

Gastric cancers with microsatellite instability exhibit high fluorodeoxyglucose uptake on positron emission tomography

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Abstract

Background Gastric cancers exhibit various degrees of ^{18}F -fluorodeoxyglucose (FDG) uptakes on positron emission tomography/computed tomography (PET/CT) imaging. The aim of this study was to evaluate whether FDG uptake in gastric cancer varies according to the microsatellite instability (MSI) status.

Methods Consecutive gastric cancer patients who underwent PET/CT imaging and MSI analysis were included in the study. The maximum standardized uptake value (SUV_{max}) of gastric cancer was assessed using PET/CT imaging.

Results Of 131 gastric cancers, 16 exhibited a high incidence of MSI (MSI-H) and 3 exhibited a low incidence of MSI (MSI-L). In 29 subjects who showed no uptake on PET/CT imaging the gastric cancers were all microsatellite stable (MSS). Gastric cancers with MSI were related to age older than 60 years ($p = 0.002$), cancer volume larger than 10 cm^3 ($p = 0.015$), and the presence of FDG uptake on PET/CT imaging ($p = 0.001$). A higher SUV_{max} of gastric cancer was linked to the presence of MSI ($p < 0.001$).

Conclusion The presence of MSI is related to FDG uptake in gastric cancer. Care should be taken with MSS

gastric cancers, because they show lower SUV_{max} on PET/CT imaging than MSI gastric cancers.

Keywords Fluorodeoxyglucose · Gastric cancer · Microsatellite instability · Positron emission tomography

Introduction

^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET) is now used for the imaging of various human cancers. This noninvasive technique that recognizes alterations in cellular glucose metabolism detects the presence of cancer cells by their increased glucose metabolism [1]. In addition to such visual analysis, an often-used semi-quantitative parameter, called the standardized uptake value (SUV) assesses the uptake of FDG. Recently, FDG-PET combined with computed tomography (FDG-PET/CT) has recently been introduced [2]. FDG-PET/CT imaging is expected to provide more precise anatomical data in addition to metabolic information. For gastric cancers, FDG-PET imaging provides important additional information concerning the prognosis of recurrent cancer, including lymph node metastases, peritoneal carcinomatosis, distant metastasis, tumor response to treatment, and overall survival [3–10]. However, some subtypes of gastric cancer exhibit reduced FDG uptake [3, 11–14], which significantly limits the use of PET in gastric cancer.

Gastric carcinogenesis is a multi-factorial process, and genomic instability is a fundamental finding in gastric cancer at the genetic level [15]. Microsatellite instability (MSI) is a marker of mutations that develop subsequent to deficient DNA mismatch repair (MMR) activity, which is characterized by the accelerated accumulation of single nucleotide mutations and alterations in the lengths of

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simple repetitive microsatellite sequences found throughout the genome [16, 17]. It is known that susceptibility to gastric cancer is caused by mutations in the DNA MMR system [18–20]. Gastric cancers with MSI tend to be located in the antrum, be of the intestinal type, be metachronous, be larger, have less lymph node metastasis, have a favorable prognosis, and occur more frequently in old age [21–23]. A study showed that the expression of glucose transporter-1 (Glut-1) in gastric cancer was associated with parameters of tumor aggressiveness, such as depth of invasion, lymphatic permeation, venous invasion, nodal involvement, and hepatic metastasis [22]. However, false negativity on PET/CT imaging cannot be solely explained by these factors (i.e., location, size, depth, cell type, Lauren's classification, microvascular invasion, and metastasis), and there is no study of FDG-PET or PET/CT imaging with regard to the MSI status of gastric cancer.

We hypothesized that MSI might be related to a higher expression of Glut-1, and that microsatellite stable (MSS) gastric cancers might be related to a lower expression of Glut-1 leading to false negativity on PET/CT imaging. In this study, we investigated whether low sensitivity of FDG uptake in detecting gastric cancers was related to the MSI status of gastric cancer.

