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ORIGINAL ARTICLE

Pretreatment F-18 FDG PET/CT Parameters to Evaluate Progression-Free Survival in Gastric Cancer

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Abstract
Purpose We performed this study to evaluate the predictive value of pretreatment F-18 FDG PET/CT for progression-free survival (PFS) in patients with gastric cancer.
Methods Of 321 patients with a diagnosis of gastric cancer, we retrospectively enrolled 97 patients (men:women = 61:36, age 59.8±13.2 years), who underwent pretreatment F-18 fluoro-2-deoxyglucose positron emission tomography/computed tomography (F-18 FDG PET/CT) from January 2009 to December 2009. Maximum standardized uptake value (SUVmax) was measured for each case with detectable primary lesions. In the remaining non-detectable cases, SUVmax was measured from the corresponding site seen on gastroduodenoscopy for analysis. In subgroup analysis, metabolic tumor volume (MTV) was measured in 50 patients with clearly distinguishable primary lesions. SUVmax, stage, depth of tumor invasion and presence of lymph node metastasis were analyzed in terms of PFS. Receiver operating characteristic (ROC) curves were used to find optimal cutoff values of SUVmax and MTV for disease progression. The relationship between SUVmax, MTV and PFS was analyzed using the Kaplan-Meier with log-rank test and Cox's proportional hazard regression methods.
Results Of 97 patients, 15 (15.5 %) had disease progression. The mean follow-up duration was 29.6±10.2 months. The mean PFS of low SUVmax group (≤5.74) was significantly longer than that of the high SUVmax group (>5.74) (30.9±8.0 vs 24.3±13.6 months, $p=0.008$). In univariate analysis, stage (I vs II, III, IV), depth of tumor invasion (T1 vs T2, T3, T4), presence of lymph node metastasis and SUVmax (>5.74 vs ≤5.74) were significantly associated with recurrence. In multivariate analysis, high SUVmax (>5.74) was the only poor prognostic factor for PFS ($p=0.002$, HR 11.03, 95 % CI 2.48–49.05). Subgroup multivariate analysis revealed that high MTV (>16.42) was the only poor prognostic factor for PFS ($p=0.034$, HR 3.59, 95 % CI 1.10–11.71).
Conclusion In gastric cancer, SUVmax measured by pretreatment F-18 FDG PET/CT has a significant predictive value for PFS. In addition, if MTV is measurable, high MTV is an independent factor for disease progression.

Keywords Gastric cancer · Progression-free survival · Prognosis · F-18 FDG PET/CT · Maximum standardized uptake value · Metabolic tumor volume

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Introduction

Gastric cancer is the most commonly diagnosed cancer in Korea and the fourth most common cancer in the world [1, 2]. Recently, mortality and 5-year survival rate associated with gastric cancer have markedly decreased in Korea, possibly due to early detection and surgery [2, 3]. Nevertheless a considerable number of patients are diagnosed in advanced stage and have a poor prognosis. Surgery is the only way to cure gastric cancer. The stage of gastric cancer, depth of tumor invasion and extent of lymph node metastasis are the most significant factors for predicting recurrence [4, 5]. But pretreatment assessment of prognosis in patients with gastric cancer is not well established.

F-18 fluoro-2-deoxyglucose positron emission tomography/computed tomography (F-18 FDG PET/CT) has become an increasingly important method for the detection, staging, and assessment of treatment response of a variety of malignancies, including squamous cell carcinoma of head and neck and non-small cell lung cancer [6–8]. Maximum standardized uptake value (SUVmax), a semiquantitative parameter in integrated F-18 FDG PET/CT, is a significant factor for prognosis and treatment guidance in many types of cancer [9–11]. Metabolic tumor volume (MTV) is a volumetric PET parameter, defined as the summed volume of tumor tissues with increased FDG uptake. Several studies suggest that MTV is an independent factor of prognosis in many types of malignancies [12–17]. F-18 FDG PET/CT is useful to detect recurrence after surgery in patients with gastric cancer [18], but the role of pretreatment PET/CT scan is still unclear, because of low sensitivities of primary tumor and lymph node metastasis [19, 20]. We hypothesized that PET parameters, SUVmax and MTV measured by pretreatment F-18 FDG PET/CT can be valuable for predicting the prognosis of patients with gastric cancer.

