The prognostic value of volume-based parameters using ^{18}F -FDG PET/CT in gastric cancer according to HER2 status

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Abstract

Background We aimed to find the clinical value of metastatic tumor burden evaluated with F18-FDG PET/CT in gastric cancer patients, considering the human epidermal growth factor receptor 2 (HER2) status.

Methods We retrospectively reviewed 124 patients with locally advanced or metastatic gastric cancer at Yonsei Cancer Center between January 2006 and December 2014 who had undergone baseline FDG PET/CT before first-line chemotherapy. We measured the maximum standardized uptake value from the primary tumor (SUV_{max}) and whole-body (WB) PET/CT parameters, including WB SUV_{mean} ,

WB SUV_{mean} , WB metabolic tumor volume (WB MTV), and WB total lesion glycolysis (WB TLG), in all metabolically active metastatic lesions (SUV threshold ≥ 2.5 or 40% isocontour for ≤ 2.5), and we determined their association with patient survival outcomes.

Results SUV_{max} was higher in HER2-positive gastric cancers (median 12.1, range 3.4–34.6) compared to HER2-negative (7.4, 1.6–39.1, $P < 0.001$). Among all patients, WB TLG > 600 , which is indicative of a high metastatic tumor burden, showed worse progression-free survival (PFS) [hazard ratio (HR), 2.003; 95% CI, 1.300–3.086; $P = 0.002$] and overall survival (OS) (HR, 3.001; 95% CI, 1.950–4.618; $P < 0.001$) than did WB TLG ≤ 600 . Among HER2-positive gastric cancer patients treated with trastuzumab, higher metabolic tumor burden predicted worse OS, but not PFS.

Conclusions HER2-positive gastric cancers had higher SUV_{max} compared to HER2-negative gastric cancers. In both HER2-negative patients and -positive patients receiving trastuzumab, FDG PET/CT volume-based parameters may have a role in further stratifying the prognosis of stage IV gastric cancer.

Ji Soo Park and Nare Lee contributed equally to this work as a first author.

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Keywords PET/CT · FDG · Volume-based parameter · Gastric cancer · HER2

Introduction

^{18}F -fluorodeoxyglucose (FDG) PET/CT is widely used in cancer patients for initial staging, evaluating therapeutic response, detecting disease recurrence, and predicting survival outcomes. Maximum standard uptake value (SUV_{max}) is the most reliable and widely used parameter to measure tumor metabolism and evaluate treatment

response. However, 2D measurements of tumor metabolism such as SUV_{max} , peak SUV (SUV_{peak}) and mean SUV (SUV_{mean}) may not accurately reflect the metabolic activity of the whole tumor. In contrast, volume-based parameters such as total lesion glycolysis (TLG) and metabolic tumor volume (MTV) evaluate global metabolism and volume. MTV is defined as the tumor volume above a certain metabolic threshold, and TLG is defined as the product of tumor volume and metabolic activity within the tumor [1, 2]. Previous studies have shown that MTV and TLG have excellent sensitivity and specificity for predicting treatment response and survival outcomes [1–3]. MTV and TLG also have the additional advantage of summing multiple lesions into one representative number, which may be helpful in further stratifying prognosis in stage IV patients. Current clinical protocols equate patients with a single metastatic site with patients with a large metastasis or multiple metastases. This may be partially due to the difficulty in quantifying the amount of metastatic burden. In this regard, MTV and TLG measurements could be used to obtain a single quantifiable value that estimates the amount of metastatic burden.

Gastric cancer is one of the leading causes of death worldwide [4]. Approximately 7–34% of gastric tumors express human epidermal growth factor receptor 2 (HER2) [5, 6]. For these patients, a phase III trastuzumab in combination with chemotherapy compared with chemotherapy alone (ToGA) trial showed that treatment with the anti-HER2 antibody trastuzumab, in combination with standard platinum-based chemotherapy, was more effective than chemotherapy alone [6]. However, although many studies have reported the predictive and prognostic values of FDG PET in gastric cancer [7–10], few have studied the correlation between FDG uptake and HER2 positivity in gastric cancer [11, 12].

The purpose of this study is to evaluate the prognostic impact of PET-derived metastatic tumor burden (MTV and TLG) in gastric cancer patients undergoing chemotherapy. We also analyzed the association between HER2 positivity and FDG uptake in the primary gastric lesion in recurrent or metastatic gastric cancer patients.

