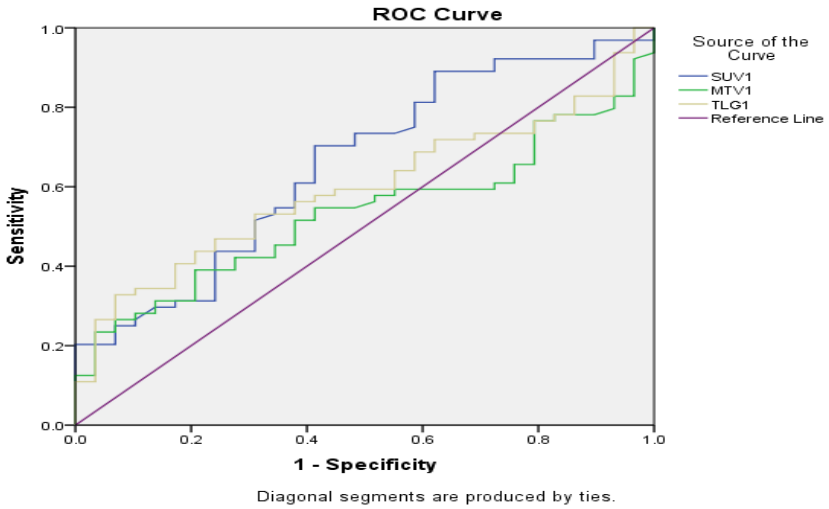
Figure 2: ROC curve analysis of initial FDG PET/CT primary volume based metabolic parameters to predict prognosis. (A) for SUVmax (B) MTV (C) (D) (E)

According to MTV's percent difference between 1st and 2nd PET/CT scans, the optimal cutoff point was 20% with a sensitivity of 72% and specificity of 57%). ROC curve for progressed disease according to MTV percent difference between 1st and 2nd PET/CT scans, the optimal cutoff point was 20% with sensitivity 72% and specificity 57% Figure. (3)

Percent TLG difference was calculated with the formula [(TLG1-TLG2)/TLG2] x100
*Percent MTV difference was calculated with the formula [(MTV1-MTV2)/MTV1] x100Cox
Regression model was done

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)
MTVdiffcox	-.668-	.538	1.542	1	.214	.513
TLGdiffCox	2.008	.749	7.192	1	.007	7.452



Cox regression univariate analysis:

Cox regression univariate analysis was done to evaluate both clinical and PET parameters as prognostic indicators. Clinical factors include age, sex and site of primary lesion and PET parameters include SUVmax, MTV, TLG, percent MTC difference& percent TLG difference; her the lesions were classified according to the cutoff point of each parameter to lesions higher and lesions lower than the cutoff point. In this analysis, only TLG percent difference was significant (hazard ratio (HR), 4.4; *p*=0.018), while MTV percent difference (HR, 0.57, p=0.23), SUVmax (HR, 1.1; p=0.76), TLG (HR, 0.7; p= 0.38), MTV (HR, 0.81, p=0.59).

Cox regression multivariate analysis:

As TLG percent difference showed significant prognostic value, multivariate analysis for TLG percent difference with each other parameters, TLG percent difference remains independent prognostic marker when adjusted to other variables.