Patients, materials, and methods

Patients

Consecutive patients who were newly diagnosed with gastric cancer at Konkuk University Medical Center between April 2006 and October 2010 who agreed to have MSI analysis and FDG-PET/CT imaging were included. After conventional staging work-up for gastric cancer, FDG-PET/CT imaging was performed before surgical resection, and MSI analysis was performed after the resection in each patient (Figs. 1, 2). Gastric cancers less than 2 cm in size (at least in one dimension) or smaller than 1 cm³ in volume (2 cm in width × 1 cm in length × 0.5 cm in depth) were excluded from the study due to the possibility of poor recognition of such small-sized gastric cancers on FDG-PET/CT imaging. All of the patients provided written informed consent prior to undergoing the procedure, and this study (KUH 1010161) was approved by the Institutional Review Board of Konkuk University School of Medicine, which confirmed that the study was in accordance with the ethical guidelines of the Helsinki Declaration.

FDG-PET/CT imaging

All patients fasted for at least 6 h and blood glucose concentration was checked before PET imaging (<120 mg/dL

for nondiabetic patients and <200 mg/dL for diabetic patients). Subjects in the resting state received an intravenous injection of FDG (4.8 MBq/kg of body weight). PET/CT images were acquired 60 min later, using a GEMINI PET/CT scanner (Philips Medical Systems, Cleveland, OH, USA). Axes of both the PET and the CT systems were mechanically aligned. CT from the skull base to the mid-thigh (without i.v. contrast) was performed for attenuation correction and anatomic localization, using a standardized protocol of 120 kV, 100 mA, a tube-rotation time of 0.75 s per rotation, a pitch of 1.5, and a section thickness of 5 mm. Immediately after CT, PET images were acquired for 2.5 min per frame, using a conventional three-dimensional protocol.

Assessment of FDG-PET/CT images was performed by two experienced nuclear medicine physicians (H. W. Chung and Y. So). The maximum standardized uptake value (SUV_{max}) was used quantitatively for the determination of FDG-PET/CT activity. To obtain the SUV_{max}, a transaxial image representing the highest tumor uptake was carefully selected, and a circular region of interest was placed in the area of FDG accumulation. SUV_{max} was defined as maximum tumor concentration of FDG divided by the injected dose, corrected for the body weight of the patient.

DNA preparation and MSI analysis

Genomic DNA from the tumor and corresponding normal tissue was obtained from paraffin blocks by microdissection. DNA was extracted from the microdissected tissues using 200 µl of proteinase K solution (190 µl of protein kinase digestion buffer with 10 µl of 10 mg/ml proteinase K) in lysis buffer containing 0.5 % Tween-20, 1 M Tris (pH 8.5), and 500 mM ethylenediamine-tetraacetic acid (EDTA; pH 8.0). Tissues were incubated overnight at 55 °C in lysis buffer solution. Following overnight incubation, the samples were heated in a 100 °C heat block and centrifuged at 14000 rpm for 15 min at 4 °C.

MSI was analyzed by polymerase chain reaction (PCR) amplification with fluorescent dye-labeled primers of mononucleotide markers (*BAT25* and *BAT26*) and dinucleotide markers (*D2S123*, *D5S346*, and *D17S250*) specific for the microsatellite loci. More than 35 cycles of PCR were performed as follows: 1 min at 94 °C, 1 min at 55 °C, and 1 min at 72 °C for the *BAT25* and *BAT26* primers. For *D2S123*, more than 35 cycles of PCR were performed as follows: 30 s at 94 °C, 1 min at 54 °C, and 1 min at 72 °C. For *D5S346*, more than 36 cycles of PCR were performed as follows: 30 s at 94 °C, 30 s at 55 °C, and 30 s at 72 °C. For *D17S250*, more than 38 cycles of PCR were performed as follows: 1 min at 94 °C, 1 min at 50 °C, and 1 min at 72 °C. An ABI 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) and Genescan