Patients and methods

Study population

This study included patients who were diagnosed with metastatic or recurrent gastric cancer between January 2006 and December 2014 at Yonsei Cancer Center (YCC) in Seoul, Republic of Korea. Patients were considered eligible if (1) they had histologically proven gastric or gastroesophageal adenocarcinoma; (2) they were

≥ 18 years of age; (3) they had inoperable locally advanced, recurrent, or metastatic disease; (4) they had at least one measurable lesion; (5) the HER2 status of their tumor was known, as determined by immunohistochemical staining (IHC) and/or fluorescence in situ hybridization (FISH)/silver in situ hybridization (SISH) of primary gastric carcinoma tissue; (6) they had FDG PET/CT performed prior to first-line therapy. Patients were excluded from the study if (1) they had another severe medical illness, (2) they had another active malignancy, or (3) if they had HER2-positive gastric cancer, but were not treated with trastuzumab as their first-line treatment. We followed the medical research protocols and ethics guidelines defined by the World Medical Association's Declaration of Helsinki throughout the study. The protocol was reviewed and approved by the local Institutional Review Board (IRB approval no. 2014-2763-001), and we retrospectively reviewed the medical records of patients. Clinicopathologic information, including sex, age at metastasis diagnosis, primary tumor location, pathological differentiation, and baseline serum concentrations of carcinoembryonic antigen (CEA), cancer antigen (CA) 19-9, and CA 72-4, were reviewed and documented.

HER2 IHC, FISH, and SISH methods

Surgically or endoscopically resected primary tumor tissues were formalin fixed and paraffin embedded prior to being analyzed by experienced pathologists at Yonsei University College of Medicine. We performed HER2 IHC analysis using the HercepTest™ Kit (Dako, Denmark), FISH analysis using the Vysis™ HER2/CEP17 FISH Probe Kit (Abbott, USA), and Dako Detection Kit (Dako Denmark), and SISH analysis using the Ventana Discovery XT system (Ventana/Roche, USA) according to the manufacturers' instructions. FISH and SISH scores were assessed by detecting the fluorescence signal in 50 malignant cell nuclei. HER2 positivity was defined as HER2 IHC 3+ or IHC 2+ and FISH/SISH positive [HER2/CEP17 (centromere enumerator probe 17) ratio ≥ 2] [5].

Treatment

In this study, HER2-positive gastric cancer patients were treated with trastuzumab in combination with fluorouracil (5-FU) and cisplatin or trastuzumab in combination with capecitabine and cisplatin [6]. HER2-negative gastric cancer patients received one of the following chemotherapy treatment regimens: infusional 5-FU and cisplatin; 5-FU, leucovorin, and oxaliplatin (modified FOLFOX6); capecitabine and cisplatin, capecitabine and oxaliplatin, S-1 and cisplatin, or S-1 and oxaliplatin. These regimens were the same as those previously described [1, 13–16].

FDG uptake quantification

All participants underwent FDG PET/CT scans using two-hybrid PET/CT scanners (Discovery 600eTM, GE Healthcare, Milwaukee, WI, USA, or Biograph TruePoint40TM, Siemens Medical Systems, CTI, Knoxville, TN, USA). Patients were fasted for at least 6 h and serum glucose levels checked before FDG injection (5.5 MBq/kg). PET and low-dose CT images (30 mA and 103 kVp for Discovery 600eTM, 36 mA and 120 kVp for Biograph TruePoint40TM) were obtained 60 min after FDG injection. PET acquisition time was 3 min/bed position in three-dimensional mode, and images were reconstructed in ordered subset expectation maximization with attenuation correction.

FDG images were reviewed by two independent nuclear medicine physicians who were blinded to the patients' clinical data. SUV_{max} , SUV_{mean} , MTV, and TLG were measured using GE Medical System Advantage Workstation 4.5 (GE Healthcare). For the primary gastric cancer, a region of interest (ROI) was drawn on the primary gastric tumor, and the SUV_{max} was recorded. SUV_{max} was calculated as (decay-corrected activity/tissue volume)/(injected dose/body weight). For metastatic lesions, a volume of interest (VOI) was drawn on each metastatic site. The VOI threshold used was an isocontour threshold of $\text{SUV} \geq 2.5$, but for metastatic lesions with a $\text{SUV} < 2.5$, a 40% isocontour method was used. Each VOI will generate SUV_{max} , SUV_{mean} , TLG, and MTV. WB SUV_{max} was defined as the single highest SUV_{max} in all the metastatic lesions. Finally, the TLG and MTV of all metastatic lesions were summed up to represent the metastatic burden.

