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ORIGINAL ARTICLE

Intra-tumor metabolic heterogeneity of gastric cancer on ^{18}F-FDG PETCT indicates patient survival outcomes

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Abstract

The present study aimed to investigate the prognostic value of intra-tumor metabolic heterogeneity on 2-[18F] Fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) for patients with gastric cancer. Fifty-five patients with advanced gastric cancer that had received neoadjuvant chemotherapy and radical surgery were included. Clinicopathological information, ^{18}F-FDG PET/CT before chemotherapy, pathological response, recurrence or metastasis, progression-free survival (PFS), and overall survival (OS) of the patients were collected. The maximum, peak, and mean standardized uptake values (SUV_{max}, SUV_{peak}, and SUV_{mean}), tumor-to-liver ratio (TLR), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) on PET/CT were measured. Heterogeneity index-1 (HI-1) was calculated as SUV_{mean} divided by the standard deviation, and heterogeneity index-2 (HI-2) was evaluated through linear regressions of MTVs according to different SUV thresholds. Associations between these parameters and patient survival outcomes were analyzed. None of the parameters on PET were associated with tumor recurrence. Pathological responders had significantly smaller TLR, MTV and HI-2 values than non-responders ($P=0.017$, 0.017 and 0.013, respectively). In multivariate analysis of PFS, only HI-2 was an independent factor (hazard ratio [HR] = 2.693, $P=0.005$) after adjusting for clinical tumor-node-metastasis (TNM) stage. In multivariate analysis of OS, HI-2 was also an independent predictive factor (HR = 2.281, $P=0.009$) after adjusting for tumor recurrence. Thus, HI-2 generated from baseline ^{18}F-FDG PET/CT is significantly associated with survival of patients with gastric cancer. Preoperative assessment of HI-2 by ^{18}F-FDG PET/CT might be promising to identify patients with poor prognosis.

Keywords Gastric cancer · Prognosis · 2-[18F] Fluoro-2-deoxy-D-glucose (^{18}F-FDG) · Positron emission tomography/computed tomography (PET/CT)

Abbreviations

^{18}F-FDG	2-[18F] Fluoro-2-deoxy-D-glucose
PET/CT	Positron emission tomography/computed tomography
SUVmax	Maximum standard uptake value
SUV_{peak}	Peak standard uptake value
MTV	Metabolic tumor volume
TLG	Total lesion glycolysis
TLR	Tumor-to-liver ratio
HI	Heterogeneity index
VOI	Volume of interest
PFS	Progression-free survival
OS	Overall survival
HR	Hazard ratio
WDA	Well differentiated adenocarcinoma
MDA	Moderate differentiated adenocarcinoma
PDA	Poorly differentiated adenocarcinoma
SRC	Signet-ring cell carcinoma
MAC	Mucinous adenocarcinoma

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Introduction

Gastric cancer is one of the most aggressive tumors and has a dismal prognosis. The 5-year survival rate has been less than < 30% [1]. Preoperative neoadjuvant chemotherapy has demonstrated significant value for patient survival [2–4]. However, there is no practical method that can precisely identify patients with unfavorable treatment responses for intensified treatment, such as adjuvant chemotherapy or target therapy. The current prognostic model, which relies mainly on the tumor-node-metastasis (TNM) staging system, seems insufficient.

In recent years, 2-[18F] Fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) has demonstrated efficiency in staging, detecting recurrence, assessing treatment response, and predicting prognosis in patients with gastric cancer [5–9]. In particular, many image-derived biomarkers in PET/CT have been reported to be effective to predict survival outcomes, such as the maximum standardized uptake value (SUV_{max}), peak SUV (SUV_{peak}), and the tumor-to-liver ratio (TLR) of SUV [7, 10]; as well as volumetric parameters, including the metabolic tumor volume (MTV) [7, 8, 11] and the total lesion glycolysis (TLG) [8, 11]. Furthermore, some studies have demonstrated positive associations between treatment response and SUV_{max} in patients with gastric cancer [5, 12]. However, none of these parameters is able to reflect the intra-tumor metabolic heterogeneity.

Malignant tumors commonly demonstrate a heterogeneous growth pattern, even those of the same pathological type and stage. Intra-tumor heterogeneity has been demonstrated to correlate with treatment failure and worse patient outcome [13–16]. Several heterogeneity indices from ^{18}F-FDG PET/CT, such as the coefficient of variance [17] and the slope of linear regression [18, 19], have been reported in previous studies to show prognostic value in various cancers, such as pancreatic, breast, cervical and oral cavity cancers [18, 20–22]. However, the prognostic value of these heterogeneity indices has not been studied in gastric cancer.

