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^{18}F-FDG PET/CT metabolic parameters and HER2 expression in colorectal cancer

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The relationship between ^{18}F-FDG uptake and HER2 expression in colorectal cancer has not been investigated yet. This study aimed to investigate the predictive efficiency of preoperative ^{18}F-FDG PET/CT for HER2 expression and prognosis in colorectal cancer. We retrospectively analyzed 131 colorectal cancer patients who underwent ^{18}F-FDG PET/CT scans in our center before surgery. HER2 positivity was defined as a score of 2+ or 3+, and HER2 negativity was defined as a score of 0 or 1+ in immunohistochemistry of HER2 expression. The relationships between ^{18}F-FDG PET/CT metabolic parameters and HER2 expression and the prognosis of colorectal patients were systematically studied. From 131 colorectal cancer patients, there were 27 (20.6%) HER2-positive patients. SUVmax of the primary tumor (mean ± SD) in the HER2-positive and the HER2-negative group was 18.238±8.912 and 14.455±6.531, respectively. SUVmax in the HER2-positive group was higher than in the negative group (p=0.034). When the cutoff was based on 5 cm, tumor size demonstrated significant positive correlations with SUVmax (p=0.012) and HER2 expression (p=0.014). Multivariate analysis showed that both SUVmax and tumor size had a significant correlation with HER2 expression (p=0.049 vs. p=0.043, respectively). There was no statistical difference in PFS between the HER2-positive and the HER2-negative group (p=0.28). ^{18}F-FDG metabolic parameters had a significant correlation with HER2 expression in colorectal cancer. SUVmax combined with primary tumor size were better for predicting the HER2 status of colorectal cancer.

Key words: ^{18}F-FDG PET-CT, SUVmax, HER2, colorectal cancer

Colorectal cancer (CRC) is one of the most commonly diagnosed cancer all over the world [1], although its epidemiology is obviously different in various regions. Accounting for an evaluated more than 49,000 deaths in the United States in 2016, CRC is also the third leading cause of cancer-related mortality [2]. In China, CRC has the fifth-highest incidence among all cancers in men and the fourth in women, and the fifth highest mortality in both men and women [3]. At the initial diagnosis, approximately 25% of CRC patients present with metastases, and a further 50% of patients will develop metastases [4]. Surgery is still the most common treatment. However, treatment outcomes for colorectal cancer remain unsatisfactory in patients with inoperable or metastatic disease. Although new cytotoxic and molecularly targeted agents have improved the overall survival of CRC patients with metastases over the past two decades but the rate of recurrence and failure remains high [5]. Therefore, effective therapeutic regimens for such patients need to be identified and developed.

Previous studies have shown that 5.2–47.4% of patients with colorectal cancer are positive for human epidermal growth factor receptor 2 (HER2) [6–8]. The HERACLES-A and MyPathway studies demonstrated that patients with HER2 amplification did not derive a survival benefit from chemoradiation therapy whereas patients without HER2 amplification derived a statistically significant survival benefit [9, 10]. Therefore, it is important to identify clinical characteristics that might be predictive of HER2 status. Although there are some practices to determine the HER2 expression in colorectal cancer patients, the procedures are invasive. Alternative noninvasive strategies, such as PET/CT, for predicting the mutation profile would therefore be of great value. Several studies have demonstrated that PET/CT has the potential to predict the phenotype of a tumor

[11–14], such as the HER2 status in gastric cancer [11] and the KRAS status in colorectal cancer [14]. ^{18}F-FDG (18fluor-fluoro-deoxyglucose) PET/CT has been widely used for diagnosis, monitoring of treatment response, surveillance, and prognostication in a variety of cancers [15, 16].

However, the relationship between ^{18}F-FDG uptake and HER2 expression in colorectal cancer, and the possible underlying mechanisms, are not clear. The present study aimed to investigate whether HER2 expression is associated with ^{18}F-FDG uptake and whether ^{18}F-FDG PET/CT can be used to predict the HER2 status and prognosis of colorectal cancer. To our knowledge, this was the first study to present evidence of the potential value of ^{18}F-FDG PET/CT scans for this use and to suggest that ^{18}F-FDG PET/CT may play a key role in determining the strategy for colorectal cancer patients by predicting their response to anti-HER2 antibody therapy.