Statistical analyses

The relationship among clinicopathologic variables, FDG uptake parameters, and HER2 positivity was analyzed using Pearson's χ^2 tests, Mann-Whitney U tests, and linear regression analyses. Receiver-operator characteristic (ROC) curve and area under the curve (AUC) analyses were used to determine the cutoff values with the highest sensitivity for SUV_{max} , MTV, and TLG parameters. To evaluate the predictive and prognostic values of clinicopathologic characteristics and metabolic parameters measured by FDG PET/CT, we assessed the progression-free survival (PFS) and overall survival (OS) of the patients. OS was defined as the time from the first day of palliative treatment to the date of death, irrespective of the cause of death. PFS was defined as the time from the first day of palliative treatment to the date of disease progression or death. The Kaplan-Meier method and Cox's proportional hazard regression model were used for survival analyses, and survival curves were compared using log-rank tests. A

P value < 0.05 was considered statistically significant. For multiple analyses in the Cox regression model, variables with P values < 0.1 in the simple linear regression analyses were selected. All statistical analyses were performed using SPSS 23 for Windows (IBM, Armonk, NY, USA) and R version 3.3.3 (<http://www.R-project.org>).

Results

Patient characteristics

Between January 2006 and December 2014, 2624 patients were diagnosed with inoperable, locally advanced, recurrent, or metastatic gastric cancer at YCC. Among 2624 patients, 1153 received PET/CT examination scanning prior to first-line treatment. HER2 status was evaluated in 160 out of 1153 patients (13.9%). After excluding 21 patients without measurable lesions, and excluding 15 HER2-positive patients who were not treated with trastuzumab, 124 patients (80 male, median age 55, range 23–80) were included in this study. In our final patient population, all HER2-positive patients were treated with trastuzumab (Fig. S1). Table 1 lists the baseline patient characteristics.

There were more HER2-positive gastric cancer patients (58.8%) with well or moderately differentiated histology than HER2-negative gastric cancer patients (22.2%, $P < 0.001$). Baseline serum CEA (median 6.1 vs. 2.4 ng/ml; $P = 0.001$) and serum CA 19-9 (median 45.8 vs. 13.0 ng/ml; $P = 0.025$) were higher in HER2-positive than in HER2-negative gastric cancer patients.

Association between HER2 status and FDG PET/CT parameters

Among all patients, the median SUV_{max} values in the primary gastric malignancy was 6.6 (range 1.0–34.6); the metastatic tumor burden (whole-body WB MTV) was 103.6 cm³ (range 0–2030.1), and the glycolytic metastatic tumor burden (WB TLG) was 423.4 (range 0–13609.8). All FDG PET/CT parameters were significantly higher in HER2-positive than in HER2-negative gastric cancer patients (Table 1). Also, because a statistically significant portion of signet-ring cell (SRC) type pathology was HER2 negative (25/28), we additionally analyzed the correlation between HER2 status and SUV_{max} in non-SRC patients (excluding SRC and other pathological differentiation, 94 patients). In non-SRC patients, the median value for the SUV_{max} of primary gastric malignancy was significantly higher in HER2-positive (9.5, range 3.0–34.60) compared to HER2-negative gastric cancers (6.3, range 1.0–28.40, $P = 0.008$).

Table 1 Baseline characteristics and PET/CT parameters of patients according to HER2 status

Variables	Total (<i>n</i> = 124) Number	HER2 status		<i>P</i> value
		Negative (<i>n</i> = 90) Number (%)	Positive (<i>n</i> = 34) Number (%)	
Sex				
Male	80	56 (62.2)	24 (70.6)	0.385
Female	44	34 (37.8)	10 (29.4)	
Age at diagnosis (years)				
Median (range)	55 (23–80)	55 (23–77)	56 (33–80)	0.554*
Pathologic differentiation				
WD	5	1 (1.1)	4 (11.8)	0.001 [†]
MD	35	19 (21.1)	16 (47.0)	
PD	54	43 (47.8)	11 (32.4)	
SRC	28	25 (27.8)	3 (8.8)	
Others	2	2 (2.2)	0 (0)	
Baseline CEA (ng/ml)				
Median (range)	3.1 (0–10,027)	2.4 (0–385)	6.1 (1–10,027)	0.001*
Baseline CA19-9 (ng/ml)				
Median (range)	15.1 (0–20,000)	13.0 (0–20,000)	45.8 (0–13,100)	0.025*
Baseline CA72-4 (ng/ml, <i>n</i> = 98)				
Median (range)	6.0 (0–600)	4.5 (1–600)	9.9 (0–600)	0.304*
Primary tumor location				
GEJ	3	2 (2.2)	1 (2.9)	0.145 [†]
Upper third	35	23 (25.6)	12 (35.3)	
Mid third	31	27 (30.0)	4 (11.8)	
Lower third	55	38 (42.2)	17 (50.0)	
FDG uptake of primary gastric cancer				
SUV _{max}	6.6 (1.0–34.6)	5.9 (1.0–28.4)	9.1 (3.0–34.6)	0.002*
FDG PET-derived metastatic tumor burden				
WB SUV _{max} , median (range)	8.5 (1.6–39.1)	7.4 (1.6–39.1)	12.1 (3.4–34.6)	<0.001*
WB SUV _{mean} , median (range)	3.5 (0–44.7)	3.3 (0–44.7)	4.5 (2.1–9.9)	<0.001*
WB MTV, median (cm ³ , range)	103.6 (0–2030.1)	93.6 (0–2030.1)	158.4 (32.3–1923.8)	0.044*
WB TLG, median (range)	423.4 (0–13,609.8)	331.5 (0–9290.7)	603.4 (92.7–13,609.8)	0.010*

