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ORIGINAL ARTICLE

Correlation of Primary Tumor FDG Uptake with Histopathologic Features of Advanced Gastric Cancer

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Abstract
Purpose Histopathologic features could affect the FDG uptake of primary gastric cancer and detection rate on FDG PET/CT. The aim of this study was to evaluate the FDG uptake of primary gastric cancer by correlating it with the histopathologic features of the tumors.
Methods Fifty patients with locally advanced gastric adenocarcinoma who were referred for preoperative FDG-PET/CT scans were enrolled in this study. The detection rate of PET/CT and maximum standardized uptake values (SUV_{max}) of the primary tumor were compared using the WHO, Lauren, Ming and Borrmann classifications and tumor size and location.
Results In 45 of the 50 patients (90 %), the primary gastric tumors were detected by FDG PET/CT. On comparison using the WHO classification, the detection rate and SUV_{max} of the tubular type were significantly higher than those of the poorly cohesive type. On comparison using the Lauren and Ming classifications, the SUV_{max}s of the intestinal type and expanding type were significantly higher than those of the diffuse and infiltrative type, respectively. On comparison using the Borrmann classification and tumor size and location, there was no significant difference in the detection rate and SUV_{max} of primary gastric tumors.
Conclusion This study demonstrates that the poorly cohesive type according to the WHO classification, diffuse type according to the Lauren classification and infiltrative type according to the Ming classification have low FDG uptake in patients with locally advanced gastric carcinoma. Understanding the relationship between primary tumor FDG uptake and histopathologic features would be helpful in detecting the primary tumor by FDG PET/CT in patients with gastric cancer.

Keywords Gastric carcinoma · WHO classification · Lauren classification · Ming classification · PET/CT · FDG

Introduction

Gastric cancer is the second most frequent cause of cancer-related death worldwide [1]. It carries a relatively poor prognosis, with a 5-year survival rate of 30–40 % [2, 3]. Adenocarcinoma of the stomach constitutes 90–95 % of all gastric malignancies, and it is subclassified according to the WHO classification, Lauren classification, and Ming and Borrmann classifications [4–7]. Prognosis of patients with gastric cancer depends on a variety of factors including tumor histology and grade, stage of the disease, presence and extent of lymph node metastasis, and extent of lymph node dissection [1, 4]. With respect to the histopathologic subtypes, it has been shown that the intestinal type according to the Lauren classification, expanding type according to the Ming classification and well-differentiated tumors were associated with a more favorable prognosis in patients with advanced gastric cancer [4, 8–10]. Also, some studies have reported that patients with the poorly cohesive type according to the WHO classification and Borrmann type IV gastric cancer had a worse prognosis [11–13].

Positron emission tomography-computed tomography (PET/CT) with F-18 fluorodeoxyglucose (FDG) has been recognized as a useful diagnostic technique in clinical oncology. Many studies have reported a correlation among the degree of

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FDG uptake, histopathologic features and the prognosis in different kinds of cancers [14–16]. However, in patients with gastric cancer, there are controversial, limited data on whether the degree of FDG uptake is predictive of prognosis. Some studies reported a longer survival in patients with negative PET than in those with positive PET [17–19], whereas other studies could not determine any difference in the survival rate between patients with high and low FDG uptake [20]. Studies according to the histopathological subtypes seem to provide better information on the association between FDG uptake and patient prognosis because histopathologic features could affect the PET/CT visibility and FDG uptake of primary cancer lesions [21–23].

Several studies have reported a correlation between several histopathologic features and the FDG uptake of the primary tumor in patients with gastric cancer [18, 19, 23, 24]. However, previous studies were not sufficient to assess the correlation between several histopathologic features and FDG uptake of the primary tumor because the patients with early gastric cancer or those with only a few specific histopathologic subtypes of gastric cancer were included in these studies. Furthermore, none of the studies reported the FDG uptake characteristics of the primary tumor according to the WHO, Lauren, Ming and Borrmann histopathologic classifications in the same patients with advanced gastric cancer. Therefore, the aim of this study was to evaluate the FDG uptake of the primary tumor by correlating it with the histopathologic features in patients with advanced gastric cancer.

Materials and Methods

Patient Population

The patients with locally advanced gastric cancer (CT stage T3 and T4) who underwent FDG PET/CT and enhanced abdominal CT for preoperative staging workup between March 2008 and February 2009 were included. The patients who received special treatment before FDG PET/CT, including surgery by gastroscopy, radiotherapy and chemotherapy, were excluded. Forty-nine patients with pathologically proven advanced gastric adenocarcinomas were evaluated retrospectively in this study: 35 male and 15 female patients, mean age 61.8±11.1 years. Forty-three of these 50 patients were classified as T3 stage, and 7 patients were classified as T4 stage by enhanced abdominal CT. The ethics committee of our institution approved this study.

Histopathologic Classification

Assessment of histopathologic features was performed by an objective histopathologic examination. The resected specimens were fixed in formalin (10 %), embedded in paraffin and cut into slices (5 mm). The sections were stained with hematoxylin and eosin and used for the histopathologic classification. Appropriate tissue samples were acquired by endoscopic biopsy or surgical resection. Microscopically, the tubular, papillary, mucinous and poorly cohesive types were classified according to the WHO classification, the intestinal type and diffuse type were classified according to the Lauren classification, and the infiltrative type and expanding type were classified according to the Ming classification, as described previously [4, 5, 25, 26]. In the tubular type of adenocarcinoma, the tumors were classified into well, moderately and poorly differentiated types according to the histological differentiation. Macroscopically, Borrmann types I–IV were classified according to the Borrmann classification [27]. Tumor size was determined by measuring the largest diameter of the pathologic specimen.