Patients and methods

Clinicopathological data. 131 CRC patients (84 males and 47 females; age ranged from 30 to 85 years) undergoing ^{18}F-FDG PET/CT scans before surgical resection were obtained from the Shanghai Cancer Center Fudan University between May 2015 and August 2018. Those who had received any chemotherapy, radiation therapy, or molecular targeted therapy before ^{18}F-FDG PET/CT scans were excluded. Every patient had surgery at the primary colorectal lesion after the specified check and the final pathology was colorectal adenocarcinoma or mucinous adenocarcinoma. Immunohistochemical results also had been received. Complete case records, including data on age, sex, tumor size, T stage, lymphatic metastasis were available. 131 patients met these criteria and gave written informed consent to participate in this retrospective study. This study protocol was approved by the institutional review board of the Shanghai Cancer Center, and all patients provided their consent for data handling.

^{18}F-FDG PET/CT protocol and imaging interpretation. ^{18}F-FDG PET/CT scans were performed using a combined PET/CT scanner (Siemens Medical Systems, Biograph 16 HR). All patients fasted for at least 6 h before ^{18}F-FDG administration and glucose levels in the peripheral blood were confirmed to be 10 mmol/L or less before the ^{18}F-FDG injection (7.4 MBq/kg; 0.2 mCi/kg) of body weight) in this study. Data acquisition that scanning included the area from the upper thigh to the skull started approximately 1 h after the injection and the low-dose CT scans were obtained with the following parameters: 40–60 mA, 120 kV, 0.6 s tube rotation, and 3.75 mm section thickness. For quantitative analysis, ^{18}F-FDG accumulation on a workstation was assessed by two experienced nuclear medicine physicians by calculating the standardized uptake value (SUV), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) in the regions of interest placed over the suspected lesions and the normal liver. SUV was calculated in a pixel as (radioactivity) / (injected dose / body weight). TLG was calculated as (mean SUV) × (MTV), in which MTV was measured with setting a margin threshold as SUV of 2.5. All values of SUVmax, MTV, and mean SUV were automatically measured by the analysis software for each lesion. For evaluating metastatic CRC, the highest SUV in a metastatic tumor was taken as SUVmax (maximum standard uptake value) and the mean SUV was taken as SUV mean.

Immunohistochemical analysis. Unlike in breast and gastric cancers, the criterion to define HER2-positive testing in CRC has not been standardized yet and has widely varied among different studies [9, 17, 18]. In our study, immunohistochemical analysis was performed on paraffin-embedded colorectal cancer tissues after microtome sectioning and staining using standard procedures. Positivity for HER2 was independently examined using light microscopy by 2 experienced pathologists. Circumferential membrane-bound staining of human epidermal growth factor receptor 2 (HER2) was evaluated as 0, 1+, 2+, or 3+, in keeping with panel recommendations on HER2 scoring. Positivity (HER2) was considered with a score of 2+ or 3+ and negativity (HER2) with a score of 0 or 1+ [11]. The HER2 antibodies used were from clone 4B5, Roche Diagnostics GmbH (Germany).

Statistical analysis. Statistical analysis was performed using SPSS software (version 21.0; SPSS, IBM Inc., Armonk, New York, USA). All continuous variables are expressed as mean ± SD. The relationship between clinicopathological characteristics and SUVmax was tested by t-test. Chi-square test was used for univariate analysis and logistic regression analysis for multivariate analysis to evaluate the preoperative predictors for HER2 expression. ANOVA way was used for the predictive efficiency of stratification based-tumor size and SUVmax for HER2 expression. Moreover, PFS (progression-free survival) was analyzed by the Kaplan-Meier method and log-rank tests were used in univariate analysis. A p-value <0.05 was considered statistically significant, and all analyses were two-sided.