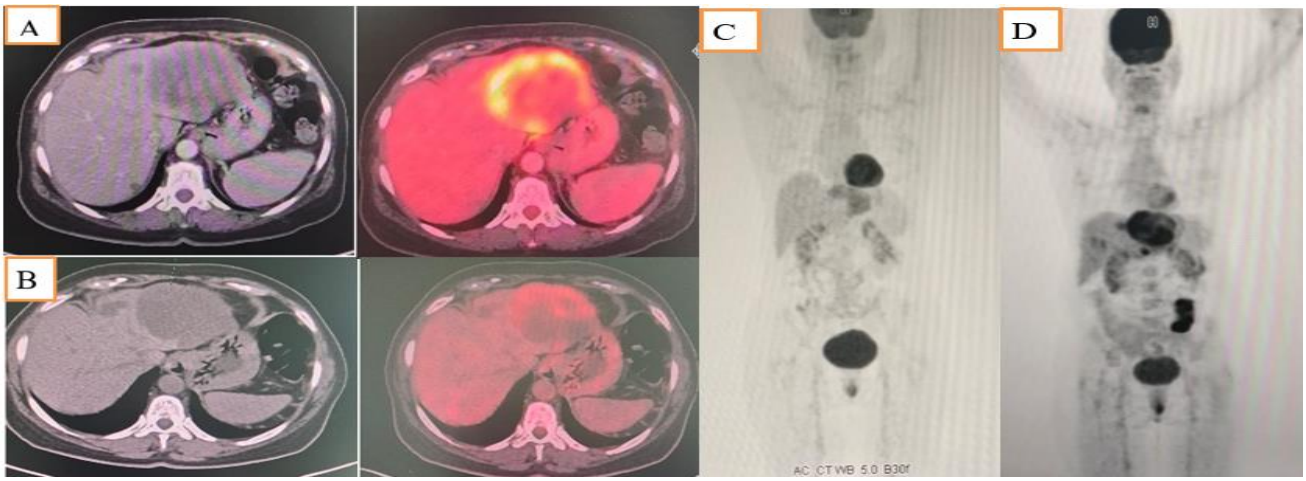


Figure (1) 63 years old male patient with metastatic colonic cancer receiving chemotherapy. (A) Pre-therapy CT and Fused FDG PET/CT images & (D) Pre-therapy MIP images shows large left hepatic lobe lesion at segment II measures 9.2x7.6 cm with SUVmax~15.4, Peak~12.8 TLG~670 and MTV~85.8. (B) Post-therapy CT and Fused FDG PET/CT images & (C) Post-therapy MIP images show significant regression in metabolic activity reaching SUVmax~6.5 Peak~4.3 TLG~162 and MTV~68.3, with mild size regression measuring 7.2x8 cm.

Discussion

SUV max is the most commonly studied metabolic parameter for semiquantitative analysis of glucose metabolism with 18F-FDG PET/CT. **(Sun, Xu et al. 2013)[6],** SUVmax represents the highest metabolic activity of the tumor, while MTV and TLG reflect the burden of the metabolically active tumor. Theoretically, the MTV and TLG could be more useful than the SUVmax in the prediction of tumor behavior because both metabolic activity and tumor burden are considered**(Kim, Lee et al. 2021) .**[7.]

In this retrospective study, we aimed to assess the value of PET metabolic parameters as prognostic indicators through analyzing these parameters in two consecutive PET/CT studies for 50 colorectal cancer patients with liver metastatic lesions with lesion per lesion analysis with maximum five lesions in multiple liver metastases. The results of the study showed that liver metastatic lesions in the 1st PET scan with SUV max more than 7.9 had better prognosis than lesions with SUV max lower than 7.9. Also, lesions with MTV more than 16.21 showed better prognosis the lesions with MTV less than 16.21 and liver metastatic lesions with TLG more than 77.5 also had better prognosis than lesions with TLG less than 77.5, although these results are statistically insignificant.

These results go well with the results of Nemeth Z et al that concluded that both SUVmax and TLG did not showed significant correlation with therapeutic effect or with survival **Nemeth Z et al;** [8],but don't go well with Watanabe A and Xia Q who concluded that high SUVmax is associated with poor prognosis **Xia Q et al.** [9.]

Percent TLG difference was studied by Kahraman et al on patients with lung cancer and they found that a cutoff value of 20% or 30% for percentage changes of TLG provides suitable results for response prediction. [10]

In our study we found that TLG percent difference with cutoff value 30% is a prognostic indicator with a statistical significance, also we studied MTV percent difference where the optimal cutoff point 20%, although it was statistically insignificant for predicting progression free survival.

The limitation of this study are the small number of cases and the retrospective nature of the study with incomplete data about interval treatment, we suggest further studies with larger number of patients with long term follow up.

Conclusion

SUV max is the most commonly used ^{18}F-FDG PET/CT parameter for diagnosis, staging and therapy monitoring. However, other quantitative PET parameters as MTV, TLG, percent MTV and TLG difference provide additional diagnostic and prognostic value in patients with colorectal patients with liver metastases and should be considered beside SUV max in follow up of these patients.

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