CA19-9 carbohydrate antigen 19-9, CA72-4 carbohydrate antigen 72-4, CEA carcinoembryonic antigen, GEJ gastroesophageal junction, HER2 human epidermal growth factor 2, MD adenocarcinoma, moderately differentiated, MTV metabolic tumor volume, PD adenocarcinoma, poorly differentiated, PET positron emission tomography, SRC signet-ring cell carcinoma, SUV_{max} maximum standardized uptake value, SUV_{mean} mean standardized uptake value, TLG total lesion glycolysis, WB whole body, WD adenocarcinoma, well differentiated

* Analyzed using the Mann-Whitney U test

[†] Analyzed using the Fisher's exact test

Among the other clinicopathologic features, well- or moderately differentiated histology was related with higher values of all PET/CT parameters than those of poorly differentiated histology (Table 2). Also, a significant, but weak, correlation was observed between the primary gastric tumor SUV_{max} and metastatic tumor burden, as assessed by the WB TLG (Spearman's rho = 0.645, *P* < 0.001). Moreover, patients with a high metastatic burden or high WB TLG had higher serum CA72-4 levels and more hepatic metastases than did those with low WB TLG (Table S1).

Survival outcomes according to HER2 status and FDG PET/CT parameters

As of 31 March 2016, we evaluated the response to the first-line chemotherapy and survival outcomes during a median time frame of 35.8 months [95% confidence interval (CI) 25.5–46.1].

In the HER2-negative group, the disease control rate (DCR, CR + PR + SD) was 85.6% (77/90) and objective response rate (ORR, CR + PR) was 24.4% (22/90).

Table 2 Differences in PET-CT parameters according to pathologic differentiation

Parameters	Pathologic differentiation		<i>P</i> value*
	WD or MD (<i>n</i> = 40) Median (range)	PD or SRC or others (<i>n</i> = 84) Median (range)	
Primary gastric cancer			
SUV _{max}	8.05 (1.0–34.6)	5.7 (1.6–30.8)	0.012
FDG PET-derived metastatic tumor burden			
WB SUV _{max}	11.05 (3.7–34.6)	7.35 (1.6–39.1)	0.001
WB SUV _{mean}	3.95 (2.1–8.6)	3.30 (0–44.7)	<0.001
WB MTV (cm ³)	178.8 (20.3–2030.1)	91.0 (0–1893.3)	0.032
WB TLG	724.05 (56.4–13609.8)	312.35 (0–13609.8)	0.012

MD adenocarcinoma, moderately differentiated, MTV metabolic tumor volume, PD adenocarcinoma, poorly differentiated, SRC signet-ring cell carcinoma, SUV_{max} maximum standardized uptake value, SUV_{mean} mean standardized uptake value, TLG total lesion glycolysis, WD adenocarcinoma, well differentiated

* Analyzed using Kruskal-Wallis test

Meanwhile, in the HER2-positive group, DCR was 91.2% (31/34) and ORR was 73.5% (25/34). Among the patients, 64.7% (22/34) of the HER2-positive group and 62.2% (56/90) of the HER2-negative group received second-line chemotherapy ($P = 0.798$), and 35.2% (12/34) of the HER2-positive group and 28.9% (26/90) of the HER2-negative group were treated with third-line chemotherapy ($P = 0.519$).