Results

Patient characteristics. Among the 131 patients including 84 males and 47 females, the HER2 expression of primary lesions were 20.6% with positivity (19.8% with a score of 2+ and 0.8% with a score of 3+) and 79.4% with negativity (51.1% with a score of 0 and 28.3% with a score of 1+). 93 patients had well or moderately differentiated adenocarcinoma, 38 had poorly differentiated adenocarcinoma. Regarding lymph node metastasis, 62.6% of samples (82/131) were detected as positive while 37.4% (49/131) as negative.

Relationship with patient characteristics and ^{18}F-FDG PET/CT parameters. The SUVmax for the primary tumors ranged from 4.84 to 43.88. Table 1 demonstrated the relationships between the clinicopathological parameters and SUVmax. Statistical analysis exhibited no significant differences in SUVmax according to sex, age, lymph node metastasis, T category, or location of the tumor. However,

there were significant differences in SUVmax according to tumor size (p=0.012, Table 1). Tumor size bigger than 5 cm had a significantly higher SUVmax than did smaller than the baseline. Tumor size ranged from 1.5 to 13.5 cm on pathological examination. Besides, no significant correlations were found between SUVmean, MTV, TLG, and patient characteristics in colorectal cancer.

Correlation between patient characteristics and HER2 expression. Patients were categorized into 2 groups according to the immunohistochemical staining for HER2: patients with HER2 expression (n=27) and patients without HER2 expression (n=104). Table 2 shows the results of the univariate analysis for each factor. No significant differences in sex, age, lymph node metastasis, or T category were found between the two groups. However, the differences between the size of the primary tumor and the HER2 expression were statistically significant (34.2% vs. 15.1%; p=0.014). The bigger primary tumor had a higher rate of HER2 positivity than the smaller ones.

Indicators for HER2 expression. Mann-Whitney U test analysis revealed that patients with HER2-positivity had a significantly higher SUVmax than the HER2-negative group (18.238±8.912 vs. 14.455±6.531; p=0.034, Figures 1–3). Additionally, HER2 status has no connection to SUVmean, MTV, or TLG in our study. Multivariate analysis revealed that SUVmax and tumor size correlated significantly with HER2 expression in colorectal cancer (p=0.049 vs. p=0.043, respectively; Table 3). Therefore, using these parameters, we categorized the patients into groups based on their potential of being HER2-positive: a low-potential group (sizes <5 cm and SUVmax <12.69), a moderate-potential group (sizes ≥5 cm and SUVmax <12.69, or sizes <5 cm and SUVmax ≥12.69), and a high-potential group (sizes ≥5 cm and SUVmax ≥12.69). The probability of HER2 expression in these groups was 13.2%, 17.6%, and 40.7%, respectively (p=0.013; Table 4). These results suggest that ^{18}F-FDG PET/CT scans can be useful for predicting the HER2 status of colorectal cancer. A cut-off level was determined by the median SUVmax.

Prognosis. The study showed that the PFS of patients with the HER2-positive group was not statistically different from that of the HER2-negative group (p=0.280). However, the HER2-positive patients did have longer median PFS than that of the HER2-negative ones (19 vs. 16 months), although not significantly different. In terms of the sizes of primary tumors, when the optimal cut-off value for PFS was determined by the sizes, there were no differences between SUVmax and the PFS of patients, either (p=0.168).

Table 1. The relationships between the clinicopathological parameters and SUVmax.

Variable	N	SUVmax (Mean ± SD)	p-value
Sex			0.661
Male	84	15.416±7.265	
Female	47	14.911±7.189	
Age (years)			0.300
<60	58	14.423±6.457	
≥60	73	15.880±7.746	
Tumor size (cm)			0.012
<5	93	14.418±6.980	
≥5	38	16.521±6.736	
Lymph node metastasis			0.104
Negative	49	16.742±8.000	
Positive	82	14.334±6.588	
Histologic differentiate			0.598
Well or moderately	93	15.147±7.493	
Poorly	38	15.451±6.570	
HER2 status			0.034
Positive	27	18.238±8.912	
Negative	104	14.455±6.531	
T stage			0.889
T1/T2	36	15.689±78.072	
T3/T4	95	15.063±6.900	
Tumor location			0.526
Proximal	107	15.040±7.079	
Distal	24	16.107±7.889	
CEA level			0.540
<5	64	15.262±8.018	
≥5	67	15.209±8.413	

SD-standard deviation; T-tumor; CEA-carcino-embryonic antigen

Table 2. The univariate analysis for HER2 expression.