In the present study, we aimed to investigate the prognostic value of heterogeneity parameters from ^{18}F-FDG PET/CT for patients with gastric cancer in comparison with conventional ^{18}F-FDG PET/CT prognostic parameters.

Methods

This study was approved by the Ethics Committee of Zhongshan Hospital of Fudan University (approval number: IRB2015-098). Written informed consent was obtained from all patients.

Study subjects

In this study, 55 patients with gastric cancer, who had received neoadjuvant chemotherapy followed by radical surgery, were included. The chemotherapy regimen was one of the following: Oxaliplatin and 5-FU; oxaliplatin and capecitabine; epirubicin, oxaliplatin and capecitabine; docetaxel, oxaliplatin and 5-FU; or docetaxel and oxaliplatin. The inclusion criteria are as follows: (1) Pathologically confirmed gastric adenocarcinoma; (2) clinical staging was cT2N3M0 or cT3-4N + M0; (3) the patient underwent ^{18}F-FDG PET/CT before chemotherapy; (4) the tumor in situ was FDG avid with an $SUV_{max} > 3.5$. The exclusion criteria are as follows: (1) A second primary malignancy; (2) another life threatening illness.

Clinicopathologic information

The clinicopathological information of the patients was recorded. According to the Japanese classification of gastric cancer [23], all tumors were classified into well differentiated adenocarcinoma (WDA, including papillary adenocarcinoma and tubular adenocarcinoma), moderately differentiated adenocarcinoma (MDA), poorly differentiated adenocarcinoma (PDA), signet-ring cell carcinoma (SRC), and mucinous adenocarcinoma (MAC). In addition, the tumors were classified into two types by the Lauren classification: Intestinal and non-intestinal (including diffuse, mixed, and unclassifiable types).

^{18}F-FDG PET/CT scanning

After fasting for at least 6 h, patients were injected with ^{18}F-FDG (3.7 MBq/kg; range, 240.5–488.4 MBq). PET/CT scanning was performed approximately 1 h (63.1 ± 12.5 min) later using a hybrid GE Discovery VCT 64 PET/CT scanner (General Electric, Milwaukee, WI, USA). Helical CT acquisition was performed initially from the skull base to the proximal thigh in a supine position (200 mAs; 120 kV; collimation, 64 × 0.6 mm; matrix size, 512 × 512; scanning time, 0.8 s per rotation; slice thickness, 1.5 mm; increments, 1.25 mm). PET acquisition of the same area was performed for 2 min every bed position in three-dimensional mode, and images were reconstructed using ordered-subsets expectation maximization iterative reconstruction.

Analysis of PET/CT images

Metabolic and volumetric parameters were measured by a reviewer who had more than 5 years of working experience on a uWS-MI R001 workstation (United Imaging, Shanghai, China), by creating a volume of interest (VOI) using

an isocontour threshold of SUV ≥ 2.5. The SUV was calculated as: SUV = (activity in the volume of interest [Bq/g])/(injected dose [Bq]/body weight [g]). The metabolic parameters included SUV_{max}, SUV_{mean}, and SUV_{peak}. SUV_{peak} was the mean SUV from a fixed 1-cm^3 spherical VOI centered over the highest metabolic part of the tumor. In addition, the tumor-to-liver ratio (TLR) was calculated as the SUV_{max} of gastric cancer divided by the SUV_{mean} of the liver. The volumetric parameters included MTV (cm^3) and TLG (g). MTV was the sum of the metabolic volume, while TLG was the product of MTV and SUV_{mean}.

In addition, two heterogeneity indices were calculated: 1) Heterogeneity index-1 (HI-1), namely the coefficient of variance, which was the ratio of the standard deviation (SD) of SUV to SUV_{mean} as described previously [22, 24]; and 2) heterogeneity index-2 (HI-2), which was the negative form of the slope of the linear regression of MTV according to various SUV thresholds (2.5, 3.0 and 3.5), calculated by a slight modification of previous methods [18, 20, 21], as shown in Fig. 1.

Treatment response assessment

Immediately after neoadjuvant chemotherapy, tumor resectability was confirmed in all patients, and radical surgery was performed within 4–6 weeks. Postoperatively, pathological response was defined if the percentage of the residual tumor volume was roughly less than two thirds of the tumor bed [23].

