



Preoperative metabolic parameters of ^{18}F -FDG PET/CT are associated with TNM stage and prognosis of colorectal cancer patients

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Background: Colorectal cancer (CRC) is the third most frequent cause of cancer-related death, while tumor/node/metastasis (TNM) stage of American Joint Committee on Cancer is the guideline of making treatment strategy and predicting survival. The aim of this study is to investigate the association of preoperative 2-deoxy-2- ^{18}F fluoro-D-glucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT), TNM stage, and prognosis of patients with CRC.

Methods: From September 2016 to August 2022, a total of 132 patients were retrospectively and consecutively enrolled in this cross-sectional study, who were diagnosed as CRC by histopathology and received preoperative ^{18}F -FDG PET/CT. Firstly, the correlation between the metabolic parameters and clinicopathological features of the primary tumors was investigated. Secondly, univariate and multivariate logistic regression analyses were used to estimate the odds ratio of the association between the clinical and metabolic parameters and the advanced TNM stage (stage III–IV). Thirdly, progression-free survival (PFS) was analyzed using Kaplan-Meier curves and Log-rank test.

Results: The results revealed that the metabolic tumor volume (MTV) $>6.6\text{ cm}^3$ and serum carcinoembryonic antigen (CEA) $>5.84\text{ ng/mL}$ were independently associated with advanced TNM stage ($P=0.0009, 0.0011$, respectively). Larger tumor size, higher tumor-to-liver standardized uptake value ratio, MTV, and total lesion glycolysis (TLG) were significantly correlated with advanced pT stage (stage 4), and higher TLG and MTV were significantly correlated with advanced pN stage (stage 1–2) ($P<0.05$), while no metabolic parameters were significantly correlated with metastasis status ($P>0.05$). Higher serum CEA and carbohydrate antigen 19-9 levels were significantly correlated with advanced pT, pN stage, and metastasis status ($P<0.05$). Patients were followed up for at least 1 year. The MTV $>6.6\text{ cm}^3$ was significantly associated with worse PFS ($P=0.032$).

Conclusions: ^{18}F -FDG PET-CT can serve as a noninvasive tool for preoperatively staging CRC. The MTV $>6.6\text{ cm}^3$ might be associated with advanced TNM stage and worse PFS.

Keywords: 2-deoxy-2- ^{18}F fluoro-D-glucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT); colorectal cancer (CRC); stage; prognosis

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Introduction

Colorectal cancer (CRC) is the second most common cancer in women and the third in men worldwide, and despite advances in treatment, CRC is still the third most frequent cause of cancer-related death (1). The traditional and current guidelines for survival prediction and surveillance recommendations for CRC remain the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) tumor/node/metastasis (TNM) anatomical classification (2). Although the five-year survival rate for CRC patients at the early stage (stage I and II) is above 60%, CRC with metastatic disease remains challenging. More than 50% of patients are diagnosed at an advanced stage (stage III and IV) associated with metastasis to lymph nodes or distant organs, the 5-year survival rate drops to 10% (3). Surgical resection is currently the primary treatment for CRC patients who have not spread to distant sites. In inoperable patients, radiotherapy, chemotherapy, immunotherapy, and targeted therapy can be selected on the basis of the actual situation of the patients (4). However, the postoperative pathological TNM (pTNM) stage may be different from the preoperative clinical TNM (cTNM) stage, according to the AJCC Cancer Staging Classification (2). Therefore, an effective and non-invasive diagnostic tool is needed to assess CRC staging and predict prognosis accurately, as that help choosing patient-specific treatment strategies preoperatively to reduce tumor progression and improve survival.

2-deoxy-2-[¹⁸F]fluoro-D-glucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) is an important molecular imaging modality that is used for diagnosing and performing TNM staging in CRC, which could accurately access the preoperative tumor localization in early-stage patients or lymph node and distant statuses in advanced-stage patients (5). ¹⁸F-FDG PET/CT is better than conventional imaging, such as serial enhanced CT from lung base to the pelvis, for the staging and follow-up of CRC in all localities, with higher sensitivity, specificity, and accuracy (6,7). PET metabolic parameters, including maximum and minimum standardized uptake value (SUV_{max}, SUV_{mean}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG), are correlated with the clinicopathological characteristics and prognosis in several tumors, such as oral squamous cell cancer, esophageal cancer, and non-small-cell lung cancer (8-10). The SUV_{max} only reflects the highest extent of glucose utilization in the tumor, the volumetric parameters such as MTV and

TLG are promising semiquantitative parameters to assess the metabolic activity of the whole tumor, which could provide additional information on intratumoral biological variation (11).

Therefore, the objective of this study was to investigate the application value of metabolic parameters of ¹⁸F-FDG PET/CT in assessments of TNM staging of CRC patients, to analyze the relationship of FDG metabolic parameters with TNM stages and serological biomarkers in CRC, and to predict the prognosis of CRC patients. We present this article in accordance with the STROBE reporting checklist (available at <https://qims.amegroups.com/article/view/10.21037/qims-23-966/rc>).

Methods

Patients and clinicopathological features, and follow up

From September 2016 to August 2022, a total of 132 patients with CRC proved by surgical pathology who underwent preoperative ¹⁸F-FDG PET/CT examination for clinical staging in our hospital were retrospectively and consecutively included in this cross-sectional study. The major inclusion criteria were as follows: (I) surgical histopathology-proven CRC; (II) PET/CT scan was performed within 2 weeks prior to surgical resection of CRC. Exclusion criteria were: (I) patients who received neoadjuvant treatment (such as chemotherapy and/or radiotherapy) before the surgery; (II) less than 18 years old; (III) patients with other malignancies. The flowchart of selection criteria is shown in *Figure 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Beijing Friendship Hospital, Affiliated to Capital Medical University (No. 2023-P2-013-01), and the requirement for informed consent was waived because of the retrospective nature of the study. The data of all patients were anonymized in this paper.