Variable	N	HER2(–)	HER2(+)	χ^2	p-value
Sex				1.464	0.226
Male	84	64	20		
Female	47	40	7		
Age (y)				1.650	0.199
<60	58	49	9		
≥60	73	55	18		
Tumor size (cm)				6.050	0.014
<5	93	79	14		
≥5	38	25	13		
Lymph node metastasis				0.002	0.965
Negative	49	39	10		
Positive	82	65	17		
Histologic differentiate				0.309	0.578
Well- or moderately	93	75	18		
Poorly	38	29	9		
T stage				1.558	0.212
T1/T2	36	26	10		
T3/T4	95	78	17		
Tumor location				0.001	0.976
Proximal	107	85	22		
Distal	24	19	5		
CEA level				1.473	0.225
<5	64	48	16		
≥5	67	56	11		

T-tumor; CEA-carcino-embryonic antigen

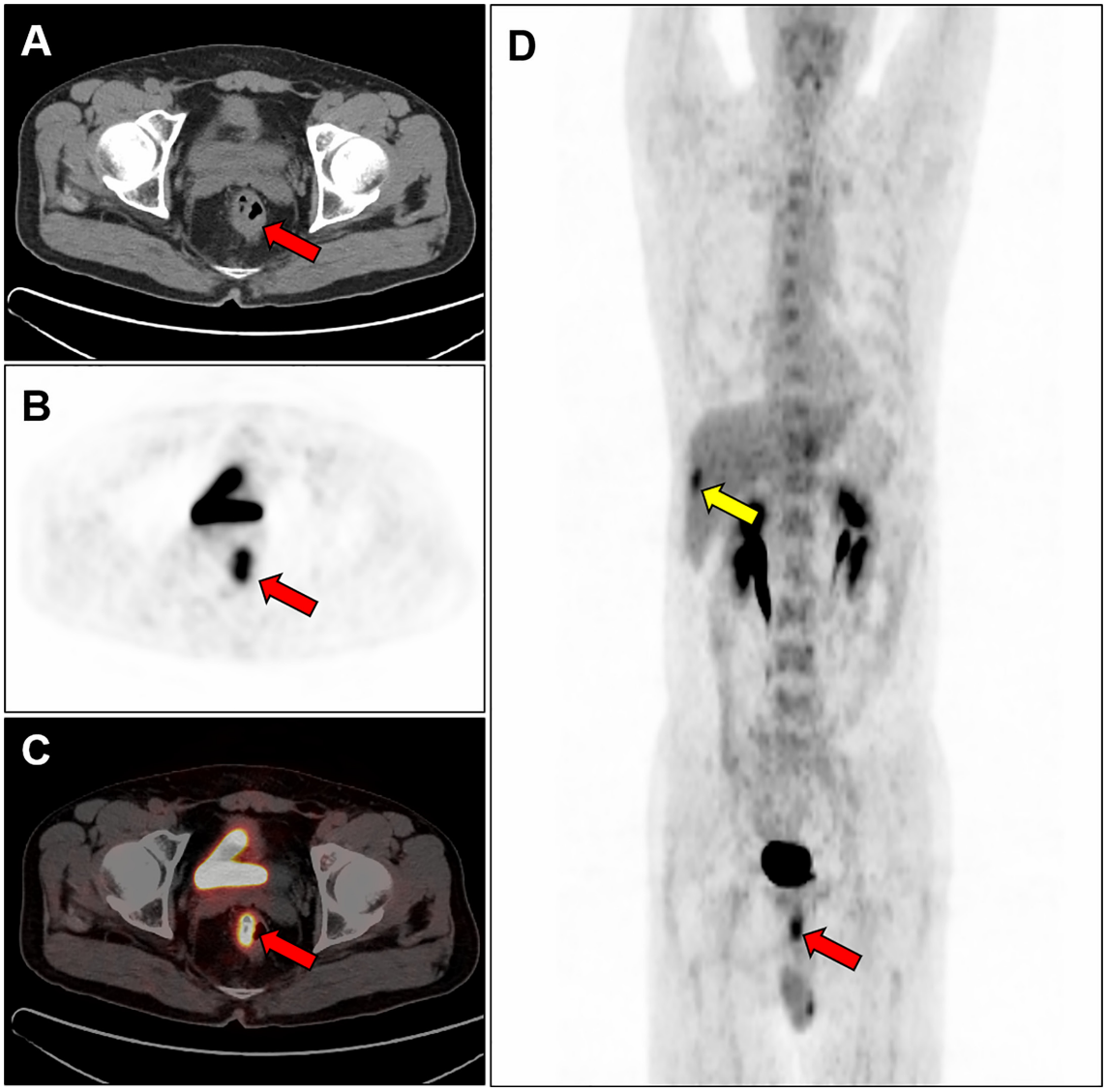

Figure 1. Representative PET/CT images. A 49-year-old male patient with HER2-positive rectal cancer. Axial computed tomography (A) showed a thickened rectal wall (red arrow) and a corresponding focal FDG uptake in the PET scan (B–D). The maximum standard uptake value (SUVmax) was 13.77 (red arrow). The SUVmax of hepatic metastases was 8.63 (yellow arrow). After surgery, immunohistochemical (IHC) staining showed that the tumor had a positive HER2 status (C).

Discussion

The HERACLES-A and MyPathway studies have shown benefit in a small number of patients with the use of combination trastuzumab-lapatinib and trastuzumab-pertuzumab, respectively [9, 10]. The testing for HER2 expression is currently practice in the management of colorectal cancer. However, the positive rate of HER2 in colorectal cancer is not consistent in domestic and foreign literature reports. Our study demonstrated a 20.6% rate of HER2 expression. PET/CT is a molecular imaging technique widely used in the diagnosis and staging of malignant tumors. Our results showed that the SUVmax in colorectal cancer was significantly higher when HER2 was expressed than when not expressed. Besides, SUVmax and the PFS of patients have significant statistical differences. To our knowledge, this was the first study to analyze the association between HER2 expression and the predictive value of ^{18}F-FDG PET/CT parameters in colorectal cancer patients.

Our data also demonstrated that HER2 expression is more common in big primary tumor size than in small size. This finding is similar to the findings of previous studies [19]. In addition, a big primary tumor had significantly higher ^{18}F-FDG uptake than a small primary tumor, partly explaining why patients with HER2 expression had a high SUVmax. But the reasons for this selective high rate of