The aim of this study was to evaluate the predictive value of the pretreatment F-18 FDG PET/CT for PFS in patients with gastric cancer.

Materials and Methods

Patients

From January 2009 to December 2009, we reviewed retrospectively the electrical medical records of 321 patients with pathologically proven gastric cancer at Chonbuk National University Hospital, Jeonju, South Korea. We enrolled 97 patients (men:women = 61:36, age 59.8± 13.2 years) who underwent pretreatment F-18 FDG PET/CT. All patients underwent gastroduodenoscopy, contrast-enhanced abdominal CT and blood test (preoperative tumor markers: CEA [carcinoembryonic antigen], CA 19–9 [carbohydrate antigen 19–9]) for cancer staging. After diagnosis, all patients underwent surgery, (subtotal gastrectomy, total gastrectomy, or exploration) and most (90/97, 92.8 %) received adjuvant chemotherapy.

Acquisition of F-18 FDG PET/CT Scan

F-18 FDG PET/CT scans were obtained on a Biograph Truepoint 40 (Siemens, Berlin, Germany) or Biograph 16 (Siemens, Berlin, Germany). All patients fasted at least 6 h before the intravenous injection of F-18 FDG (3.7–5.5 MBq/kg). Prior to injection of F-18 FDG, blood glucose levels were checked in order to determine whether the levels were within the reference range (<130 mg/dl for nondiabetic patients and <200 mg/dl for diabetic patients). A CT scan from the skull base to the upper thigh was performed prior to PET for attenuation correction and anatomic localization using a standard protocol of 120 kVp, 80 mA (adjusted for body thickness), and a section thickness of 3 mm. Immediately after CT, whole-body PET images were acquired at 50-60 min after intravenous administration of F-18 FDG. Standard PET protocol was used to scan from the skull base to the upper thighs with an acquisition time of 2.5 min per bed position in three-dimensional (3-D) mode. Patients sat quietly in a separate room during the uptake phase and during the scan, patients were supine with their arms raised above their head in the fused PET/CT scanner with a single gantry and table. A limited breath-hold technique was used in order to avoid motion-induced artifacts near the diaphragm.

Measurement of PET Parameters

All images were reviewed at a workstation (Syngo MI applications, Flexible Display 7.0.7.7; Siemens Medical Solutions, Erlangen, Germany). Two types of PET parameters, SUVmax and MTV were measured. First, SUVmax was measured in all patients. In visual analysis, SUVmax was measured from each case with detectable primary lesion (Fig. 1). Detectable primary lesion was defined as FDG-avid focus localized in the gastric wall greater than surrounding gastric wall regardless of intensity of uptake. A region of interest (ROI) was drawn in 3-D planes where the lesion seemed to have the highest uptake according to intensity. Calculation of SUVmax was as follows: $SUVmax = C_{max}/(IA/TBW)$ (where C_{max} is the activity concentration in the voxel of highest tumor activity (Bq/ml), TBW is the total body weight [kg], and IA is the injected activity [kBq]). In the remaining non-detectable cases, SUVmax was measured based on the corresponding site seen on gastroduodenoscopy or contrast-enhanced CT (Fig. 2). On the other hand, MTV was measured in 50 patients with clearly distinguishable images. MTV was defined as the summed volume in cubic centimeters in the primary tumor. We used a fixed threshold method of SUV 2.5 to measure MTV like previous studies [12, 13]. MTV was measured from attenuation-corrected F-18 FDG PET/CT images using an SUV-based automated contouring program (Syngo MI applications, Volumetric Analysis 7.0.7.7; Siemens Medical Solutions). The ROI was drawn slightly large enough to incorporate tumor in the axial, coronal and sagittal FDG PET/CT images. The contour around the tumor inside the ROI was automatically produced, and voxels presenting SUV > 2.5 within the contouring margin were incorporated to define the tumor volumes (Fig. 1).