Among all patients, the median PFS and OS were 5.7 months (95% CI 5.2–6.2) and 12.5 months (95% CI 10.3–14.7), respectively. HER2-positive gastric cancer patients showed significantly longer PFS (median 6.6 months; 95% CI 5.4–7.8) than did those with HER2-negative gastric cancer (median 5.5 months; 95% CI 4.8–6.2; $P = 0.018$; Fig. S2A); however, the median OS between these two groups was not statistically different (HER2-positive median OS, 14.7 months; 95% CI 12.7–16.7 vs. HER2-negative median OS, 11.3 months; 95% CI 9.4–13.2; $P = 0.247$; Fig. S2B).

Among all patients, PFS and OS were not associated with the SUV_{max}, WB SUV_{max}, or WB SUV_{mean} (Fig. 1a, b, Fig. S3A–D). However, patients with a high metabolic metastatic burden (WB TLG >600) showed a worse PFS [hazard ratio (HR) 2.003; 95% CI 1.300–3.086; $P = 0.002$; Table 3; Fig. 1c] and worse OS (HR 3.001; 95% CI 1.950–4.618; $P < 0.001$; Table 3; Fig. 1d) than did patients with low metastatic burden (WB TLG ≤600). In addition, patients with a WB MTV >100 cm³ showed a worse PFS (HR 1.848; 95% CI 1.256–2.719; $P = 0.002$; Table 3; Fig. S3E) and worse OS (HR 2.008; 95% CI 1.361–2.963; $P < 0.001$; Table 3; Fig. S3F) than did patients with a WB MTV ≤100 cm³.

Differences in prognostic roles of FDG PET/CT parameters according to HER2 status

In HER2-negative gastric cancer patients, WB MTV and WB TLG, which are indicative of metastatic burden, and WB SUV_{max} were all associated with PFS and OS (Fig. 2c; Table S2). Patients with highly metabolically active metastases (WB SUV_{max} > 10) showed significantly worse PFS (HR 1.682; 95% CI 1.040–2.722; $P = 0.034$; Table S2) and OS (HR, 1.678; 95% CI 1.038–2.713; $P = 0.035$; Fig. 2a; Table S2) than did patients with less metabolically active foci (WB SUV_{max} ≤ 10). Among HER2-negative patients, PFS and OS were not associated with primary tumor SUV_{max} or WB SUV_{mean} (Table S2).

In HER2-positive gastric cancer patients, metabolic metastatic burden, as indicated by WB TLG and WB MTV parameters, was associated with OS. More specifically, HER2-positive gastric patients with WB TLG >600 (HR 2.703; 95% CI 1.127–6.478; $P = 0.026$; Fig. 2d; Table S3) and WB MTV > 100 cm³ (HR 2.887; 95% CI 1.216–6.855; $P = 0.016$; Table S3) showed worse OS. However, among HER2-positive patients, WB TLG and WB MTV were not associated with PFS (Table S3). Moreover, PFS and OS of HER2-positive patients were not associated with the primary tumor or WB SUV_{max}, or WB SUV_{mean} (Fig. 2b; Table S3).

Discussion

In the present study, we assessed the prognostic value of measuring metabolically active metastatic burden using pretreatment FDG PET/CT in recurrent or metastatic gas-

Fig. 1 PFS and OS according to WB SUV_{max} and WB TLG in all patients ($n = 124$). **a** PFS according to WB SUV_{max} ; **b** OS according to WB SUV_{max} ; **c** PFS according to WB TLG; **d** OS according to WB

TLG. OS overall survival, PFS progression-free survival, SUV_{max} maximum standardized uptake value, TLG total lesion glycolysis, WB whole body

tric cancers treated with first-line chemotherapy. We found a significant association between HER2 positivity and FDG uptake in primary gastric lesions. In addition, for all patients, a large metabolically active metastatic tumor burden, as indicated by large WB MTV and WB TLG measurements, was correlated with worse survival outcomes. We further showed that WB MTV and WB TLG parameters had superior prognostic value compared with those of SUV_{max} , particularly in HER2-positive gastric

cancer, where these volume-based parameters predicted worse OS outcome better than did SUV_{max} or WB SUV_{max} .