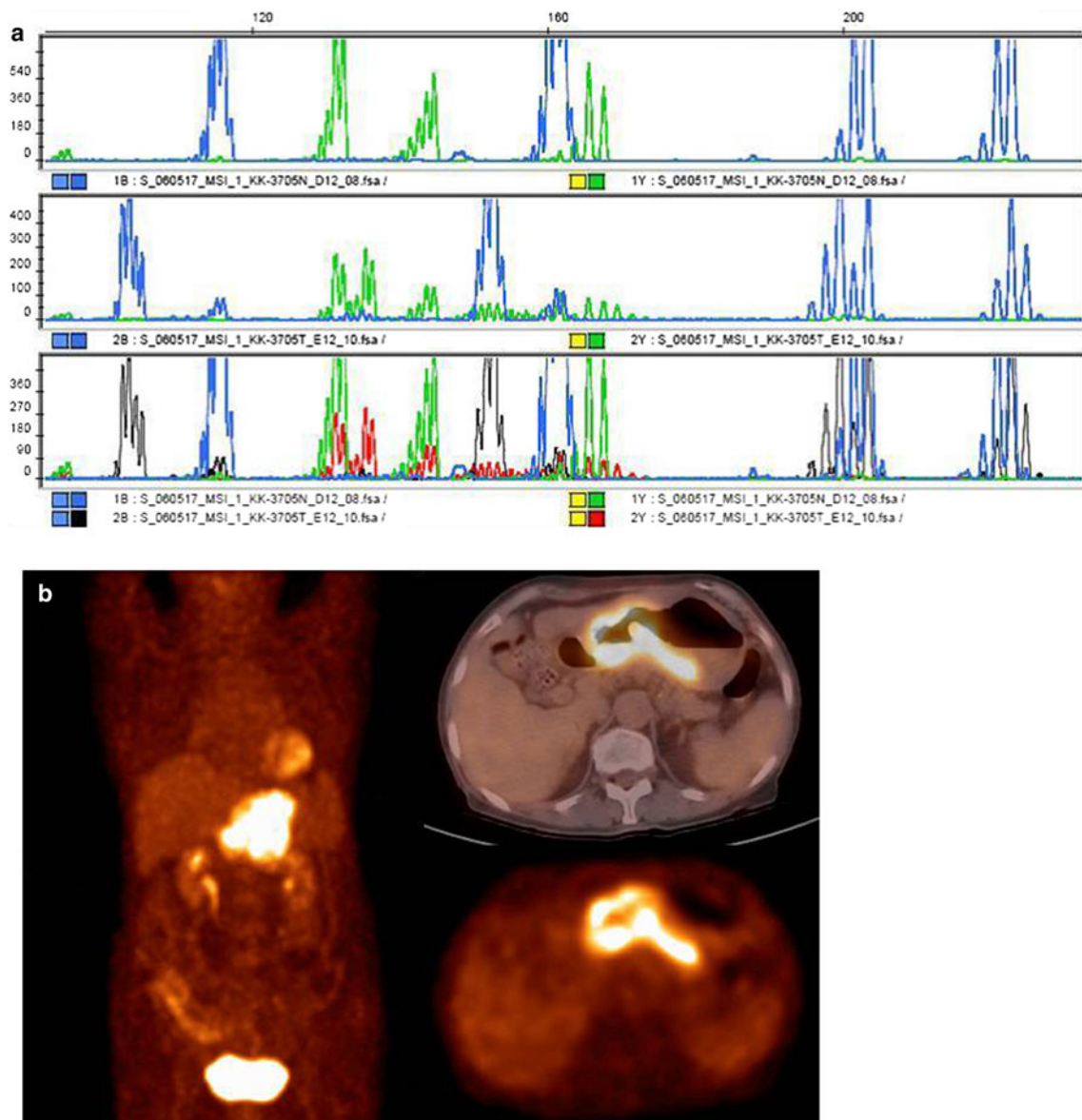


Fig. 1 A gastric cancer with a high incidence of microsatellite instability (*MSI-H*) showing a high maximum standardized uptake (SUV_{max}) on ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) imaging. A Bormann type 3 advanced gastric cancer was found on the lesser curvature side of the

antrum. The size of the cancer was 14 cm × 7.5 cm × 1.8 cm, and the pathology revealed a poorly differentiated adenocarcinoma. The level of invasion reached the subserosal layer, and lymph node metastases were found in 4 of the 65 resected lymph nodes. **a** MSI analysis revealed *MSI-H*. **b** The SUV_{max} value was 8.6

software (Applied Biosystems) were used for the detection of fluorescence-labeled PCR products.

MSI was defined as a band shift in either of the two alleles or the appearance of a differently sized band in the tumor sample. Detection of instability in more than 30 % of markers was categorized as a high incidence of MSI (*MSI-H*) and detection of instability in less than 30 % of markers was categorized as a low incidence of MSI (*MSI-L*). Microsatellite stability (*MSS*) was defined when there was no definite evidence of MSI.