Clinicopathological information was obtained from the medical records. General information such as gender and age, and serological biomarkers such as serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) levels, were obtained 2 weeks within the PET/CT scan. Primary tumor information was generated from the surgical pathology reports, including tumor location, tumor size, differentiation, vascular invasion, lymphovascular invasion, pathological T (pT) stage, and pN stage. The metastasis status (M stage) was accessed by the preoperative imaging evaluation such as CT, MRI, and

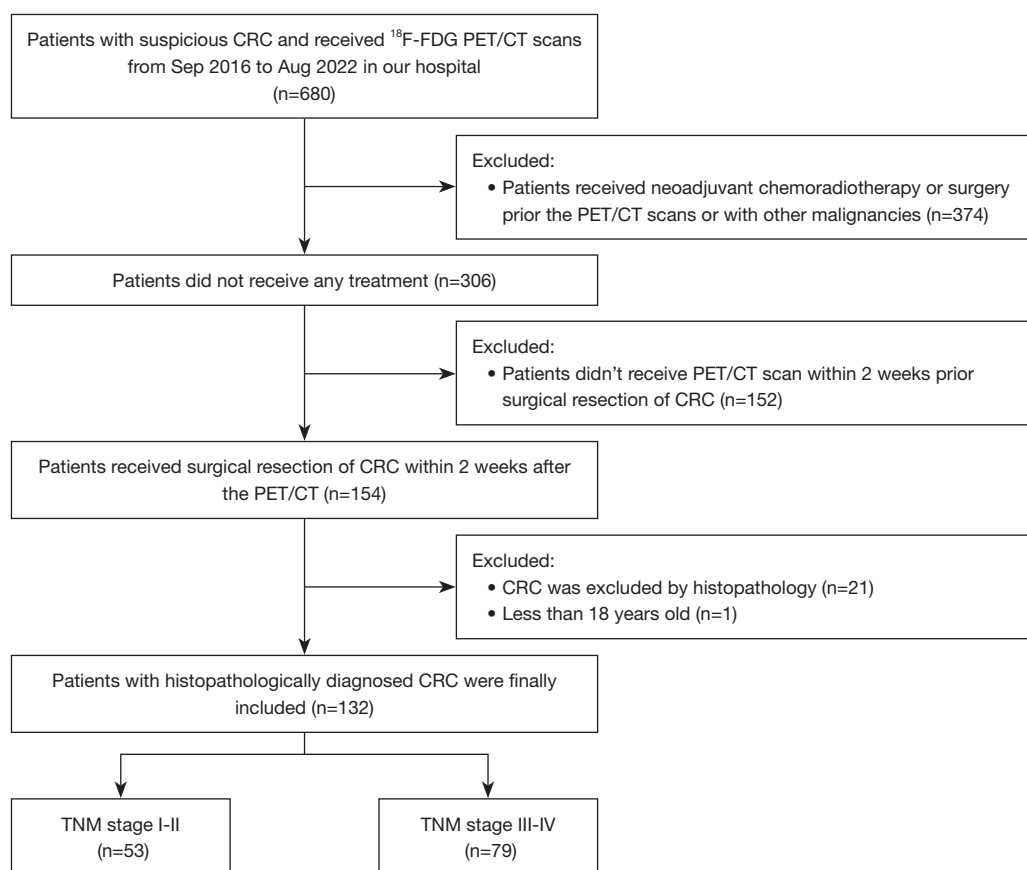


Figure 1 The flowchart of selection criteria. CRC, colorectal cancer; ¹⁸F-FDG, 2-deoxy-2[¹⁸F]fluoro-D-glucose; PET/CT, positron emission tomography/computed tomography; TNM, tumor/node/metastasis.

¹⁸F-FDG PET/CT. The pT, pN, and M stage, and cancer TNM stage are defined according to the AJCC 8th edition staging system (2).

Postoperative follow-up data were collected from medical records and telephone consultations. Imaging evaluations such as chest-abdominal-pelvis CE-CT, plain CT, pelvis magnetic resonance imaging (MRI), or whole-body ¹⁸F-FDG PET/CT were performed regularly after surgery (once every 3–6 months). Progression-free survival (PFS) was defined as the time from the operative PET/CT scan to disease progression accessed by imaging evaluation. All patients were followed up for at least 1 year. Patients without progression were censored at the date of the last follow-up visit.

PET/CT imaging

All PET/CT examinations were performed using a

Biograph mCT S64 (Siemens Healthineers Medical Solutions), which collects PET and CT data simultaneously. All patients were required to fast for more than 6 h prior to PET/CT examinations, intravenous injection of ¹⁸F-FDG (approximately 4.4 MBq/kg) was performed when the blood glucose level was <11.1 mmol/L. The PET/CT scan started 1h after the tracer injection. Thereafter, the patient was asked to void and subsequently was placed in a supine position with the arms up in the scanner. Patients were scanned from the skull base to the upper one-third of the femur. The CT scan (120 kV, 200 mA, and slice thickness of 3 mm) was performed for attenuation correction and anatomical localization. The following PET scan was performed in a three-dimensional (3D) mode (2.5 min/bed position, 6–8 beds). PET images were reconstructed using the ordered subset expectation maximization iterative method with CT data for attenuation correction.