In this method, we could obtain a highly constant MTV value in repetitive measurement, and only these 50 patients were included in MTV measurable group.

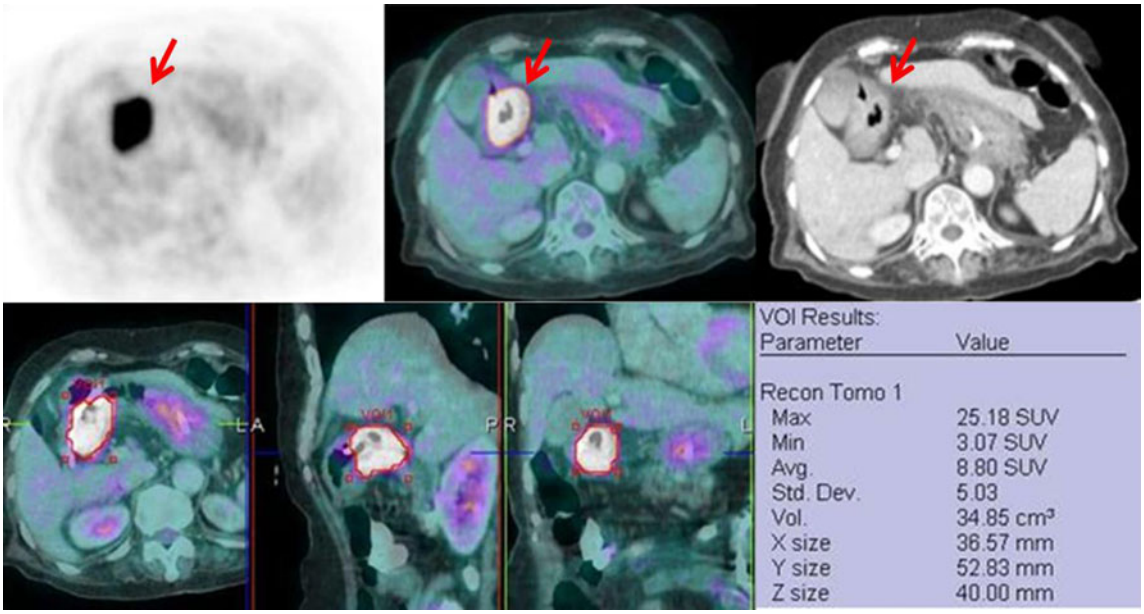

Fig. 1 The *upper panels* show F-18 FDG PET, fused F-18 FDG PET/CT and CT images of an 81-year-old man with gastric cancer. Intense FDG-avid wall thickening (SUVmax=25.18) is shown at antrum (*arrows*). The *lower panels* show an example of measuring metabolic tumor volume (MTV) in axial, sagittal and coronal planes from fused images in the same patients (MTV=34.85 cm^3)

Clinical Follow-Up

All patients were evaluated regularly by physical examination, blood sampling (tumor marker: CEA and CA 19–9), gastroduodenoscopy and imaging study (contrast-enhanced abdominal CT and/or F-18 FDG PET/CT), for follow-up every 6 months in the first year and then 12 months every subsequent year. When abnormality was detected, further evaluations such as pathologic confirmation or additional imaging study were performed. Recurrence was defined as the reappearance of disease during the follow-up period and was confirmed by cytologic or histopathologic examination or by a suggestive lesion in imaging studies. Progression-free survival (PFS) was defined as the time interval from the date