Previous studies have reported that tumors with signet-ring cell and poorly differentiated histology generally have lower FDG uptake in PET scan images [17–20]. Consistent with these data, we also observed higher FDG uptake in primary lesions with well- or moderately differentiated histology than in those with poorly differentiated or signet-ring cell histology (Table 2). We also showed that a larger

Table 3 Simple linear and multiple Cox analyses of PFS and OS according to clinicopathologic features and PET-CT parameters in all patients ($n = 124$)

Variable	N	PFS						
		Median, month	Simple linear		Multiple*		Multiple†	
			HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Sex								
Male	80	5.8	0.995 (0.681–1.454)	0.979				
Female	44	5.6	1					
Age at diagnosis, years								
≥65	23	6.9	0.696 (0.435–1.113)	0.130	0.826 (0.513–1.330)	0.432	0.706 (0.438–1.140)	0.155
<65	101	5.5	1		1		1	
Differentiation								
PD/SRC/others	84	5.7	1.419 (0.945–2.131)	0.091	1.330 (0.865–2.045)	0.194	1.233 (0.809–1.880)	0.331
WD/MD	40	6.6	1		1		1	
Baseline CEA, ng/ml								
≥5	54	5.8	1.008 (0.696–1.459)	0.967				
<5	70	5.6	1					
Baseline CA19-9, ng/ml								
≥37	45	5.7	0.981 (0.672–1.431)	0.920				
<37	79	5.7	1					
Baseline CA72-4, ng/ml ($n = 98$)								
≥8	46	5.7	0.912 (0.602–1.380)	0.662				
<8	52	5.5	1					
Primary tumor location								
Distal	55	6.5	0.919 (0.638–1.325)	0.650				
Proximal	69	5.3	1					
HER2 status								
Positive	34	6.6	0.594 (0.382–0.923)	0.021	0.614 (0.387–0.973)	0.038	0.539 (0.336–0.866)	0.011
Negative	90	5.5	1		1		1	
Hepatic metastasis								
Present	29	6.6	0.764 (0.492–1.185)	0.229				
Absent	95	5.7	1					
Peritoneal metastasis								
Present	69	5.3	1.218 (0.843–1.761)	0.293				
Absent	55	6.8	1					
SUV _{max} (primary tumor)								
>10	27	5.6	0.813 (0.507–1.305)	0.391				
≤10	97	5.7	1					
WB SUV _{max}								
>10	46	5.3	1.142 (0.777–1.680)	0.499				
≤10	78	5.9	1					
WB SUV _{mean}								
>4	39	5.3	1.096 (0.733–1.639)	0.655				
≤4	85	5.9	1					
WB MTV (cm ³)								
>100	72	5.2	1.704 (1.170–2.482)	0.005	1.848 (1.256–2.719)	0.002		
≤100	52	6.8	1					
WB TLG								
>600	35	5.2	1.561 (1.041–2.342)	0.031			2.003 (1.300–3.086)	0.002
≤600	89	5.8	1				1	
Variable	N	OS						
		Median, month	Simple linear		Multiple**		Multiple†	
			HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Sex								
Male	80	12.2	0.953 (0.647–1.404)	0.807				
Female	44	13.7	1					

Table 3 continued

Variable	N	OS						
		Median, month	Simple linear		Multiple**		Multiple†	
			HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age at diagnosis, years								
≥65	23	12.3	1.086 (0.674–1.750)	0.736				
<65	101	12.8	1					
Differentiation								
PD/SRC/others	84	11.6	1.528 (1.017–2.296)	0.041	1.660 (1.102–2.498)	0.015	1.709 (1.133–2.578)	0.011
WD/MD	40	14.7	1		1		1	
Baseline CEA, ng/ml								
≥5	54	12.5	0.946 (0.650–1.378)	0.773				
<5	70	12.5	1					
Baseline CA19-9, ng/ml								
≥37	45	13.2	1.104 (0.751–1.622)	0.614				
<37	79	12.5	1					
Baseline CA72-4, ng/ml (n = 98)								
≥8	46	11.2	1.028 (0.679–1.558)	0.895				
<8	52	12.5	1					
Primary tumor location								
Distal	55	14.7	0.904 (0.622–1.314)	0.597				
Proximal	69	11.1	1					
HER2 status								
Positive	34	14.7	0.78 (0.510–1.192)	0.250				
Negative	90	11.3	1					
Hepatic metastasis								
Present	29	11.6	0.993 (0.636–1.551)	0.974				
Absent	95	13.6	1					
Peritoneal metastasis								
Present	69	10.8	1.461 (1.002–2.132)	0.049	1.524 (1.040–2.231)	0.031	1.747 (1.183–2.581)	0.005
Absent	55	14.9	1		1		1	
SUV _{max} (primary tumor)								
>10	27	12.8	1.022 (0.644–1.623)	0.926				
≤10	97	12.5	1					
WB SUV _{max}								
>10	46	10.4	1.216 (0.826–1.789)	0.321				
≤10	78	13.7	1					
WB SUV _{mean}								
>4	39	11.1	1.050 (0.700–1.576)	0.813				
≤4	85	13.7	1					
WB MTV (cm ³)								
>100	72	10.2	1.908 (1.295–2.812)	0.001	2.008 (1.361–2.963)	<0.001		
≤100	52	14.7	1		1			
WB TLG								
>600	35	8.2	2.500 (1.648–3.792)	<0.001			3.001 (1.950–4.618)	<0.001
≤600	89	14.9	1				1	