Statistical analysis

Significant differences of variable characteristics between groups were compared by *t* tests or the Mann–Whitney *U*-test for the continuous variables, and χ^2 tests or Fisher’s exact test for the categorical variables. Logistic regression analysis was performed to determine the independent significant clinicopathological factors that showed a causal relationship with a dependent variable. PASW statistics 17.0 for windows (SPSS, Chicago, IL, USA) was used for

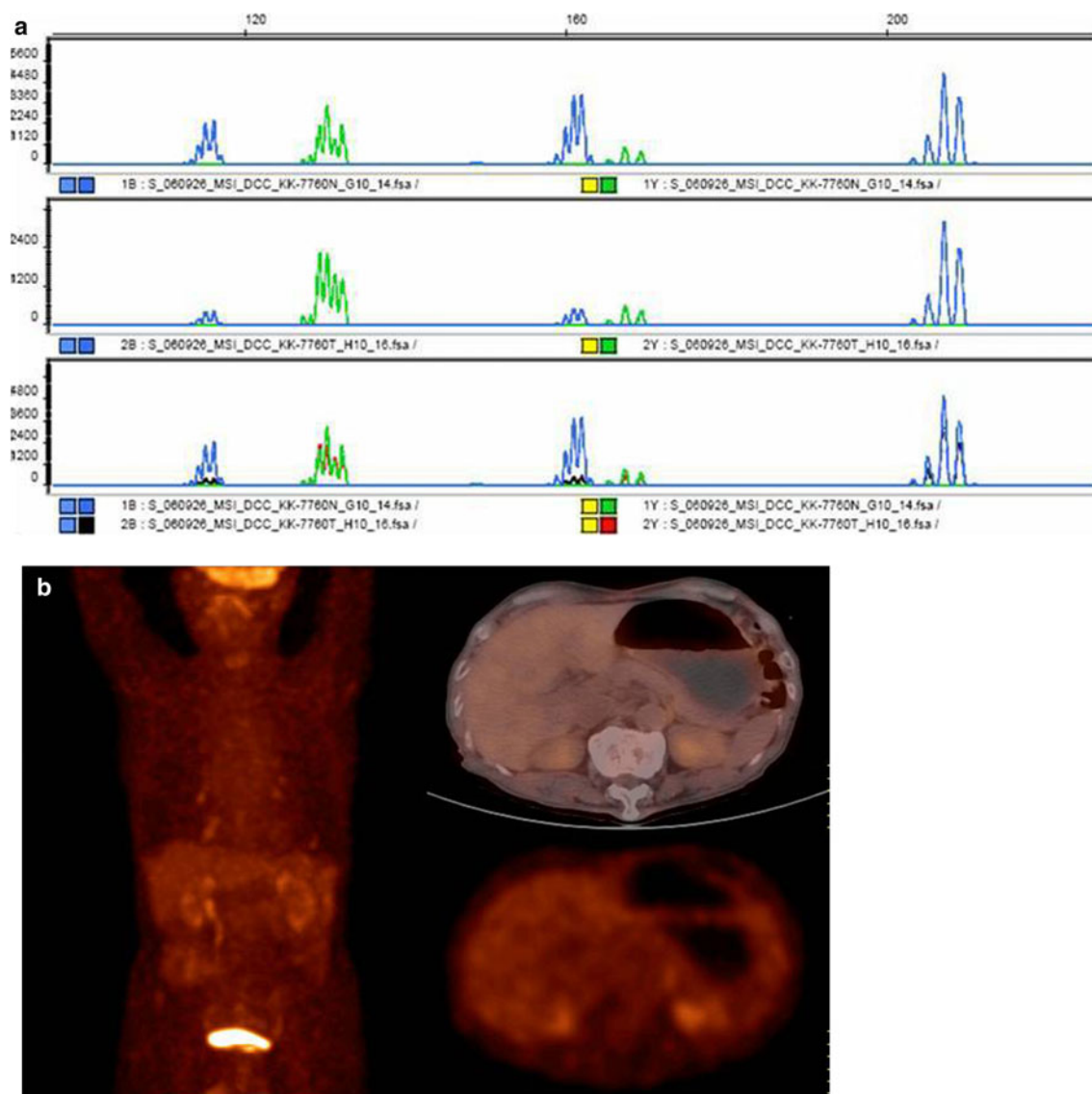


Fig. 2 A gastric cancer with microsatellite stability (MSS) showing a low SUV_{max} on FDG-PET/CT imaging. A Bormann type 3 advanced gastric cancer was found on the anterior side of the fundus. The size of the cancer was 3.5 cm \times 3 cm \times 3 cm, and the pathology