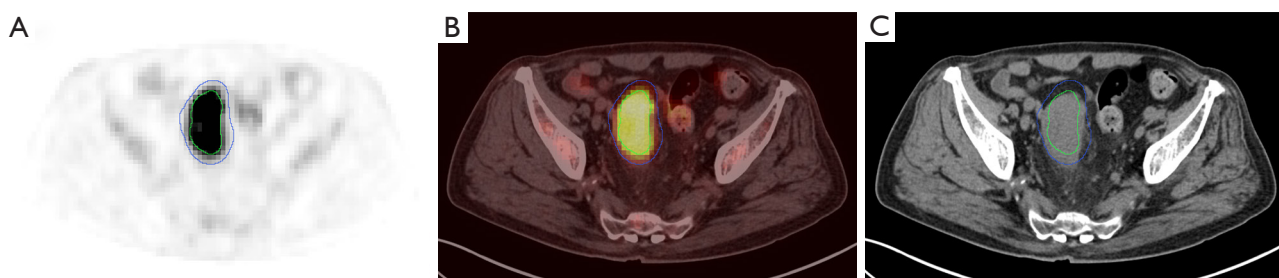


Figure 2 An example of the VOI of the tumor shown in the transaxial PET (A), PET/CT (B), and CT (C) image. The primary VOI is shown in blue, while the secondary VOI, based on SUV_{max} 40%, is showed in green. VOI, volume of interests; PET/CT, positron emission tomography/computed tomography; SUV_{max} , maximum standard uptake value.

Image analysis

Two experienced nuclear medicine physicians with more than 5-year experience in PET/CT diagnosis, who were masked to the medical history of the participants, independently reviewed the PET/CT images on a dedicated workstation (syngo MultiModality Workplace, Siemens, Erlangen, Germany). Any disagreement would be discussed with another senior expert (experience >15 years) till an agreement was reached. The volume of interest (VOI) of the primary tumor was delineated using 3D slicer, a free open-source platform for medical image computing. To improve the accuracy and repeatability of imaging analysis, the VOI was drawn in two steps for each patient by two experienced nuclear medicine physicians. Firstly, a primary VOI around the margin of the primary tumor was delineated in 3D on the PET image manually. The inner and outer edges of the tumor were mainly determined by PET image, with consideration of CT image. The boundary between tumor and normal physiological uptake was carefully determined. Then a final secondary VOI based on SUV_{max} (40%) was automatically delineated, as the cut-off is commonly used (12). An example of the VOI is illustrated in *Figure 2*. The SUV_{max} , TLG, and MTV of the secondary VOI were obtained and recorded for FDG semi-quantitative analysis. The mean liver SUV (SUV_{liver}) was determined by the average of SUV_{mean} of 3 sphere VOIs approximately 3 cm in diameter on the normal right and left liver. Tumor-to-liver standardized uptake value ratio (SUV_r) of the primary tumors was computed as the ratio of the tumor SUV_{max} to SUV_{liver} .

Statistical analysis

Data were analyzed with Madcalc software (version 19.0),

and figures were generated using GraphPad Prism 8 (GraphPad Software, San Diego, CA) and R 4.0.2 software (Bell Laboratories, Holmdel, NJ, USA). Continuous variables with a skewed distribution were reported as median [interquartile range (IQR)], and categorical variables by numbers (percentages). Continuous variables were compared with Mann-Whitney *U* test, and categorical variables with the two-sided Pearson Chi-square test. Each continuous parameter that was significantly associated with the advanced TNM stage (stage III–IV) was analyzed as categorical variables using cut-points determined by receiver operator characteristic (ROC) curve analysis, while others were analyzed as categorical variables using the median as cut-points. The possible risk factors associated with the advanced TNM stage were investigated by the univariate logistic regression analysis to estimate the odds ratio (OR) and 95% confidence interval (CI), using the backward stepwise method. Then the factors with $P < 0.05$ were included in the multivariate logistic regression analysis (backward stepwise method). Factors that remained significant at $P < 0.05$ were considered to be independent predictors of the advanced TNM stage. PFS was analyzed using Kaplan-Meier curves and Log-rank test. All tests were two-sided with a significance level of $P < 0.05$.

Results

Patients characteristics

A total of 132 patients (84 male (63.6%)) conformed to our inclusion criteria were included in the study, with a median age of 65 [interquartile range (IQR), 58–74] years. The primary tumor of 36 (27.3%) patients was localized in the right hemi-colon. According to primary tumor pathology, the moderately-differentiated tumor

Table 1 Patients' characteristics

Characteristics	Value
General information	
Age, M [IQR], years	65 [58–74]
Gender, n (%)	
Male	84 (63.6)
Female	48 (36.4)
Primary tumor information, n (%)	
Tumor location	
Right	36 (27.3)
Left	96 (72.7)
Tumor size, M (IQR), (cm)	5.0 (3.5–6.0)
Differentiation	
Well	5 (3.8)
Moderately	114 (86.4)
Poorly	13 (9.8)
Vascular invasion	
Yes	48 (39.3)
No	74 (60.7)
Lymphovascular invasion	
Yes	33 (28.7)
No	82 (71.3)
Staging, n (%)	
pT stage	
T1	3 (2.3)
T2	9 (6.8)
T3	85 (64.4)
T4	35 (26.5)
pN stage	
N0	61 (46.2)
N1	45 (34.1)
N2	26 (19.7)
M stage	
M0	97 (73.5)
M1	35 (26.5)

Table 1 (continued)**Table 1** (continued)

Characteristics	Value
TNM stage	
I	10 (7.6)
II	43 (32.6)
III	44 (33.3)
IV	35 (26.5)

TNM stages are defined according to the American Joint Committee on Cancer 8th edition staging system. M, median; IQR, interquartile range; TNM, tumor/node/metastasis.

was the most common histologic grade (86.4%), while well- and poorly-differentiated tumors represented 3.8% and 9.8%, respectively. The majority of patients were pT3 (64.4%), pN1–2 (53.8%), M0 (73.5%), and TNM III–IV (59.8%) stage. There were only 122 patients with information on vascular invasion status and 115 patients with lymphovascular invasion status, as the other data were not available in some early pathological reports. And 48 (39.3%) of 122 patients had vascular invasion and 33 (28.7%) of 115 patients had lymphovascular invasion. The clinicopathological characteristics of CRC patients are exhibited in *Table 1*.