MD adenocarcinoma, moderately differentiated, MTV metabolic tumor volume, PD adenocarcinoma, poorly differentiated, SRC signet-ring cell carcinoma, SUV_{max} maximum standardized uptake value, SUV_{mean} mean standardized uptake value, TLG total lesion glycolysis, WB whole body, WD adenocarcinoma, well differentiated

* This model used WB MTV, not WB TLG (−2-log likelihood ratio: 896.0)

** This model used WB MTV, not WB TLG (−2-log likelihood ratio: 878.6)

† This model used WB TLG, not WB MTV (−2-log likelihood ratio: 896.8)

‡ This model used WB TLG, not WB MTV (−2-log likelihood ratio: 869.4)

proportion of HER2-positive gastric cancers had a more differentiated histology; thus, the correlation that we observed between HER2 positivity and higher PET/CT

parameters could be influenced by these histologic characteristics. However, after we adjusted several clinico-pathologic features, we found that HER2 positivity was an

Fig. 2 OS according to WB SUV_{max} and WB TLG in the HER2-negative gastric cancer group ($n = 90$) and HER2-positive gastric cancer group ($n = 34$). **a** OS according to WB SUV_{max} in the HER2-negative gastric cancer group; **b** OS according to WB SUV_{max} in the HER2-positive gastric cancer group; **c** OS according to WB TLG in

the HER2-negative gastric cancer group; **d** OS according to WB TLG in the HER2-positive gastric cancer group. *HER2* human epidermal growth factor receptor 2, *OS* overall survival, *PFS* progression-free survival, *SUV_{max}* maximum standardized uptake value, *TLG* total lesion glycolysis, *WB* whole body

independent factor related to high primary tumor SUV_{max} ($\beta = 0.261$; $P = 0.014$) and WB SUV_{max} ($\beta = 0.248$; $P = 0.019$) in recurrent and metastatic gastric cancer, using multiple logistic regression analyses (Table S1).

High FDG uptake in the stomach has been reported to be a poor prognostic marker for gastric cancer patients [7, 9, 10, 12]; however, several of these studies only evaluated the prognostic value of conventional PET

parameters of the primary tumor, such as primary tumor SUV_{max} [7, 9, 12]. Although WB SUV_{max} is a quick and easily reproducible method to determine the metabolic activity of a single lesion, it does not contain volumetric data. Recently, volume-based parameters, such as MTV and TLG, have been used for predicting disease prognosis and evaluating treatment response in various malignancies [2, 3, 10, 21, 22]. MTV is the tumor volume (ml, cc, or

cm³) above a certain metabolic threshold, and TLG factors the metabolic activity into the volume. Here, we showed that estimation of the whole-body metastatic burden, WB MTV, and WB TLG, predicted patient prognosis better than did the SUV_{max} of the primary lesion or highest metabolically active metastasis (WB SUV_{max}). Our findings suggest that MTV and TLG can further stratify stage IV patients by estimating their amount of metastatic burden.

In this study, HER2-positive gastric cancer patients with higher volume-based parameters showed significantly worse OS than did those with lower volume-based parameters as shown by multiple Cox regression analyses. However, these volume-based parameters were not associated with PFS in HER2-positive gastric patients treated with first-line, trastuzumab-based chemotherapy. Instead, baseline serum CEA ≥ 5 ng/ml (vs. CEA < 5 ng/ml; HR 3.300; 95% CI 1.046–7.747; $P = 0.006$) and HER2 2+ at IHC/amplification by ISH (vs. HER2 3+ at IHC; HR 2.354; 95% CI 1.388–3.993; $P = 0.001$) predicted worse survival outcomes following first-line, trastuzumab-based chemotherapy in HER2-positive gastric cancer patients (Table S3), which is consistent with previous findings [23]. Thus, large-scale clinical trials using serial FDG PET or other metabolic imaging modalities to measure volume-based parameters are needed to accurately predict treatment response following trastuzumab-based chemotherapy.