Patient follow-up

Patients were followed up every 3–4 months in the first 3 years and every 4–6 months thereafter, according to the National Comprehensive Cancer Network guidelines [25]. Recurrence and metastasis were diagnosed based on either a positive biopsy or unequivocal clinical/radiographical evidence. The overall survival (OS) and progression-free survival (PFS) times were recorded, which were defined as the time (in months) from the date of baseline PET/CT to the date when patients died of any cause and to the date when progression was confirmed, respectively. Progression was defined as at least a 20% increase in the sum of the diameters of the lesions, according to the Response Evaluation Criteria in Solid Tumor (RECIST 1.1) criteria [26].

Statistical analysis

Statistical analyses were performed using SPSS 20 (IBM Corp., Armonk, NY, USA) and all hypothesis tests were two sided with a significance level of 0.05. Comparisons of categorical variables were performed using the Chi square test or Fisher's exact test. Comparisons of continuous variables were conducted using Student's t test when normal distributions were obtained, otherwise the Mann–Whitney U test was used. The cutoff value for classifying high and low PET parameter groups was the median value of each variable. Kaplan–Meier survival analysis with the log-rank test was performed to compare PFS and OS between patient groups. Univariate and multivariate Cox regression were conducted and hazard ratios (HR) were calculated to compare the predictive values of clinicopathological factors and PET parameters with patient clinical outcomes.

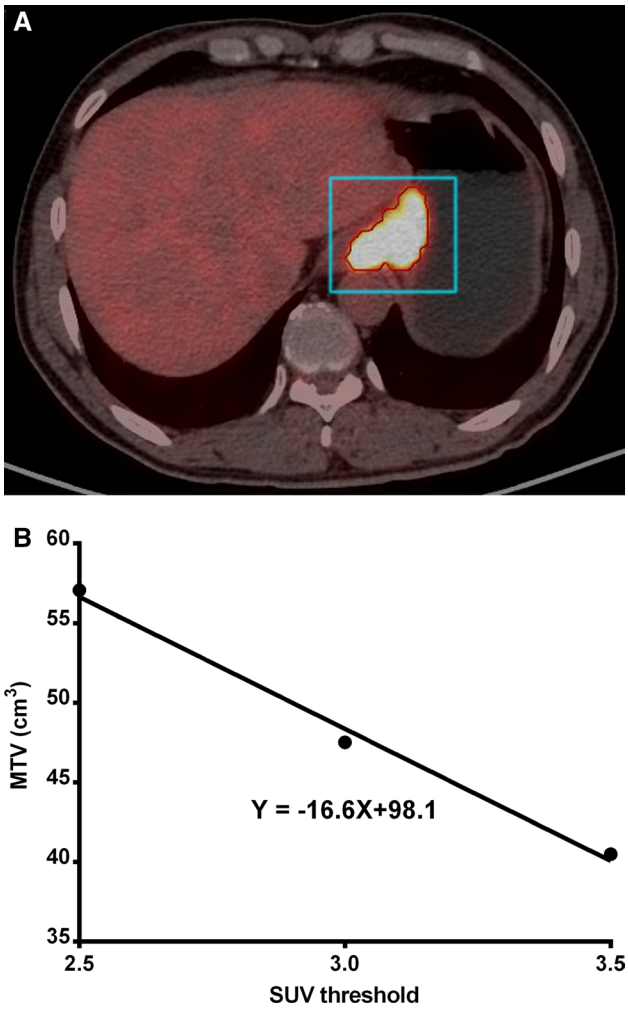

Fig. 1 Process of measuring metabolic heterogeneity indices on ^{18}F-FDG PET/CT. **a** Fused PET/CT image showing an ^{18}F-FDG avid tumor in the cardiac area of the stomach. A rectangle (blue) was drawn to include the whole tumor and an isocontour volume of interest (VOI; red) was automatically generated by using a SUV cutoff of 2.5. Heterogeneity index-1 was defined as the coefficient of variance, which was calculated as standard deviation of the SUV divided by SUV_{mean}. **b** Metabolic tumor volumes (MTVs) were calculated at three different SUV cutoffs (2.5, 3.0, and 3.5) and general linear regression was performed to determine the slope of MTVs. The slop was − 16.6 in this case and heterogeneity index-2 was its negative form, namely, 16.6

Results

Patient basic information

Basic information about the patients is shown in Table 1. None of these clinical and pathological characteristics were significantly associated with tumor recurrence (Table 2).