Correlation between metabolic parameters and advanced TNM stage in CRC

To explore the relationship between metabolic parameters and tumor stage, we defined early and advanced groups according to the TNM (stage I–II *vs.* III–IV), pT (stage 1–3 *vs.* 4), pN (stage 0 *vs.* 1–2), and M (stage 0 *vs.* 1) stage based on prior similar studies (13,14), respectively.

The results showed that metabolic parameters of MTV, TLG and serological biomarker of CEA, and CA19-9 in the advanced TNM stage group (stage III–IV) were significantly higher than the early group ($P=0.005$, 0.016 , 0.0003 , 0.033 , respectively). Besides, larger tumor size, higher SUVR, MTV, and TLG were significantly correlated with advanced pT stage (stage 4), and higher MTV, and TLG were significantly correlated with advanced pN stage (stage 1–2) ($P<0.05$), while no metabolic parameters were significantly correlated with metastasis status ($P>0.05$). Higher CEA and CA19-9 levels were significantly correlated with advanced

Table 2 Comparison of the early and advanced TNM stage (TNM stage I–II vs. III–IV)

Characteristics	TNM stage		P value
	I–II (n=53)	III–IV (n=79)	
General information			
Age, M [IQR], years	65 [55.5–75.5]	66 [59–73]	0.424
Gender, n (%)			0.639
Female	18 (13.6)	30 (22.7)	
Male	35 (26.5)	49 (37.1)	
Primary tumor information			
Tumor location, n (%)			0.168
Right	11 (8.3)	25 (18.9)	
Left	42 (31.8)	54 (40.9)	
Tumor size, M (IQR), cm	4.5 (3.1–5.6)	5.0 (3.5–6.5)	0.237
Metabolic parameters, M (IQR)			
SUV _{max} (g/cm ³)	15.7 (11.6–19.8)	14.9 (11.2–19.8)	0.952
SUVR	4.6 (3.3–6.7)	5.0 (3.5–6.6)	0.797
MTV (g/cm ³)	10.4 (5.8–22.8)	18.8 (10.7–28.2)	0.005**
TLG (g)	81.3 (50.1–197.2)	141.6 (87.5–265.9)	0.016*
Serum tumor marker, M (IQR)			
CEA (ng/mL)	3.32 (1.67–4.79)	6.06 (2.79–17.84)	0.0003***
CA19-9 (U/mL)	15.30 (5.26–55.96)	16.80 (9.20–69.10)	0.033*

*, P<0.05; **, P<0.01; ***, P<0.001. TNM, tumor/node/metastasis; M, median; IQR, interquartile range; SUV_{max}, maximum standard uptake value; SUVR, tumor-to-liver standardized uptake value ratio; MTV, metabolic tumor volume; TLG, total lesion glycolysis; CEA, serum carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

pT, pN stage, and metastasis status (P<0.05) (Tables 2,3, Figures 3,4).

Logistic regression analysis for prediction advanced TNM stage

The four continuous variables associated with the advanced TNM stage, including MTV, TLG, CEA, and CA19-9, were computed into categorical variables using cut-points determined by ROC curve analysis (MTV >6.6 cm³, P=0.005; TLG >88.5 g, P=0.016; CEA >5.84 ng/mL, P=0.0003; CA19-9 >47.2 U/mL, P=0.033, respectively), while other continuous variables were computed into categorical variables by media in the Table 1, which were similar with the previous literature (15–17). In univariate logistic regression, MTV >6.6 cm³ (OR =7.37, 95% CI: 2.71–20.01, P=0.0001), TLG >88.5 g (OR =3.51, 95% CI:

1.66–7.47, P=0.0011), CEA >5.84 ng/mL (OR =5.27, 95% CI: 2.27–12.24, P=0.0001), and CA19-9 >47.2 U/mL (OR =3.94, 95% CI: 1.39–11.17, P=0.0098) were significantly correlated with advanced TNM stage. In multivariate logistic regression, MTV >6.6 cm³ (OR =5.81, 95% CI: 2.05–16.44, P=0.0009) and CEA >5.84 ng/mL (OR =4.30, 95% CI: 1.79–10.34, P=0.0011) were significantly correlated with advanced TNM stage independently (Table 4).

Prognosis value of metabolic parameters and TNM stage for PFS

The mean postoperative follow-up duration was 27.1 (IQR, 15.6–47.4; range, 1.9–73.7) months. Seven patients developed disease progression in 1 year, while other patients were followed up for at least 1 year. A total of 119 patients enrolled, and 38 (31.9%) patients with disease progress were