revealed a signet ring cell carcinoma. The level of invasion reached the proper muscle layer, and lymph node metastasis was found in 1 of the 26 resected lymph nodes. **a** MSI analysis revealed MSS. **b** The SUV_{max} value was 1.2

the performance of statistical analysis; $p < 0.05$ was considered statistically significant.

Results

Clinicopathological findings according to the MSI status of gastric cancer

Of 162 gastric cancers in 162 patients, 31 cases were excluded because of their small size (either <2 cm in size or <1 cm³ in volume). Of the 131 remaining cases, 19 showed MSI (16 MSI-H and 3 MSI-L), whereas 112 cases

showed MSS (Table 1). Patients with MSI gastric cancers were found to be older than those having gastric cancers without MSI ($p = 0.001$). Gastric cancers with MSI were located predominantly in the antrum (63.2%), whereas more than half of the MSS gastric cancers were found in the body (55.4%). The volume calculated by three dimensions of the cancer was significantly higher in MSI gastric cancers than in MSS cancers ($p = 0.034$).

FDG uptake on PET/CT imaging

The median SUV_{max} of gastric cancer with MSI was significantly higher than that of gastric cancer without MSI

(7.40 vs. 3.85, $p < 0.001$). Age greater than 60 years ($p = 0.002$), cancer volume larger than 10 cm^3 ($p = 0.015$), and the presence of FDG uptake on PET/CT imaging ($p = 0.001$) were significantly related to the presence of MSI (Table 2).

Gastric cancers without FDG uptake on PET/CT imaging

Twenty-nine gastric cancers that were not detected on PET/CT imaging were all MSS gastric cancers. When we compared the characteristics of gastric cancers with FDG uptake ($n = 102$) versus gastric cancers without FDG uptake ($n = 29$), there were significant differences in the MSI status ($p = 0.007$), age of the subject ($p = 0.020$), volume of the cancer ($p < 0.001$), T stage ($p < 0.001$), and N stage ($p = 0.001$) (Table 3). Of these variables, the presence of MSI was significantly related to higher SUV_{max} of gastric cancer ($p < 0.001$) (Table 4).

Discussion

To the best of our knowledge, this is the first study to demonstrate that SUV_{max} is higher in MSI gastric cancers than in MSS gastric cancers. Notably, in our study, 29 gastric cancers that were not detected on PET/CT imaging were all MSS gastric cancers. Although there are several studies that have shown different degrees of FDG uptake in primary gastric cancer on PET imaging [3, 11–13], this is the first study that shows the significance of MSI in detecting gastric cancers using PET/CT imaging.

Our result suggests that there might be a link between MSI itself and the glycolytic activity that increased FDG accumulation, potentially due to inflammation. The

metabolic difference that can be associated with different grades of MSI might provide important information for the individual patient when assessing the risk of cancer development. A recent study, by Tessem et al., showed that there were metabolic differences in normal colon mucosa between MSI-H and MSS patients [24]. In their study, several metabolites, such as lactate, taurine, glycine, myo-inositol, scyllo-inositol, phosphocholine, glycerophosphocholine, creatine, and glucose were identified as potential biomarkers for cancer detection. Their results are based on the fact that altered metabolites in gastrointestinal cancer tissues are associated with expected metabolic perturbations, such as elevated tissue glycolysis, hypoxia, nucleotide biosynthesis, lipid metabolism, inflammation, and steroid metabolism. Further studies investigating the aberrations in signal transduction pathways leading to increased glycolytic activity in MSI tumors, as compared with MSS tumors, will verify this issue.