^{18}F-FDG PET/CT and quantitative parameters

The metabolic parameters on PET were 9.8 ± 5.74 (mean ± SD) for SUV_{max}, 7.9 ± 4.72 for SUV_{peak}, 4.2 ± 1.17 for SUV_{mean} and 5.4 ± 3.20 for TLR. For the volumetric parameters, the MTV and TLG were 61.9 ± 55.12 mL and 335.4 ± 396.63 g, respectively. The heterogeneity indices were calculated as 0.79 ± 0.20 for HI-1 and 36.5 ± 27.09 for HI-2 (Table 1). None of these quantitative parameters were significantly associated with tumor recurrence (Table 2). Restricted by the retrospective nature of this study, information regarding pathological response was only available for 36 patients. Pathological responders had significantly smaller TLR, MTV, and HI-2 than non-responders ($P = 0.017$, 0.017, and 0.013, respectively), while the other parameters were not significant factors (Table 3).

Univariate and multivariate analyses for PFS

Univariate and multivariate analyses for associations with PFS are summarized in Table 4. Baseline carbohydrate antigen 19-9 (CA19-9) (HR = 1.947, $P = 0.036$), clinical TNM stage ($P = 0.002$), and HI-2 (HR = 1.967, $P = 0.026$; Fig. 2) were significantly correlated with PFS. Multivariate analysis showed that HI-2 (HR = 2.639, $P = 0.005$) was an independent variable that was significantly associated with PFS after correction for clinical TNM stage.

Univariate and multivariate analyses for OS

The results of univariate and multivariate analyses for significant variables with OS are summarized in Table 5. In univariate analysis, recurrence (HR = 2.285, $P = 0.020$; Fig. 3a) and HI-2 on PET (HR = 2.447, $P = 0.005$; Fig. 3b) were significant variables. On multivariate analysis, both of these variables independently correlated with patient OS, with HRs being 2.054 and 2.281, and P values of 0.043 and 0.009 for distant metastasis and HI-2, respectively.

Table 1 Baseline clinicopathological information of patients

Variables	Value
Sex	
Male	37 (67.3%)
Female	18 (32.2%)
Median age (range)	62 (37–82)
Location	
Esophagogastric junction	14 (25.5%)
Siewert I	0
Siewert II	6 (10.9%)
Siewert III	8 (14.6%)
Stomach	41 (74.5%)
Pathological types	
WDA	15 (27.3%)
MDA	19 (34.5%)
PDA	17 (30.9%)
MAC/SRC	4 (7.3%)
Lauren classifications	
Intestinal	25 (62.5%)
Non-intestinal	15 (37.5%)
Clinical TNM stage	
II	4 (7.3%)
III	16 (29.1%)
IVa	35 (63.6%)
Median (range) CEA (ng/ml)	3.4 (0.4–776.4)
Median (range) CA19-9 (U/ml)	9.5 (0.6–807.1)
Median (range) CA72-4 (U/ml)	2.5 (0.8–131.2)
Pathological response ($n = 36$)	
Responder	14 (38.9%)
Non-responder	22 (61.1%)
Recurrence	
Yes	37 (67.3%)
No	18 (32.7%)
Parameters on PET	
SUV_{max} (mean ± SD)	9.8 ± 5.74
SUV_{peak} (mean ± SD)	7.9 ± 4.72
SUV_{mean} (mean ± SD)	4.2 ± 1.17
TLR (mean ± SD)	5.4 ± 3.20
MTV (mL, mean ± SD)	61.9 ± 55.12
TLG (g, mean ± SD)	335.4 ± 396.63
HI-1 (mean ± SD)	0.79 ± 0.20
HI-2 (mean ± SD)	36.5 ± 27.09

WDA, well differentiated adenocarcinoma; MDA, moderate differentiated adenocarcinoma; PDA, poorly differentiated adenocarcinoma; SRC, signet-ring cell carcinoma; MAC, mucinous adenocarcinoma; TNM, tumor-node-metastasis; CA19-9, carbohydrate antigen 19-9; CA72-4, carbohydrate antigen 72-4; CEA, carcinoembryonic antigen; PET/CT, positron emission tomography/computed tomography; SUV, standardized uptake value; Max, maximum; TLR, tumor-to-liver ratio; MTV, metabolic tumor volume; TLG, total lesion glycolysis; HI-1, heterogeneity index-1, namely the coefficient of variance of SUV; HI-2, heterogeneity index-1, namely the negative value of the slope of linear regression of MTVs according to various SUV thresholds (2.5, 3.0 and 3.5)

Table 2 Comparisons of clinicopathological characteristics and PET parameters according to tumor recurrence