Table 3 Comparison of the early and advanced pT, pN and M stage

Characteristics	pT stage			pN stage			M stage		
	1–3 (n=97)	4 (n=35)	P	0 (n = 61)	1–2 (n=71)	P	0 (n=97)	1 (n=35)	P
General information									
Gender			0.127			0.996			0.352
Female	39 (29.5)	9 (6.8)		22 (16.7)	26 (19.7)		33 (25.0)	15 (11.4)	
Male	58 (43.9)	26 (19.7)		39 (29.5)	45 (34.1)		64 (48.5)	20 (15.2)	
Age (years)	66 (57–75.5)	64 (59–73)	0.470	65 (57–75.5)	65 (59–73)	0.862	65 (57–75.5)	65 (59–73.0)	0.777
Primary tumor information									
Tumor location			0.277			0.069			0.809
Right	24 (18.2)	12 (9.1)		12 (9.1)	24 (18.2)		27 (20.5)	9 (6.8)	
Left	73 (55.3)	23 (17.4)		49 (37.1)	47 (35.6)		70 (53.0)	26 (19.7)	
Tumor size (cm)	4.5 (3.2–4.5)	5.5 (4.5–6.5)	0.020*	4.5 (3.1–5.5)	5.0 (3.5–6.5)	0.079	5.0 (3.25–5.75)	5.0 (3.5–7.0)	0.490
Metabolic parameters									
SUV _{max} (g/cm ³)	14.3 (11.3–18.9)	18.5 (11.8–21.9)	0.132	14.7 (11.1–18.9)	15.4 (11.4–21.2)	0.629	15.7 (11.7–21.7)	13.7 (10.4–18.8)	0.288
SUVR	4.5 (3.4–6.2)	6.1 (3.5–7.6)	0.031*	4.6 (3.1–6.2)	5.0 (3.7–6.9)	0.291	5.2 (3.4–7.1)	4.2 (3.5–6.4)	0.251
MTV (g/cm ³)	12.1 (6.5–26.0)	20.5 (11.6–25.1)	0.040*	10.4 (6.0–22.2)	19.6 (11.6–28.7)	0.0004***	14.3 (6.7–26.4)	15.5 (10.6–24.9)	0.402
TLG (g)	102.1 (57.9–207.1)	175.2 (116.5–275.8)	0.010*	80.6 (50.1–188.4)	152.5 (97.8–275.8)	0.001**	107.5 (61.1–231.1)	129.8 (87.5–235.6)	0.447
Serum tumor markers									
CEA (ng/mL)	3.50 (2.04–7.49)	12.89 (4.78–38.42)	<0.0001***	3.44 (2.04–5.21)	6.06 (2.77–18.95)	0.001**	3.88 (2.17–8.10)	9.04 (2.92–18.95)	0.003**
CA19-9 (U/mL)	11.40 (5.43–23.25)	45.40 (15.60–134.10)	<0.0001***	16.00 (5.15–23.81)	16.80 (9.91–74.20)	0.024*	15.30 (6.27–22.75)	32.90 (9.91–134.10)	0.001**

Data are presented as M (IQR) or number (percentages). *, P<0.05; **, P<0.01; ***, P<0.001. SUV_{max}, maximum standard uptake value; SUVR, tumor-to-liver standardized uptake value ratio; MTV, metabolic tumor volume; TLG, total lesion glycolysis; CEA, serum carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; M, median; IQR, interquartile range.

documented during the follow-up. The prognostic analysis demonstrated that MTV >6.6 cm³ was the only metabolic parameter significantly associated with worse PFS (P=0.032). Besides, the older age (>65 years), vascular invasion, advanced TNM (stage III–IV), pT (stage 4), pN (stage 1–2), M (stage 1) stage, CEA >5.84 ng/mL, and CA19-9 >47.2 U/mL were significantly related to worse PFS (P=0.044, 0.034, 0.0002, 0.001, 0.008, <0.0001, 0.001, 0.0005, respectively) (Table 5, Figure 5).

Discussion

The present study evaluated the value of metabolic

parameters of ¹⁸F-FDG PET/CT in predicting the TNM stage and prognosis in CRC. The results demonstrated that metabolic parameters, especially MTV, were associated with the advanced TNM stage, which was associated with patients' PFS. MTV >6.6 cm³ was associated with worse PFS. Therefore, we conclude that the metabolic parameters derived from ¹⁸F-FDG PET/CT were promising image biomarkers to evaluate tumor TNM stage and predict the prognosis of CRC noninvasively.

The malignant tumor stage proposed by the UICC/AJCC TNM classification is a mainstay tool in the assessment of treatment effectiveness and survival in the clinical decision-making process (18). The degree

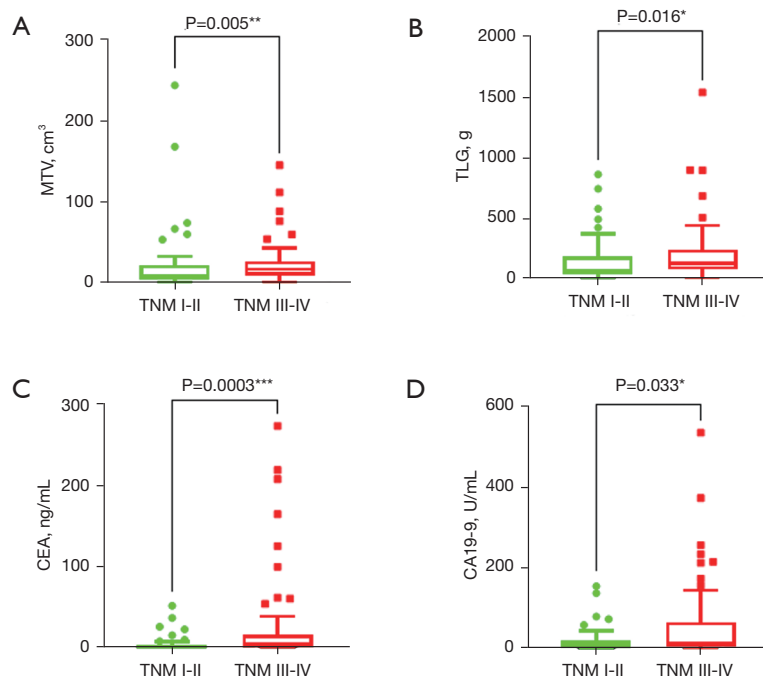


Figure 3 Comparison of metabolic parameters and serological biomarkers between the early and advanced TNM stage (TNM stage I–II, green, *vs.* TNM stage III–IV, red). The higher MTV (A), TLG (B), CEA (C) and CA19-9 (D) were significantly correlated with advanced TNM stage ($P=0.005$, 0.016 , 0.0003 , 0.033 , respectively). *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$. TNM, tumor/node/metastasis; MTV, metabolic tumor volume; TLG, total lesion glycolysis; CEA, serum carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