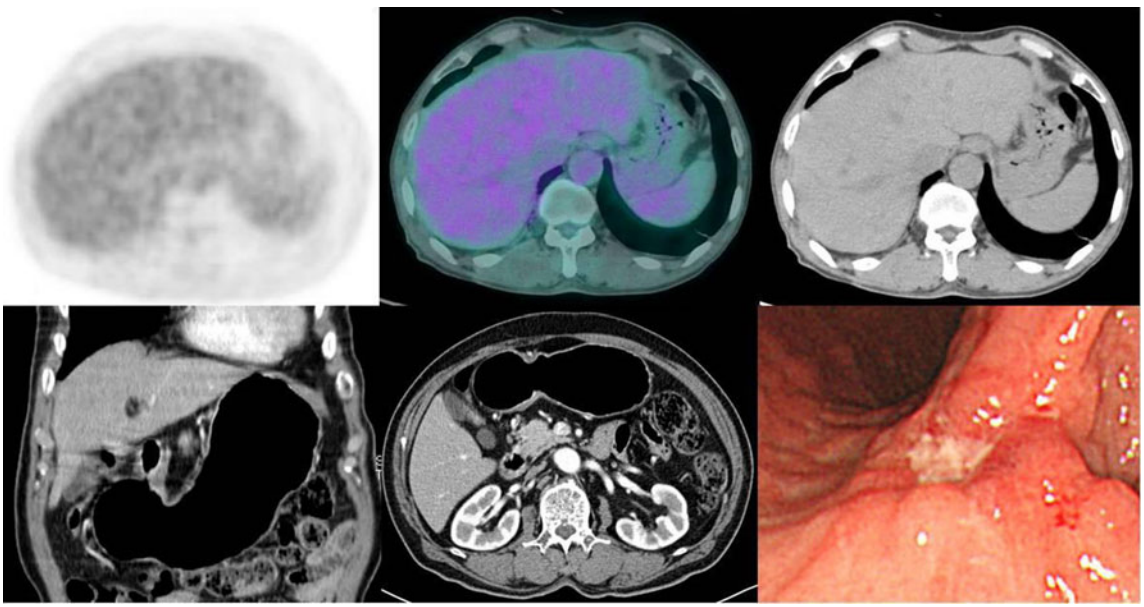

Fig. 2 Upper endoscopy shows a flat depressed and deep ulcerative lesion with irregular margin at gastric angle in a 75-year-old man with gastric cancer (*right bottom*). The *upper panels* show F-18 FDG PET, fused F-18 FDG PET/CT and CT images, but no abnormal focal FDG-avid lesion is seen. Neither abnormal mass nor wall thickening is seen in contrast-enhanced CT images (*left* and *middle bottom*)

of surgery to the date of the disease progression detected on imaging study or pathologic confirmation, or if no event occurred, to the date of the last follow-up.

Statistical Analysis

Statistical analysis was performed using SPSS software (Version 20.0; SPSS, Chicago, IL, USA). The independent *t*-test and Pearson's chi-square test were used to evaluated the significances of differences between continuous and categorical variables, respectively. Known prognostic factors, SUVmax, stage, depth of tumor invasion and presence of lymph node metastasis were analyzed in terms of PFS. Receiver operating characteristic (ROC) curves were used to find optimal cutoff values of SUVmax and MTV for disease progression. PFS was evaluated with the Kaplan-Meier method after surgery. Comparison of the PFS between groups was examined using the log-rank test in univariate analysis. The Cox proportional hazard model using forward conditional stepwise selection was used to evaluate prognostic variables for multivariate analysis, and an estimated hazard ratio (HR) with 95 % confidence interval (95 % CI) was presented. Null hypotheses of no difference were rejected if p values were less than 0.05 or, equivalently, if the 95 % CIs of hazard ratio estimates excluded.