Variables	Recurrence		*P* value
	Yes	No	
Sex (M/F)	25/12	12/6	0.947†
Age (mean ± SD)	60.1 ± 11.1	59.8 ± 11.6	0.935*
Location			0.701†
Esophagogastric junction	10	4	
Stomach	27	14	
Pathological types			0.840†
WDA/MDA	12	23	
PDA/MAC/SRC	16	13	
Lauren classifications			0.191‡
Intestinal	15	10	
Non-intestinal	12	3	
Pathological response			1.000‡
Responder	9	5	
Non-responder	14	8	
Median CEA (ng/ml)	3.2	4.4	0.961#
Median CA19-9 (U/ml)	9.3	9.5	0.388#
Median CA72-4 (U/ml)	2.3	3.2	0.913#
Parameters on PET/CT			
SUV_{max} (median)	8.2	7.9	0.747#
SUV_{peak} (median)	6.2	6.5	0.809#
SUV_{mean} (median)	4.0	3.8	0.929#
TLR (median)	4.8	3.7	0.667#
MTV (mL, median)	49.3	44.3	0.389#
TLG (g, median)	240.0	231.7	0.507#
HI-1 (median)	0.8	0.9	0.296#
HI-2 (median)	28.3	28.4	0.147#

WDA, well differentiated adenocarcinoma; MDA, moderate differentiated adenocarcinoma; PDA, poorly differentiated adenocarcinoma; SRC, signet-ring cell carcinoma; MAC, mucinous adenocarcinoma; CA19-9, carbohydrate antigen 19-9; CA72-4, carbohydrate antigen 72-4; CEA, carcinoembryonic antigen; PET/CT, positron emission tomography/computed tomography; SUV, standardized uptake value; Max, maximum; TLR, tumor-to-liver ratio; MTV, metabolic tumor volume; TLG, total lesion glycolysis; HI-1, heterogeneity index-1, namely the coefficient of variance of SUV; HI-2, heterogeneity index-1, namely the negative value of the slope of linear regression of MTVs according to various SUV thresholds (2.5, 3.0 and 3.5); *, student's t test; †, Chi square test; ‡, Fisher's exact test; #, Mann–Whitney U test

Table 3 Comparisons of PET parameters according to pathological response

Variables	Pathological response		*P* value
	Yes	No	
SUV_{max} (median)	5.7	8.7	0.087#
SUV_{peak} (median)	4.7	7.1	0.305#
SUV_{mean} (median)	3.5	3.9	0.305#
TLR (median)	2.9	5.6	0.017#
MTV (mL, median)	36.7	76.9	0.017#
TLG (g, median)	171.5	338.5	0.087#
HI-1 (median)	0.73	0.77	0.732#
HI-2 (median)	25.1	39.7	0.013#

PET/CT, positron emission tomography/computed tomography; SUV, standardized uptake value; Max, maximum; TLR, tumor-to-liver ratio; MTV, metabolic tumor volume; TLG, total lesion glycolysis; HI-1, heterogeneity index-1, namely the coefficient of variance of SUV; HI-2, heterogeneity index-1, namely the negative value of the slope of linear regression of MTVs according to various SUV thresholds (2.5, 3.0 and 3.5); #, Mann–Whitney U test

Discussion

In the present study, the heterogeneity index-2 (HI-2), calculated by the slope of linear regression of serial MTVs under different SUV cutoffs, was significantly associated with the response to neoadjuvant chemotherapy. Furthermore, this index independently predicted PFS and OS. When compared with the conventional PET quantitative parameters, HI-2 showed superiority in predicting patient clinical outcomes. To the best of our knowledge, this is the first study to investigate the prognostic value of metabolic heterogeneity on ^{18}F-FDG PET/CT to survival outcomes of patients with gastric cancer.

Malignant tumors always grow in a heterogeneous pattern. The differences in properties, such as gene expression, cellular proliferation, growth rate, vascularity, necrosis, and hypoxia in tumor cells contribute to tumor heterogeneity [19, 27–29]. Tumor heterogeneity is a major challenge to personalized medicine and always results in treatment failure [28]. The distribution of ^{18}F-FDG PET activity correlates highly with several physiological processes, including glucose metabolism, necrosis, vascularization, and angiogenesis [30]. Analyzing metabolic heterogeneity on PET/CT has the potential to assess the heterogeneous characteristics of tumors. In the current study, patients that did not respond to neoadjuvant chemotherapy presented significantly larger metabolic heterogeneity of their primary tumors. Besides, the risk of disease progression and death increased with increasing metabolic heterogeneity index. These findings highlighted the importance of tumor heterogeneity and the possibility that it might be a powerful predicator of patient clinical outcomes. In addition, this imaging parameter has the potential to improve risk stratification and optimize patient selection for more aggressive treatment.