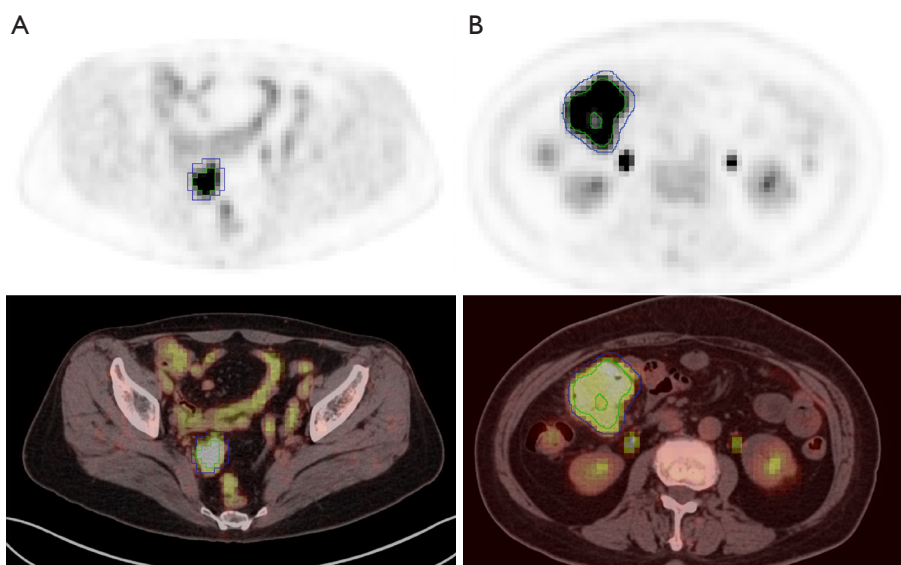


Figure 4 Example of early and advanced TNM stage (TNM stage I–II, A, *vs.* TNM stage III–IV, B). (A) A 51-year-old woman staged as T1N0M0, with MTV =5.11 cm³, TLG =49.06 g, CEA =1.02 ng/mL, and CA19-9 =5.10 U/mL. (B) A 61-year-old woman staged as T4N2M0, with MTV =44.26 cm³, TLG =438.62 g, CEA =573.00 ng/mL, and CA19-9 =535.80 U/mL. The primary VOI is shown in blue, while the secondary VOI, based on SUV_{max} 40%, is shown in green. TNM, tumor/node/metastasis; MTV, metabolic tumor volume; TLG, total lesion glycolysis; CEA, serum carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; VOI, volume of interests; SUV_{max} , maximum standard uptake value.

Table 4 Univariate and multivariate logistic regression analysis for advanced TNM stage (stage III–IV)

Characteristics	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
General information				
Age (>65 vs. ≤65 years)	1.239 (0.617–2.490)	0.547	–	–
Gender (female vs. male)	1.190 (0.575–2.465)	0.639	–	–
Primary tumor information				
Tumor location (right vs. left hemi-colon)	0.566 (0.250–1.279)	0.171	–	–
Tumor size (>5.0 vs. ≤5.0 cm)	1.395 (0.677–2.875)	0.367	–	–
Metabolic parameters				
SUV _{max} (>15.0 vs. ≤15.0 g/cm ³)	0.939 (0.468–1.883)	0.859	–	–
SUVR (>4.9 vs. ≤4.9)	1.065 (0.531–2.136)	0.859	–	–
MTV (>6.6 vs. ≤6.6 cm ³)	7.37 (2.71–20.01)	0.0001***	5.81 (2.05–16.44)	0.0009***
TLG (>88.5 vs. ≤88.5 g)	3.51 (1.66–7.47)	0.0011**	–	–
Serum tumor marker				
CEA (>5.84 vs. ≤5.84 ng/mL)	5.27 (2.27–12.24)	0.0001***	4.30 (1.79–10.34)	0.0011*
CA19-9 (>47.2 vs. ≤47.2 U/mL)	3.94 (1.39–11.17)	0.0098**	–	–

*, P<0.05; **, P<0.01; ***, P<0.001. TNM, tumor/node/metastasis; OR, odds ratio; CI, confidence interval; SUV_{max}, maximum standard uptake value; SUVR, tumor-to-liver standardized uptake value ratio; MTV, metabolic tumor volume; TLG, total lesion glycolysis; CEA, serum carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

of tumor progression and invasion, patient outcome, treatment allocation, as well as clinical trial enrolment, are estimated based on this staging system (19). The National Comprehensive Cancer Network (NCCN) clinical practice guidelines proposed that neoadjuvant therapy should be performed for patients with advanced-stage CRC (TNM stage III–IV) to reduce the recurrence rate and improve survival after surgery (20). Conventional tumor clinical staging modalities rely on multiple-site MRI or CT scans for the T and N stage and biopsy or clinical follow-up of suspected metastases to regional lymph nodes or distant sites for the N and M stage, which is difficult to reflect the overall tumor appearance and whole-body status in such way (21). Thus, a need for an accurate diagnosis, prognosis, and treatment guidelines has led radiologists to focus on whole-body molecular imaging to predict the TNM stage and prognosis effectively and non-invasively.