Results

Patient Characteristics

Patient characteristics are summarized in Table 1. A total of 97 patients were evaluated. The mean age was 59.8±13.2 years. Gastric cancer was staged according to TNM classification by 7th edition of the AJCC cancer staging manual [21]. There were 46 patients with T1 (47.4 %), 13 patients with T2 (13.4 %), 24 patients with T3 (24.7 %), and 14 patients with T4 stage (14.4 %). Lymph node metastasis was positive in 36 patients (37.1 %). There were 51 patients with stage I (52.6 %, indeed one patient with Tis stage, stage 0 was included in stage I category), 16 patients with stage II (16.5 %), 22 patients with stage III (22.7 %), and 8 patients with stage IV (8.2 %). Mean SUVmax and MTV of the primary lesion were 6.8±5.3 and 33.2±48.5 cm^3 respectively. Patients characteristics according to disease progression are summarized in Table 2. Age, T stage, presence of lymph node metastasis, TNM stage and SUVmax were significantly different between groups (Table 2). Comparison of MTV measurable and non-measurable groups are displayed in Table 3. Age, pathologic type, T stage, presence of lymph node metastasis, TNM stage and SUVmax were significantly different between groups (Table 3).

Table 1 Patient characteristics

Characteristics	Value (%)
Age (years, mean ± SD)	59.8±13.2
Sex	
Male	61 (62.9 %)
Female	36 (37.1 %)
Pathologic type	
Well differentiated	20 (20.6 %)
Moderately differentiated	30 (30.9 %)
Poorly differentiated	32 (33.0 %)
Signet ring cell/mucinous	15 (15.5 %)
T stage	
T1[a]	46 (47.4 %)
T2	13 (13.4 %)
T3	24 (24.7 %)
T4	14 (14.4 %)
Lymph node metastasis	
Positive	36 (37.1 %)
Negative	61 (62.9 %)
TNM stage	
I[a]	51 (52.6 %)
II	16 (16.5 %)
III	22 (22.7 %)
IV	8 (8.2 %)
Operation	
Subtotal gastrectomy	73 (75.3 %)
Total gastrectomy	20 (20.6 %)
Exploration	4 (4.1 %)
SUVmax (mean ± SD)	6.8±5.3
MTV[b] (cm^3, mean ± SD)	33.2±48.5

[a] One patient with Tis stage was included

[b] MTV was measured in clearly distinguishable 50 patients

Progression-Free Survival for Gastric Cancer

Of 97 patients, 15 (15.5 %) had disease progression during follow-up period. Among these 15 patients, five were pathologically confirmed and ten were verified by follow-up imaging study. Pathologically proven recurrent sites were gastric anastomotic sites (four patients with gastroduodenoscopy) and left supraclavicular lymph node (one patient with fine-needle aspiration cytology). Other recurrent sites verified by follow-up imaging study were peritoneum (four), lymph node (three), liver (two), lung (two), retroperitoneum (two), bone (one), brain (one) and adrenal gland (one). One patients had at least one or more recurrent sites (numbers of the patients were noted in parentheses). Mean follow-up duration of the all patients was 29.6±10.2 months. Optimal cutoff values determined by ROC curves analyses were SUVmax 5.74 and MTV 16.42 cm^3. Area

Table 2 Comparison of disease progression and non-progression groups

Characteristics	Disease progression	Non-progression	*p* value
Age (years, mean ± SD)	69.7±7.6	57.0±14.9	0.002
Sex			0.136
Male	3	49	
Female	12	33	
Pathologic type			0.470
Well differentiated	3	17	
Moderately differentiated	7	23	
Poorly differentiated	4	28	
Signet ring cell/mucinous	1	14	
T stage			0.001
T1	3	43[a]	
T2	2	11	
T3	3	21	
T4	7	7	
Lymph node metastasis			0.002
Positive	11	25	
Negative	4	57	
TNM stage			0.001
I	3	43[a]	
II	2	11	
III	3	21	
IV	7	7	
Operation			0.681
Subtotal gastrectomy	10	63	
Total gastrectomy	4	16	
Exploration	1	3	
SUVmax (mean ± SD)	10.8±6.6	5.7±4.8	0.001
MTV (cm^3, mean ± SD)	45.5±56.6[b]	27.4±44.6[c]	0.248