Glut-1 expression is the most important factor for determining the degree of FDG uptake, and in gastric carcinoma, Glut-1 is known to be expressed during gastric carcinogenesis [13, 22, 25]. Identification of gastric cancer by FDG-PET imaging is known to be influenced by several determinants, including background signaling, the gastric location of the tumor, tumor size or stage, and histological subtypes [14, 26]. Incidental FDG accumulation in the gastrointestinal tract in PET/CT imaging is known to indicate a substantial risk of an underlying cancerous or precancerous lesion [2], and accumulation of FDG in the stomach is strongly associated with mucosal inflammation, including superficial gastritis and erosive gastritis [26]. FDG uptake corresponds largely to mucosal inflammation, including superficial gastritis and erosive gastritis, and, therefore, inflammatory mucosa was assumed to be the main cause of non-specific FDG accumulation [25]. When considering the

Table 1 Characteristics of gastric cancers according to microsatellite instability (MSI) status

	Gastric cancers with MSI ($n = 19$)	Gastric cancers without MSI ($n = 112$)	p value
Age, years (mean \pm SD)	69.32 \pm 10.39	59.93 \pm 11.39	0.001*
Male:female ratio	14:5	78:34	0.722 [†]
Volume of the cancer, cm^3 , median (range)	35.0 (1.4–517.6)	8.1 (1.1–692.6)	0.034 [‡]
Location (antrum:body:fundus/cardia)	12:5:2	44:62:6	0.062 [†]
Pathology (WDA:MDA:PDA:SRC:others)	1:11:7:0:0	8:43:35:18:8	0.189 [§]
Lauren's classification (intestinal:diffuse:mixed)	12:6:1	55:44:13	0.474 [†]
T stage (T1:T2:T3:T4)	4:2:7:6	33:30:25:24	0.231 [§]
N stage (N0:N1:N2:N3)	6:4:2:7	65:20:12:15	0.055 [§]
SUV_{max} , median (range)	7.40 (2.50–20.40)	3.85 (0–19.30)	<0.001 [‡]

MDA moderately differentiated adenocarcinoma, *others* mucinous or papillary adenocarcinoma, PDA poorly differentiated adenocarcinoma, SD standard deviation, SRC signet ring cell carcinoma, SUV_{max} maximum standardized uptake value, WDA well-differentiated adenocarcinoma p values were calculated using the * two-sample t test, [†] χ^2 test, [‡] Mann–Whitney U -test, and [§] Fisher's exact test

fact that the accumulation of MSI in dysplasia and intestinal metaplasia of the gastric mucosa is an early molecular event occurring during gastric carcinogenesis [21], it is not strange

Table 2 Predictive factors for the presence of microsatellite instability

Variables	Odds ratio	95 % confidence interval	<i>p</i> value
Age (>60 years)	1.092	1.032–1.156	0.002
Gender (male)	1.220	0.407–3.658	0.722
Location			
Antrum	0.818	0.146–4.582	0.373
Body	0.242	0.038–1.526	0.039
Fundus/cardia	1 (reference)		
Pathology (WDA or MDA)	2.050	0.752–5.594	0.161
Lauren's classification			
Intestinal type	2.836	0.338–23.807	0.242
Diffuse type	1.773	0.195–16.085	0.941
Mixed type	1 (reference)		
Volume (>10 cm ³)	1.006	1.001–1.012	0.015
T stage			
T1	0.485	0.123–1.908	0.604
T2	0.267	0.049–1.442	0.157
T3	1.12	0.329–3.816	0.144
T4	1 (reference)		
N stage			
N0	0.198	0.058–0.674	0.071
N1	0.429	0.106–1.736	0.955
N2	0.357	0.062–2.045	0.799
N3	1 (reference)		
SUV _{max} (>0)	1.197	1.079–1.328	0.001

MDA moderately differentiated adenocarcinoma, SUV_{max} maximum standardized uptake value, WDA well-differentiated adenocarcinoma

that the presence of MSI might lead to a higher FDG uptake. We speculate that the higher SUV_{max} in MSI-positive gastric cancers found in our study is related to gastritis-related tumorigenesis in these cancers, because the inflammatory process leads to a deficiency of DNA MMR in gastric epithelial cells, and this increases the risk of the accumulation of mutations in gastric mucosa cells and the risk of gastric cancer during gastric carcinogenesis.