¹⁸F-FDG PET/CT is a useful imaging tool for staging, restaging, treatment response monitoring, and prognosis predicting in many tumors, including CRC (22). As the Warburg effect shows, the rapidly proliferating tumor cells

need glycolysis to increase energy supply, and the increased expression of glucose transporter 1 (GLUT-1) in tumor cells increases glucose absorption (23). Thus, high levels of FDG uptake of the primary tumor before treatment were associated with more aggressive tumor biological behavior (24). Consistent with our findings, patients with advanced stage are prone to a higher ¹⁸F-FDG uptake of primary lesions. The SUV_{max} only reflects the highest glucose metabolism as measured in the highest pixels within a designated region of interest. But the MTV and TLG are suggested to provide more accurate prediction on the tumor burden and tumor behavior in an entire tumor mass as the MTV is defined as the volume of tumor cells with high glucose uptake, while TLG is defined according to the SUV and the volume of the tumor. However, only a few studies have accessed the correlation between the volumetric parameters and the TNM stage in CRC, as well as their predictive value in patients' tumor progress and survival (15,25,26).

It is reported that ¹⁸F-FDG PET/CT parameters are higher in advanced-stage tumors than in early-stage

Table 5 Survival analysis for progression-free survival

Characteristics	Progression-free survival	
	χ^2	P value
General information		
Age (>65 vs. ≤65 years)	4.060	0.044*
Gender (female vs. male)	0.165	0.684
Primary tumor information		
Tumor location (right vs. left hemi-colon)	0.632	0.427
Tumor size (>5.0 vs. ≤5.0 cm)	1.012	0.314
Differentiation (poor vs. well and moderate)	0.344	0.558
Vascular invasion (yes vs. no)	4.492	0.034*
Lymphovascular invasion (yes vs. no)	0.710	0.399
Staging		
TNM (III–IV vs. I–II)	13.740	0.0002***
pT (4 vs. 1–3)	11.277	0.001**
pN (1–2 vs. 0)	7.028	0.008**
M (1 vs. 0)	45.131	<0.0001***
Metabolic parameters		
SUV _{max} (>15.0 vs. ≤15.0 g/cm ³)	0.029	0.864
SUVR (>4.9 vs. ≤4.9)	0.161	0.688
MTV (>6.6 vs. ≤6.6 cm ³)	4.619	0.032*
TLG (>88.5 vs. ≤88.5 g)	0.612	0.434
Serum tumor marker		
CEA (>5.84 vs. ≤5.84 ng/mL)	10.643	0.001**
CA19-9 (>47.2 vs. ≤47.2 U/mL)	12.145	0.0005***

*, P<0.05; **, P<0.01; ***, P<0.001. TNM, tumor/node/metastasis; SUV_{max}, maximum standard uptake value; SUVR, tumor-to-liver standardized uptake value ratio; MTV, metabolic tumor volume; TLG, total lesion glycolysis; CEA, serum carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

tumors (15). To our knowledge, however, few previous studies have investigated the relationship of metabolic parameters in predicting the postoperative pTNM stage, the gold standard for making clinical decisions. Besides, the absence of universally accepted thresholds limits the predicted value of the TNM stage in the individual patient (15). Li *et al.* compared the preoperative clinical early- and advanced-stage groups based on the PET/CT in only

88 patients and suggested that higher SUV_{max} correlated with advanced clinical stage (stage III–IV) (27). Suzuki *et al.* reviewed the TNM stage of 138 patients but only found a trend in correlation with SUV_{max}, MTV2.5, and TLG2.5 (Spearman correlation coefficient =0.171, 0.357, 0.340, respectively, P<0.05) (15). In our study, we compared the early- and advanced-stage groups based on the postoperative pathology and follow-up, and found that metabolic parameters and serum tumor markers, especially MTV and CEA, were significantly higher in the latter group. In addition, we suggested meaningful cut-off values of MTV >6.6 cm³ and CEA >5.84 ng/mL to independently predict the advanced TNM stage (stage III–IV). The correlation between metabolic parameters of ¹⁸F-FDG PET/CT and TNM stage needs to be further investigated.

The previous studies also found a correlation among the metabolic parameters, the pT, pN, and M stage. Suzuki reported that MTV2.5 and TLG50% were reliable diagnostic biomarkers for discriminating T, N, and M stage, with a cut-off value of MTV2.5 =9.35 and 63.33 cm³, TLG50% =328.1 g, and TLG50% =94.81 g, respectively (15). Our previous small-size study demonstrated the higher SUV_{max}, TLG40%, and MTV40% values of the primary tumor lesion were correlated with an advanced T stage (stage 3–4), SUV_{mean} correlated with M status, and no metabolic parameters correlated with N stage (28). However, the results of Kido *et al.* revealed that SUV_{max}, MTV 3.5, and TLG 40% correlated with the N stage (26). On the contrary, a study with a small sample size of 66 patients found that SUV_{max} was not related to the pT, pN, or M stage (29). Our present study included a relatively larger number of patients and found that SUVR and TLG differed between pT1–3 and pT4 groups, indicating that SUVR and TLG may be related to the depth of tumor invasion. We also found that TLG and MTV significantly differed between pN0 and pN1–2 groups, indicating that TLG and MTV may be related to the status of lymphovascular invasion. Contradictorily, the metabolic parameters including MTV and TLG were not significantly related to the status of lymphovascular invasion in our present study. This might be caused by the missing data, which was not available in some early pathological reports. Differently from some previous studies, our present study revealed that no metabolic parameters significantly differed between M0 and M1 groups, which may be caused by the biased results from the relatively small numbers of patients with distant metastasis. Further investigation is needed to explore whether MTV and TLG are related to the depth of invasion, lymphovascular invasion, and distant metastasis.