[a] One patient with Tis stage was included

[b, c] Results from 13 of 50 and 37 of 50 patients in MTV measurable group, respectively

Table 3 Comparison of MTV measurable and non-measurable groups

Characteristics	MTV measurable	Non-measurable	*p* value
Age (years, mean ± SD)	62.0±12.4	56.6±16.4	0.047
Sex			0.513
Male	33	28	
Female	17	19	
Pathologic type			0.013
Well differentiated	5	15	
Moderately differentiated	21	9	
Poorly differentiated	18	14	
Signet ring cell/mucinous	6	9	
T stage			<0.001
T1	10	36	
T2	8	5	
T3	19	5	
T4	13	1	
Lymph node metastasis			<0.001
Positive	29	7	
Negative	21	40	
TNM stage			<0.001
I	12	39 [a]	
II	11	5	
III	20	2	
IV	7	1	
Operation			0.091
Subtotal gastrectomy	33	40	
Total gastrectomy	14	6	
Exploration	3	1	
SUVmax (mean ± SD)	10.1±5.5	2.8±1.0	<0.001
MTV (cm^3, mean ± SD)	33.2±48.5	Not applicable	

[a] One patient with Tis stage was included

under the curve (AUC) of SUVmax and MTV were 0.76 (sensitivity 86.7 %, specificity 67.1 %) and 0.67 (sensitivity 69.2 %, specificity 64.9 %), respectively. Of 97 patients, 57 had SUVmax equal or below 5.74. The remained 40 patients had SUVmax over 5.74. Mean PFS of low SUVmax group (≤5.74) was 30.9±8.0 months and that of high SUVmax group (>5.74) was 24.3±13.6 months. The mean PFS of the low SUVmax group was significantly longer than that of the high SUVmax group (p =0.008). In univariate analysis, depth of tumor invasion (T1 vs T2, T3, T4), presence of lymph node metastasis, stage (I vs II, III, IV), and SUVmax (>5.74 vs ≤5.74) were significantly associated with recurrence. Figure 3 shows the PFS differences between respective groups. In multivariate analysis, high SUVmax (>5.74) was the only poor prognostic factor for PFS (p =0.002, HR 11.03, 95 % CI 2.48–49.05) (Table 4). In MTV measurable subgroup analysis (n =50), high MTV (>16.42) was the only poor prognostic factor for PFS (p =0.034, HR 3.59, 95 % CI 1.10–11.71) (Table 5).

Discussion

This study investigated the predictive value of PET parameters (SUVmax and MTV) determined from pretreatment F-18 FDG PET/CT scans for PFS in patients with gastric cancer. The results of this study show that SUVmax and MTV are significant independent prognostic factors for PFS in patients with gastric cancer. Previous studies have shown that F-18 FDG PET/CT has a low detection rate (47–96 %) for primary gastric cancer [22–24], especially for early gastric cancer (below 50 %) and pathologic subtype such