Different from colorectal cancers, larger size and histological heterogeneity are often encountered in MSI-positive gastric cancers especially in the aged population [27]. Therefore, it is possible that rapidly growing gastric cancers can be easily detected by PET/CT imaging. It is also known that FDG-PET imaging plays no role in primary tumor detection due to its low sensitivity, especially in early gastric cancer and the nonintestinal type [11]. Another study showed that the detection rate with FDG-PET was significantly higher for tumors of the intestinal type than for nonintestinal-type tumors [3]. MSI gastric cancers tend to have favorable histology and better prognosis, which may contribute to a possible spurious correlation between MSI and high FDG uptake on PET. However, when we analyzed the cell types of the 29 gastric cancers that were not detected on PET/CT imaging in our study, most were moderately or poorly differentiated adenocarcinomas. In addition, all mucinous adenocarcinomas in our study revealed FDG uptake. Therefore, we suspected that factors other than cell types in gastric cancer would affect FDG uptake, and we found that all gastric cancers that showed no uptake on PET/CT imaging were MSS gastric cancers. The metabolic differences between MSI-H and MSS may be very interesting in the early detection of cancer development and could be of high clinical importance in the work of improving the diagnosis and characterization of gastric cancer using PET/CT imaging.

Table 3 Clinicopathological features of gastric cancers according to the presence of FDG uptake on PET/CT imaging

	Gastric cancers with no FDG uptake (<i>n</i> = 29)	Gastric cancers with FDG uptake (<i>n</i> = 102)	<i>p</i> value
Age, years (mean ± SD)	56.86 ± 11.24	62.55 ± 11.57	0.020*
Male:female ratio	18:11	74:28	0.276 [†]
Volume of the cancer, cm ³ , median (range)	2.70 (1.12–40.04)	17.38 (1.19–692.55)	<0.001 [‡]
Location (antrum:body:fundus/cardia)	8:20:1	48:47:7	0.093 [†]
Pathology (WDA:MDA:PDA:SRC:others)	2:11:11:5:0	7:43:31:13:8	0.577 [§]
Lauren's classification (intestinal:diffuse:mixed)	13:13:3	54:37:11	0.695 [†]
T stage (T1:T2:T3:T4)	16:10:2:1	21:22:30:29	<0.001 [§]
N stage (N0:N1:N2:N3)	25:1:1:2	46:23:13:20	0.001 [§]
Presence of MSI	29:0	83:19	0.007 [§]

FDG ¹⁸F-fluorodeoxyglucose, PET/CT positron emission tomography/computed tomography, MDA moderately differentiated adenocarcinoma, MSI microsatellite instability, others mucinous or papillary adenocarcinoma, PDA poorly differentiated adenocarcinoma, SD standard deviation, SRC signet ring cell carcinoma, WDA well-differentiated adenocarcinoma

p values were calculated using the * two sample *t*-test, [†] χ^2 test, [‡] Mann–Whitney *U*-test, and [§] Fisher's exact test

Table 4 Risk factors related to higher SUV_{max} of gastric cancer

Variable	Number of the subjects	Median SUV_{max}	<i>p</i> value
Age			0.314
≤50 years	25	2.50	
>50 to ≤60 years	31	3.90	
>60 to ≤70 years	44	4.50	
>70 years	31	4.40	
Volume			0.587
≤3 cm ³	36	2.35	
>3 to ≤10 cm ³	26	2.70	
>10 to ≤30 cm ³	25	4.40	
>30 to ≤50 cm ³	17	4.30	
>50 cm ³	27	9.50	
T stage			0.222
T1	37	2.20	
T2	32	3.05	
T3	32	6.45	
T4	30	6.00	
N stage			0.659
N0	71	2.90	
N1	24	4.35	
N2	14	7.00	
N3	22	7.85	
MSI status			<0.001
Absent	112	3.85	
Present	19	7.40	

MSI microsatellite instability, SUV_{max} maximum standardized uptake value

In conclusion, higher FDG uptake on PET/CT imaging was related to the status of MSI in gastric cancer. Care should be taken with MSS gastric cancers, because they show lower SUV_{max} on PET/CT imaging than MSI gastric cancers. It seems that PET/CT imaging might be useless not only in small gastric cancers but also in MSS cancers, because some of the MSS gastric cancers showed no FDG uptake despite their large volumes. Taken as a whole, the MSI status should be strongly considered when interpreting the results of PET/CT imaging in gastric cancer patients.

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