Several methods have been proposed to investigate the heterogeneity of tumors on ^{18}F-FDG PET/CT, among which texture analysis is used widely. Recent studies have shown that the heterogeneity index on ^{18}F-FDG PET/CT from texture analysis was useful to predict therapy response and prognosis in many patients with cancer [31–33]. However, texture analysis is not clinically available, because a standard

Table 4 Univariate and multivariate COX regression assessing associations between parameters and PFS

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Sex						
Male	0.894	0.486–1.644	0.718			
Female*	1.000					
Age (years)						
≥ 62	1.806	0.999–3.263	0.052			
< 62*	1.000					
Location						
EGJ	0.906	0.469–1.750	0.768			
Stomach*	1.000					
Pathological types						
WDA/MDA	0.818	0.441–1.516	0.523			
PDA/MAC/SRC*	1.000					
Lauren classifications						
Intestinal	0.767	0.390–1.508	0.442			
None-intestinal*	1.000					
Clinical TNM stage			0.002			0.004
II*	1.000			1.000		
III	5.111	0.668–39.12	0.116	6.27	0.784–50.136	0.083
IVa	13.293	1.780–99.260	0.012	16.29	2.068–98.436	0.008
Baseline CEA (ng/ml)						
≥ 3.4	1.001	0.550–1.822	0.998			
< 3.4*	1.000					
Baseline CA19-9 (U/ml)						
≥ 9.5	1.947	1.045–3.628	0.036	1.627	0.856–3.092	0.136
< 9.5*	1.000			1.000		
Baseline CA72-4 (U/ml)						
≥ 2.5	0.828	0.408–1.679	0.601			
< 2.5*	1.000					
SUV_{max} (≥ 7.9 vs. < 7.9)	1.462	0.814–2.627	0.204			
SUV_{peak} (≥ 6.4 vs. < 6.4)	1.380	0.768–2.480	0.282			
SUV_{mean} (≥ 3.9 vs. < 3.9)	1.513	0.841–2.719	0.167			
TLR (≥ 4.6 vs. < 4.6)	1.682	0.930–3.402	0.085			
MTV (≥ 48.2 vs. < 48.2)	1.229	0.684–2.209	0.491			
TLG (≥ 234.7 vs. < 234.7)	1.049	0.583–1.887	0.874			
HI-1 (≥ 0.81 vs. < 0.81)	1.273	0.709–2.287	0.419			
HI-2 (≥ 28.4 vs. < 28.4)	1.967	1.084–3.572	0.026	2.639	1.349–5.161	0.005

PFS, progression-free survival; HR, hazards ratio; CI, confidence index; EGJ, esophagogastric junction; WDA well differentiated adenocarcinoma; MDA moderate differentiated adenocarcinoma; PDA, poorly differentiated adenocarcinoma; SRC, signet-ring cell carcinoma; MAC, mucinous adenocarcinoma; TNM, tumor-node-metastasis; CA19-9, carbohydrate antigen 19-9; CA72-4, carbohydrate antigen 72-4; CEA, carcinoembryonic antigen; PET/CT, positron emission tomography/computed tomography; SUV, standardized uptake value; Max, maximum; TLR, tumor-to-liver ratio; MTV, metabolic tumor volume; TLG, total lesion glycolysis; HI-1, heterogeneity index-1, namely the coefficient of variance of SUV; HI-2, heterogeneity index-2, namely the negative value of the slope of linear regression of MTVs according to various SUV thresholds (2.5, 3.0 and 3.5)

method has not been established, the software remains inaccessible in most PET viewing workstations, and it is a complicated and time-consuming process. In addition, most studies using texture analysis to characterize tumor heterogeneity considered volumes greater than 3–5 cm^3, indicating that texture analysis might not be suitable to assess the heterogeneity of tumors with smaller volumes [33]. Adequate MTV is necessary for the efficient use of texture features in texture

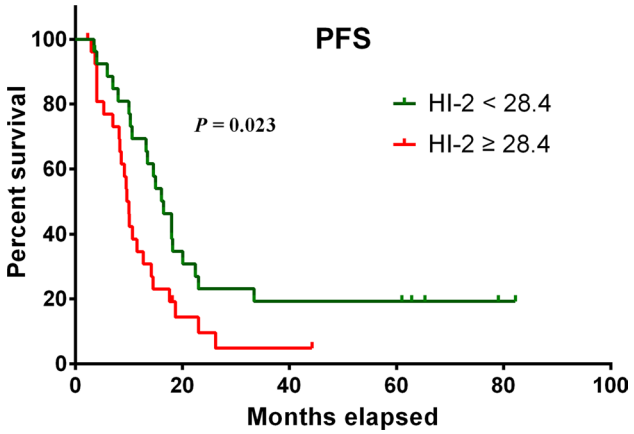

Fig. 2 Kaplan–Meier curves for comparing PFS according to HI-2 > 28.4 and HI-2 ≤ 28.4

analysis. By contrast, HI-2 can be easily achieved on the commonly used workstation, and thus is suitable for clinical practice.