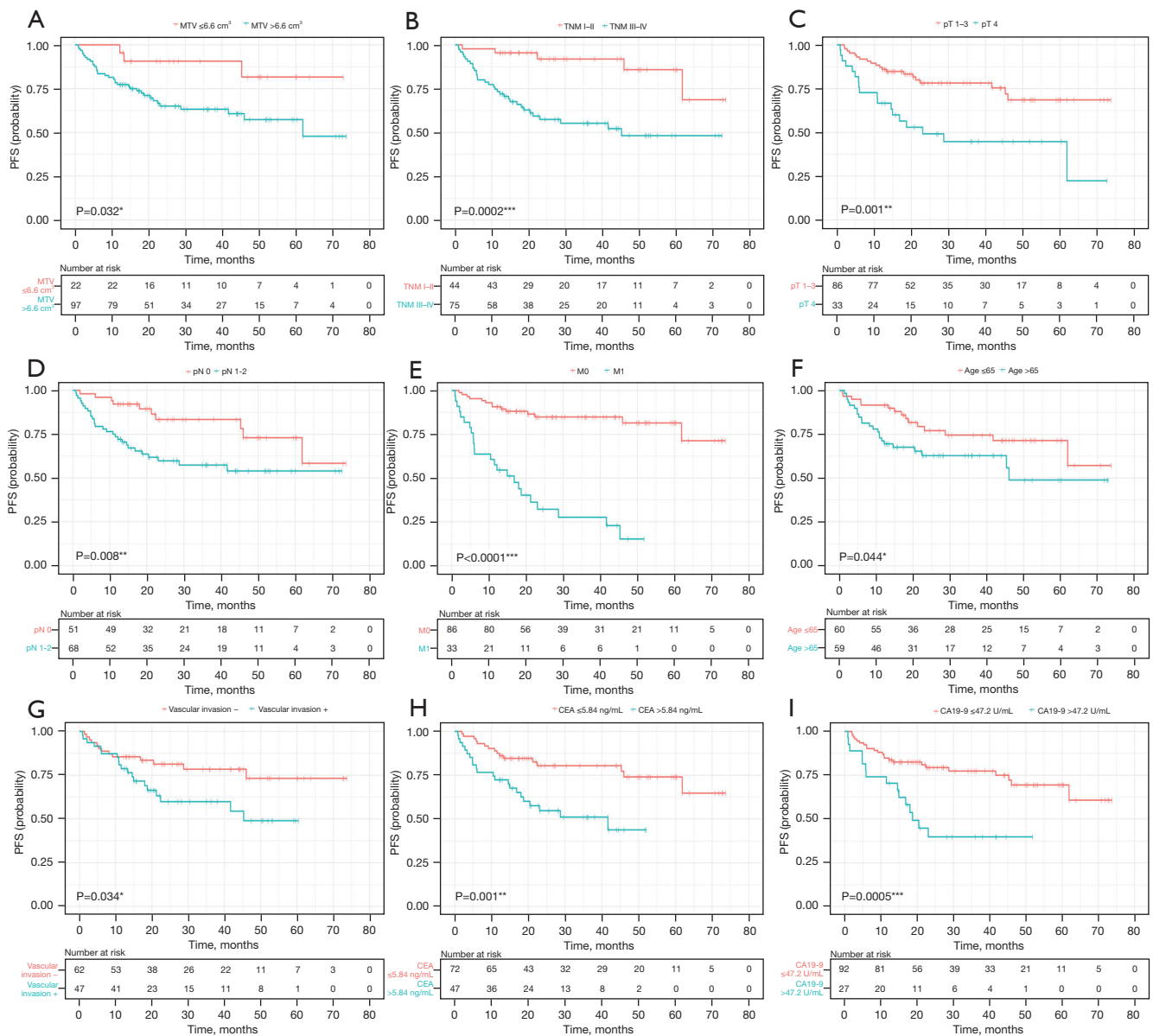


Figure 5 Kaplan-Meier curves of PFS of colorectal cancer patients. The higher MTV (A), TNM stage (B), pT stage (C), pN stage (D), M stage (E), the older age (F), the positive tumor vascular invasion status (G), and the higher CEA (H) and CA19-9 (I) were associated with worse PFS. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$. PFS, progression-free survival; MTV, metabolic tumor volume; TNM, tumor/node/metastasis; CEA, serum carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

The tumor TNM classification system is the most commonly used prognostic factor in patients with CRC recommended by AJCC (30). ¹⁸F-FDG PET/CT metabolic and volumetric parameters, reflecting the glucose metabolism, have also been used to predict the prognosis of CRC patients. Shi *et al.* revealed that TNM stage and SUV_{max} were associated with survival by multivariate

analysis (31). Two volumetric parameters MTV and TLG, which have already been recognized as markers of tumor aggressiveness and tumor burden, have also been found to be of prognostic significance in the previous studies (25,32). Xu *et al.* reported that N-stage status, and MTV40% were significantly associated with patients' disease-free survival (14). Jo *et al.* reported that advanced TNM stage,

high MTV, and high TLG, were associated with worse recurrence-free survival and overall survival in rectal cancer (13). Our study demonstrated that the advanced TNM stage, pT, pN, and M stage, as well as elevated MTV, were significantly associated with worse PFS, while MTV $>6.6 \text{ cm}^3$ could be an optimal cutoff value.

Limitations

Some limitations should be mentioned. Firstly, the study was limited by its retrospective design and by its relatively small sample size. Importantly, the various treatment methods after the surgery may affect the accuracy of the results. Besides, the observation time is limited. In the future, more extensive prospective studies involving many subjects are required to confirm the findings.

Conclusions

Baseline ^{18}F -FDG PET-CT-derived parameters can serve as a noninvasive tool for preoperatively staging CRC. The metabolic and volumetric parameters, especially MTV $>6.6 \text{ cm}^3$, might be associated with the advanced TNM stage. In addition, MTV $>6.6 \text{ cm}^3$ and advanced TNM stage were associated with worse PFS.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Beijing Friendship Hospital, Affiliated to Capital Medical University (No. 2023-P2-013-01), and individual consent for this retrospective analysis was waived.

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