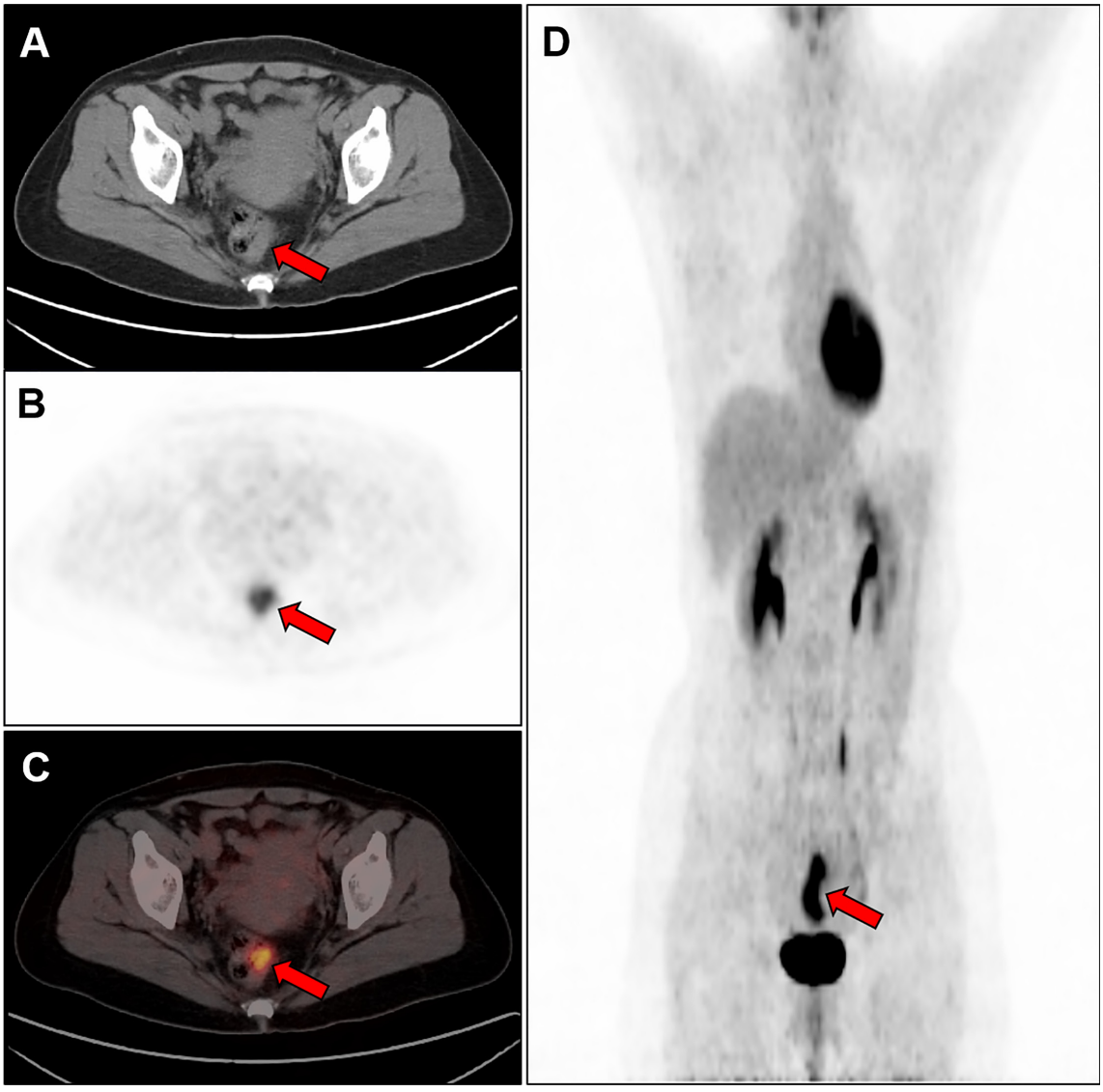

Figure 2. Representative PET/CT images. A 49-year-old female patient with HER2-negative rectal cancer: A) CT scan; B–D) the primary tumor had a lower radio-uptake SUVmax = 9.1