The method for generating HI-2 in this study was slightly different from that of previous studies. A percentage threshold method (usually 40%, 50%, 60% and 80% of SUV_{max}) had been proposed to generate an MTV-based heterogeneity index, and had demonstrated significant prognostic value in breast cancer [20] and oral cavity cancer [21]. However, the percentage threshold method relies strongly on the SUV_{max} of the tumor, leading to a large variance between cancer lesions with high FDG uptake. In addition, the physiological uptake by the adjacent normal gastric wall might hamper accurate evaluation of the gastric-cancer margin, especially in tumors with low FDG uptake, such as MAC/SRC. In contrast, Kim et al. [18] chose the absolute SUV threshold method (2.0, 2.5, and 3.0) to obtain the slope of linear regression in patients with pancreatic cancer. However, physical uptake by the gastric wall commonly has an SUV_{max} higher than 2.0. The MTV generated from an SUV cutoff of 2.0 commonly cannot accurately reflect the real metabolic volume of the tumor. Therefore, we altered the method to use SUV cutoffs of 2.5, 3.0, and 3.5 to generate the slope of linear regression and a significant result was achieved.

Another easily acquired parameter to characterize metabolic tumor heterogeneity is the coefficient of variance, namely HI-1. Previous studies have demonstrated the prognostic values of this index in many cancers, such as uterine cervical cancer [22] and ovarian cancer [24]. However, this index failed to correlate with the clinical outcomes of patients with gastric cancers in the current study. Negative result was also identified in pancreatic ductal carcinoma [18]. Thus, the prognostic value of HI-1 is inconstant across different types of cancer, and should not be recommended for clinical practice. The underlying reason might be related to its threshold-dependent property, because the VOI under different SUV thresholds might generate different SDs and different SUV_{mean} values, while different types of cancer have different optimal thresholds for VOI delineation.

The metabolic parameters, including SUV_{max}, SUV_{mean}, SUV_{peak}, and TLR, are commonly used in the clinic. Some studies have advocated the prognostic values of these parameters in patients with cancer [34–36]. However, the prognostic value of these parameters was negative in patients with gastric cancer in the current study, although TLR was associated significantly with treatment response. This might be related to the heterogeneity of the tumor, a partial volume effect, the time of SUV evaluation, and body size [37]. In recent years, the volumetric parameters, including the metabolic tumor volume (MTV) and total lesion glycolysis (TLG), have demonstrated excellent performance in predicting clinical outcomes of patients with gastric cancer [10, 11]. One problem is that these volumetric parameters cannot escape from influences of volume effects from adjacent lesions with high radioactivity, for example, metastatic lymph nodes.

Several limitations of this study should be mentioned. Firstly, this study was a retrospective review of a small patient cohort who had been treated with various regimens of adjuvant chemotherapy. The heterogeneity of treatment modality could have confounded the prognostication. Secondly, restricted by the method for calculating HI-2, we only included patients with SUV_{max} higher than 3.5; therefore, the bias in patient selection might have influenced the results of the survival analysis. Thirdly, the relationship between intra-tumor heterogeneity and the underlying biological mechanisms remains unclear.

Conclusions

The HI-2 value generated by the MTV-based linear regression from baseline ^{18}F-FDG PET/CT was significantly associated with survival outcomes of patients with gastric cancer. The method for determining this index is simple and convenient. Preoperative assessment of HI-2 by ^{18}F-FDG PET/CT might be a promising method to identify patients with poor prognosis.

Table 5 Univariate and multivariate COX regression assessing associations between parameters and OS