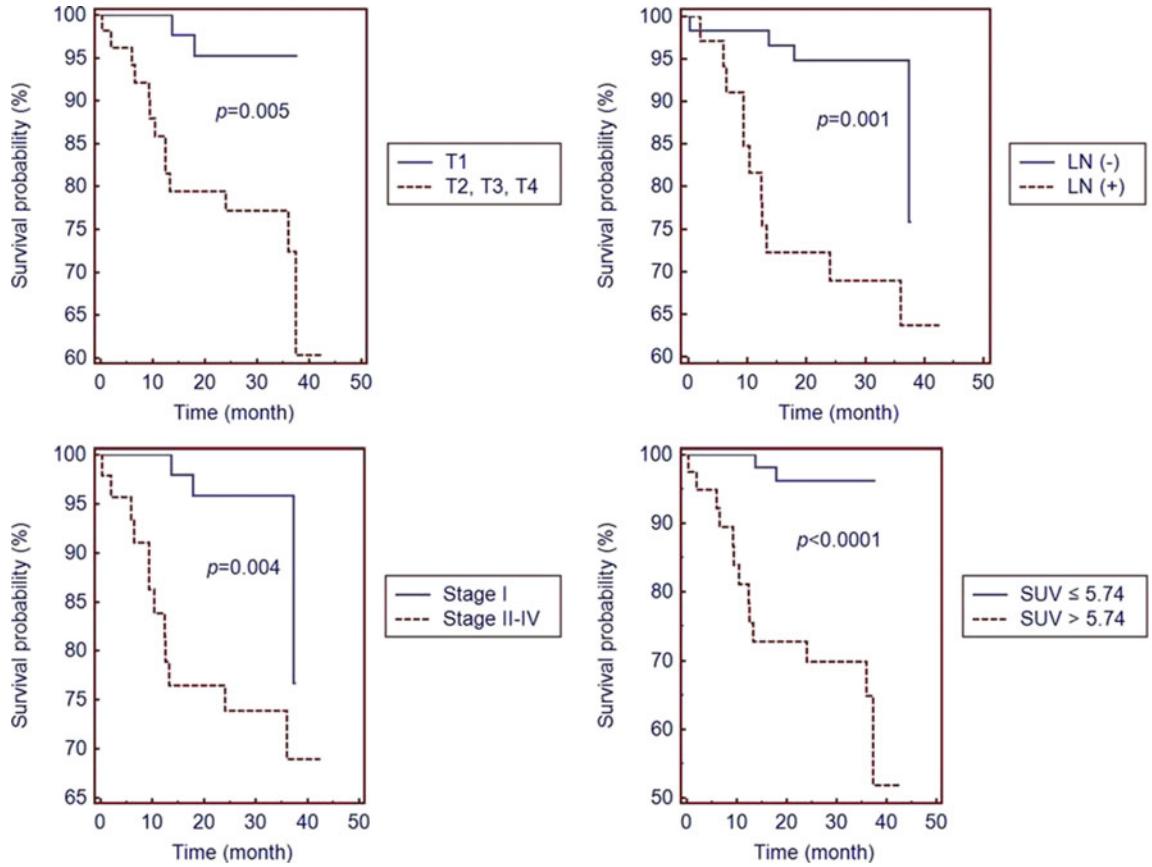

Fig. 3 Differences in progression-free survival (PFS) in patients with gastric cancer stratified by the depth of tumor invasion (T1 vs T2, T3, T4), absence or presence of lymph node metastasis [LN (−) vs LN (+)], stage (I vs II, III, IV) and SUVmax (>5.74 vs ≤5.74). In patients with T1, absence of lymph node metastasis [LN (−)], stage I and SUV ≤5.74 show significantly better survival than those with T2-T4, presence of lymph node metastasis (LN[+]), stage II-V

as signet ring cell carcinoma [25, 26]. Normally, FDG uptake of gastric wall can exceed SUV 2.5 and physiologic or benign conditions such as gastric mucosal inflammation can show diffuse or focal FDG uptake pattern [26–28]. In this study, SUVmax was measured from all primary lesion including non-detectable cases. Although SUVmax was measured based on a corresponding site seen on gastroduodenoscopy or contrast-enhanced CT, a considerable proportion of the primary lesions may not reflect the true metabolism of the tumor, especially in patients with T1 stage (47.4 %) or signet ring cell carcinoma. In the present study, we assumed that low FDG uptake in gastric wall can represent tumor status (T stage) and so included non-detectable cases in analysis. Fifteen cases with signet ring cell (11 cases) and mucinous