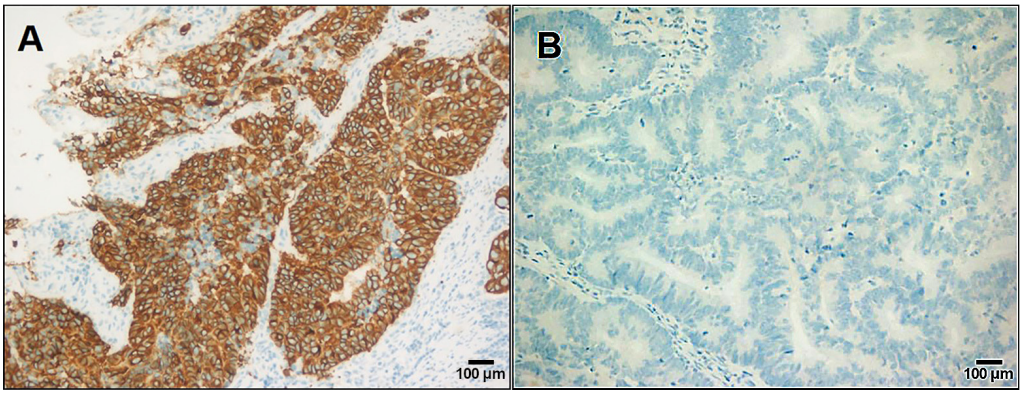

Figure 3. Postoperative IHC. The two 49-year-old patients with HER2 status: A) HER2-positive; B) HER2-negative.

Table 3. Multivariate analysis for HER2 expression.

	p-value	Odds Ratio	95% CI
Tumor size	0.043	2.533	1.031–6.224
SUVmax	0.049	1.060	1.000–1.123

CI-Confidence interval

Table 4. Stratification based-tumor size and SUVmax for predicting HER2 expression.

Stratification	N (%)	HER2 N (%)		p-value
		(–)	(+)	
Low	53 (40.5)	46 (35.1)	7 (5.4)	0.013
Moderate	51 (38.9)	42 (32.1)	9 (6.8)	
High	27 (20.6)	16 (12.2)	11 (8.4)	
Total	131 (100)	104 (79.4)	27 (20.6)	

HER2 expression in big primary tumor sizes remain unclear. Multivariate analysis revealed that both the SUVmax of the primary tumor and the tumor size correlated significantly with HER2 expression. We further categorized patients into groups based on their potential for being HER2-positive: high-potential, moderate-potential, and low-potential. HER2 was expressed in 40.7% of the high-potential group while in 13.2% of the low-potential group, implying that anti-HER2 therapies are not effective for patients with a low potential of being HER2-positive. For these reasons, noninvasive methods, such as molecular imaging, for predicting HER2 status have great clinical relevance. In our study, SUVmax has the independent potential to evaluate the HER2 status in colorectal carcinoma with metastatic lesions. Meanwhile, SUVmax united to the sizes of the primary tumors can also precisely forecast the HER2 expression in colorectal cancer.

The "Trastuzumab for Gastric Cancer" trial on metastatic gastric cancer demonstrated a significant overall survival benefit when trastuzumab was combined with chemotherapy [20]. HER2 status is routinely used to predict the efficacy of anti-HER2 therapies. Actually, the role of HER2 as a prognostic factor in colorectal cancer had been controversial [21]. The HERACLES-A and MyPathway studies demonstrated that patients with HER2 amplification did not derive a survival benefit from chemoradiation therapy whereas patients without HER2 amplification derived a statistically significant survival benefit. Some studies failed to find an association with prognosis [22, 23], whereas others found a direct correlation between HER2 expression or amplification and poor survival [24, 25]. In our study, there was no significant statistical difference between HER2 expression and the PFS of patients, we could attribute this result to the lack of anti-HER2 therapies on the selected patients. In a future study, we intend to collect specific anti-HER2 therapy cases to elucidate the correlations between HER2 expression, progression-free survival, and the ^{18}F-FDG uptake of anti-HER2 therapy patients.

This study was partly limited by its retrospective design and no HER2-targeted molecular therapies. Although PET/CT may have a moderate diagnostic performance, as we all know, it cannot replace conventional methods in the clinical setting. Nonetheless, our results may be relevant for the development of noninvasive strategies to predict prognosis and HER2 expression in colorectal cancer patients. Advances in PET radiotracers may increase the sensitivity and specificity of this technique and enable full molecular assessment of colorectal cancer.

In conclusion, ^{18}F-FDG PET/CT was a potential predictor for HER2 expression status in colorectal cancer, and patients with HER2-positive expression show higher FDG uptake. The combination with primary tumor size, SUVmax showed more predictive efficiency for HER2 expression. Our study potentially contributed to anti-HER2 target therapy in inoperable advanced colorectal cancer patients by evaluating HER2 expression of tumor noninvasively.

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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