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Sex						
Male	0.930	0.98–1.736	0.820			
Female*	1.000					
Age (years)						
≥ 62	1.378	0.756–2.502	0.297			
< 62*	1.000					
Location						
EGJ	0.952	0.489–1.854	0.886			
Stomach*	1.000					
Pathological types						
WDA/MDA	0.950	0.509–1.775	0.873			
PDA/MAC/SRC*	1.000					
Lauren classifications						
Intestinal	0.612	0.303–1.235	0.170			
None-intestinal*	1.000					
Baseline CEA (ng/ml)						
≥ 2.9	1.165	0.629–2.159	0.627			
< 2.9*	1.000					
Baseline CA19-9 (U/ml)						
≥ 9.0	1.633	0.856–3.115	0.136			
< 9.0*	1.000					
Baseline CA72-4 (U/ml)						
≥ 2.8	0.937	0.451–1.947	0.861			
< 2.8*	1.000					
Clinical TNM stage			0.200			
II*	1.000					
III	2.242	0.501–10.039	0.291			
IVa	3.209	0.762–13.504	0.112			
Recurrence						
Yes	2.285	1.140–4.580	0.020	2.054	1.021–4.129	0.043
No*	1.000					
SUV_{max} (≥ 7.9 vs. < 7.9)	1.235	0.679–2.249	0.489			
SUV_{peak} (≥ 6.4 vs. < 6.4)	1.074	0.590–1.957	0.815			
SUV_{mean} (≥ 3.9 vs. < 3.9)	1.212	0.666–2.207	0.529			
TLR (≥ 4.6 vs. < 4.6)	1.268	1.696–2.310	0.438			
MTV (≥ 48.2 vs. < 48.2)	0.990	0.543–1.803	0.973			
TLG (≥ 234.7 vs. < 234.7)	1.030	0.564–1.880	0.924			
HI-1 (≥ 0.81 vs. < 0.81)	1.015	0.557–1.849	0.961			
HI-2 (≥ 28.4 vs. < 28.4)	2.447	1.317–4.545	0.003	2.281	1.228–4.239	0.009

OS, overall survival; HR, hazards ratio; CI, confidence index; EGJ, esophagogastric junction; WDA well differentiated adenocarcinoma; MDA moderate differentiated adenocarcinoma; PDA, poorly differentiated adenocarcinoma; SRC, signet-ring cell carcinoma; MAC, mucinous adenocarcinoma; TNM, tumor-node-metastasis; CA19-9, carbohydrate antigen 19-9; CA72-4, carbohydrate antigen 72-4; CEA, carcinoembryonic antigen; PET/CT, positron emission tomography/computed tomography; SUV, standardized uptake value; Max, maximum; TLR, tumor-to-liver ratio; MTV, metabolic tumor volume; TLG, total lesion glycolysis; HI-1, heterogeneity index-1, namely the coefficient of variance of SUV; HI-2, heterogeneity index-1, namely the negative value of the slope of linear regression of MTVs according to various SUV thresholds (2.5, 3.0 and 3.5)

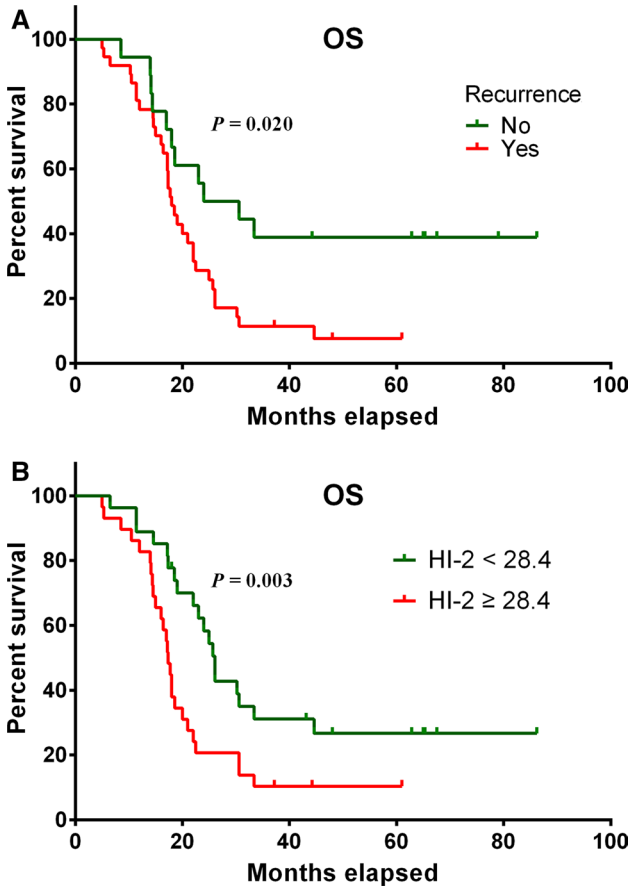

Fig. 3 Kaplan–Meier curves to analyze the associations between OS and tumor recurrence (**a**), and for comparing OS according to HI-2 > 28.4 and HI-2 ≤ 28.4 (**b**)

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Authors' contributions GL and YH conceived and wrote this article. GL, HY, and XC collected the study materials or patients. XC, YW and YH performed the data analysis and interpretation. TL and HS controlled the quality of the study. All authors have read and approved the manuscript for publication.

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Availability of data and materials The dataset used and/or analyzed in current study are available from the corresponding author on reasonable request.

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Consent for publication Written informed consents were obtained from included patients for publication.

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