Table 4 Univariate and multivariate analyses for progression-free survival

Factors	Univariate ($n=97$)	Multivariate ($n=97$)	
	p value	HR (95 % CI)	p value
Depth of tumor invasion (T1 vs T2, T3, T4)	0.005		0.249
Lymph node metastasis (negative vs positive)	0.001		0.148
Stage (I vs II, III, IV)	0.004		0.349
SUVmax (≤5.74 vs >5.74)	<0.0001	11.03 (2.48–49.05)	0.002

HR hazard ratio, *CI* confidential interval

Table 5 Multivariate analysis in MTV measurable subgroup for progression free survival

Factors	Multivariate ($n=50$)	
	HR (95 % CI)	p value
Depth of tumor invasion (T1 vs T2, T3, T4)		0.266
Lymph node metastasis (negative vs positive)		0.138
Stage (I vs II, III, IV)		0.389
SUVmax (≤5.74 vs >5.74)		0.160
MTV (≤16.42 vs >16.42)	3.59 (1.10–11.71)	0.034

HR hazard ratio, [b] *CI* confidential interval

adenocarcinoma (four cases) are included (SUVmax, mean 4.0±2.2, range 1.59–9.09). A validation study by pathologic subtypes will be needed.

Several studies suggested that SUVmax of the primary lesion is a prognostic factor in advanced gastric cancer [29–31]. Hur et al. [29] reported that high SUV of the primary tumor (>5) and positive FDG uptake in local lymph nodes at PET/CT could predict non-curative resection in locally advanced gastric cancer. Chung et al. [30] reported that high FDG uptake of the primary tumor (>8) in patients with metastatic gastric adenocarcinoma is associated with poor overall survival. In a similar study, Park et al. [31] included more patients and undifferentiated histologic type carcinoma, and reported that a high SUVmax of stomach (≥6) showed the strongest association with clinical outcome. In the present study, the determined cutoff value SUVmax 5.74 is similar to previous studies.

The well-established prognostic factors for lower survival rate in patients with gastric cancer are the stage of gastric cancer, depth of tumor invasion and extent of LN metastasis [4, 5]. In 2012, Lee et al. [32] performed a retrospective study on 271 consecutive patients with gastric cancer who underwent F-18 FDG PET/CT and subsequent curative surgery, and found that only depth of invasion, positive F-18 FDG uptake and SUVmax had significance in the prediction of gastric cancer recurrence in multivariate analysis. The current study is similar in that SUVmax is a significant predictor of PFS. In addition, MTV, a volumetric PET parameter is used in this study because several studies suggest that MTV is an independent factor of prognosis in many types of malignancies [12–17]. Consequently MTV is the strongest factor for disease progression. To the best of my knowledge there is no previous study using MTV as prognostic factor in patients with gastric cancer. Use of MTV is limited since MTV could not be measured in almost half of patients (47/97, 48.5 %). Although we used an SUV-based automated contouring program to measure MTV, definite tumor segmentation was difficult in some small or infiltrating cancers due to low or diffuse FDG uptake. Some studies recommended to acquire additional PET image with gastric distension for differentiating primary or recurrent gastric malignancy from physiologic uptake [33, 34]. We did not use this method, but it will be helpful to find additional SUV measurable lesion or delineate more accurate tumor boundary by applying this method.

This study has some limitations. First, this was a retrospective study with variations in treatment protocols that may have biased prognostication. Therefore, a prospective validation study in a more homogenous group will be needed. Second, the number of patients was small, and the median follow-up duration was relatively short. Last, MTV was not applicable in all patients and we did not apply gastric distension method for more precise tumor segmentation.

Conclusion

Although there is a limitation in measuring MTV in all cases, we expect that SUVmax and MTV measured on the pretreatment F-18 FDG PET/CT can be used as useful prognostic factors for predicting PFS in patients with gastric cancer.

Conflict of Interest None.

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