SUV_{max} and WB SUV_{max} were not associated with PFS or OS in recurrent or metastatic gastric cancer patients, which is not concordant with data from previous reports [7, 9, 12]. In subgroup analysis, high SUV_{max} and high WB SUV_{max} could predict poor survival outcome only in HER2-negative gastric cancer patients. The discrepancy in the HER2-positive group is probably owing to intra- and intertumor heterogeneity of HER2 expression and the incorporation of targeted agent chemotherapy. Generally, a lesion with higher FDG uptake has higher proliferation and reduced doubling time of tumor cells [24]. This can be seen in lung cancer patients, as primary lung cancer lesions showing higher SUV_{max} generally have higher mass (MTV) [25, 26]. However, the high metabolic activity in one primary site (SUV_{max}) and metastatic site (WB SUV_{max}) may not always be associated with a large metastatic burden. This discrepancy was more clearly found in HER2-positive gastric cancer compared to HER2-negative gastric cancer patients in this study. A positive correlation was found between WB SUV_{max} and WB MTV in HER2-negative gastric cancers (Spearman's rho, 0.775; $P < 0.001$). However, there was no significant correlation between WB SUV_{max} and WB MTV in HER2-positive gastric cancer (Spearman's rho, 0.291; $P = 0.094$). As a result, WB SUV_{max} was insufficient to reflect total metastatic tumor burden in HER2-positive gastric cancer.

In addition, we suggest that the change of first-line standard treatment in HER2-positive gastric cancer may also explain the results of our study. Our study included HER2-positive gastric cancer patients who were treated with trastuzumab, whereas previous studies included patients who received only cytotoxic chemotherapy [7, 9]. Considering that HER2-positive gastric cancer has higher FDG uptake and higher metabolic tumor burden compared with HER2-negative gastric cancer, the survival outcome of the high-risk group (defined as a larger TLG) might also be influenced by trastuzumab therapy, resulting in compensation of the difference in survival outcomes according to tumor FDG uptakes.

The classic cytotoxic chemotherapeutic agents, including DNA-reacting alkylating agents and antimetabolites that inhibit DNA replication, influence the glucose metabolism of cancer cells because cancer cells use a large amount of glucose to synthesize DNA [27]. Conversely, targeted agents present diverse responses to metabolic imaging. For instance, the PI3K/AKT/mTOR pathway is glucose dependent; thus, the PI3K/AKT/mTOR pathway inhibitors cause notable effects on FDG uptake. Conversely, inhibitors of the RAS/RAF/MEK/MAPK pathway do not exhibit sufficient glycolytic effects on FDG PET images [28]. However, whether trastuzumab can influence the glucose metabolism of HER2-positive gastric cancer is not fully revealed. Many researchers attempted to predict the early response of neoadjuvant trastuzumab treatment using serial FDG PET [29, 30], and others investigated trastuzumab-based HER2 images using ⁸⁹Zr-trastuzumab and ⁶⁴Cu-trastuzumab [31]. Further studies will help to understand glucose metabolism and the influence of trastuzumab in HER2-positive gastric cancer.

There are several limitations to this study. First, because of the small number of patients and retrospective nature of the study, several clinicopathologic features and PET/CT parameters were possibly underestimated. Second, serial FDG PET/CT scans were not conducted; therefore, the changes in glucose metabolism of cancer cells were not assessed. Third, a validation of volume-based PET/CT parameters was not performed. In this study, we opted to use the widely used cutoff value for tumor volume determination. Because volume-based parameters can be affected by the tumor delineation method, multiple methods of ROI determination should have been used, which would likely increase the reproducibility in other studies.

Despite these limitations, our data suggest that using volumetric PET metrics to assess metastatic tumor burden may facilitate further stratification of stage IV recurrent or metastatic gastric cancer patients, allowing for the improved prediction of chemotherapy response and prognosis even after considering HER2 status. Recently, targeted agents, such as trastuzumab and ramucirumab, have

become standard treatment options for recurrent or metastatic gastric cancer [6, 32]. Therefore, it is critical to confirm whether conventional prognostic factors are still reliable in patients treated with these targeted agents and to investigate other predictive and prognostic markers for these treatments. Based on data from this study, we propose that the use of volume-based parameters, such as MTV and TLG, may be helpful in estimating metastatic tumor burden, which may be useful in predicting survival outcomes of recurrent or metastatic gastric cancer patients. Moreover, future large-scale clinical trials should be conducted using these volume-based PET/CT parameters to better assess their predictive and prognostic value in HER2-positive and -negative, recurrent, metastatic gastric cancer.

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Compliance with ethical standards

Conflict of interest The authors have declared no conflicts of interest.

Human rights statement and informed consent All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The protocol was reviewed and approved by the local Institutional Review Board (IRB approval no. 2014-2763-001). The institutional IRB decided to waive the informed consent of this study because it was an observational study using retrospectively collected, anonymized data.

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