PET/CT Imaging

In all of the patients, the blood glucose level was checked, and PET/CT examination was performed after a normal blood glucose level had been ensured. All of the patients fasted for at least 6 h prior to PET/CT examination. Patients received an intravenous injection of 7 MBq/kg of FDG and then rested for approximately 60 min before image acquisition. Image acquisition was performed with an integrated PET/CT device (Discovery STE; GE Medical Systems, Milwaukee, WI). CT scanning was first performed from the head to the pelvic floor with the following standardized protocol: 120 kV, 60–150 mA according to the patient's body weight, tube rotation time 0.8 s, pitch 1.75 and section thickness 3.75 mm, which corresponded to the PET image section thickness. All of the patients were allowed to perform shallow breathing during CT scanning, and no contrast material or water was administered. Immediately following CT acquisition, the PET data were acquired in the same anatomical locations with an acquisition time of 3 min per bed position in a three-dimensional mode. The CT data were used for attenuation correction, and PET images were reconstructed using an ordered-subset expectation maximum iterative reconstruction algorithm (20 subsets and two iterations).

Image Analysis

FDG PET/CT images were evaluated by two experienced observers blinded to the clinical data and histopathology results. Areas with focally increased FDG uptake compared to the surrounding tissue were read as positive. Diffusely increased FDG accumulation in the stomach, which was compatible with physiological gastric uptake, was read as negative. In case of differences in the interpretation, a consensus was reached between the two observers. Subsequently, all positive sites were compared with the known location of the tumor

according to the available morphological imaging data (endoscopy, computed tomography). The PET/CT result was classified as false positive if the location of the FDG accumulation was not consistent with the tumor site in the morphological studies and as false negative if no discrete FDG uptake was seen at the tumor site in the morphological studies. Detection rates were calculated for each histopathologic tumor type.

For quantitative analysis, circular regions of interest (ROIs) with a 1.5-cm diameter were placed in the area with the highest tumor activity. Maximum standardized uptake values (SUV_{max}) were calculated from each ROI as described previously [28]. When the primary gastric tumor was not detected by FDG PET/CT, the ROI was placed in the area that was consistent with the tumor site in the morphological studies. The mean SUV_{max} of the primary gastric tumor was compared among each group of the T stage, WHO classification, histologic grade, Lauren classification, Ming classification, Borrmann classification and tumor location.

Statistical Analysis

Fisher's exact test was performed to determine the differences in the detection rate among each subgroup. Receiver-operating characteristic analysis was used to determine the optimal cutoff values for the tumor size. The Mann-Whitney *U* test was used for comparisons of SUV_{max} among each group of the T stage, histologic grade, Lauren classification and Ming classification. The Kruskal-Wallis test was used for comparisons of the SUV_{max} among each group of tumor location, WHO classification and Borrmann classification. The correlation between the tumor size and SUV_{max} was evaluated by performing Pearson's correlation analysis. Quantitative values were expressed as mean ± SD. *P* values lower than 0.05 were considered statistically significant.

Results

Patient Characteristics

The patient characteristics are presented in Table 1. According to the WHO classification, 32 patients were classified into the tubular type, 1 into the mucinous type and 17 into the poorly cohesive type. Among the patients with a tubular type of adenocarcinoma, 6 were classified into the moderately differentiated type and 26 into the poorly differentiated type. According to the Lauren classification, 18 patients were classified into the intestinal type and 32 into the diffuse type. According to the Ming classification, 39 patients were classified into the infiltrative type and 11 into the expanding type. According to the Borrmann classification, 4 patients were classified into type I, 6 into type II, 35 into type III and 5 into type IV. The tumor size was 7.7±2.9 cm, and all primary tumors were >2.8 cm in size. There were no significant differences in the tumor size according to the WHO, Lauren, Ming and Borrmann classifications ($p>0.05$).

Table 1 Patient characteristics

Characteristic	Number of patients ($n=50$)
Age (years)	61.8±11.1
Sex	
Male	35
Female	15
T stage	
T3	43
T4	7
Tumor size (cm)	7.7±2.9 (2.8–16.0)
<6.5	17
>6.5	33
Tumor location	
Upper	6
Middle	20
Lower	24
WHO classification	
Papillary adenocarcinoma	0
Tubular adenocarcinoma	32
Well differentiated	0
Moderately differentiated	6
Poorly differentiated	26
Mucinous adenocarcinoma	1
Poorly cohesive carcinoma	17
Lauren classification	
Intestinal	18
Diffuse	32
Ming classification	
Infiltrative	39
Expanding	11
Borrmann classification	
Type I	4
Type II	6
Type III	35
Type IV	5

Detection Rate of FDG PET/CT

The overall detection rate of PET/CT for primary gastric cancer was 90.0 %. On comparison using the WHO classification, the detection rate of the tubular type was 100 %, of the mucinous type was 100 % and of the poorly cohesive type was 70.6 % (Fig. 1). The detection rate of the tubular type was significantly higher than that of the poorly cohesive type ($p=0.003$) (Table 2). On comparison using the Lauren

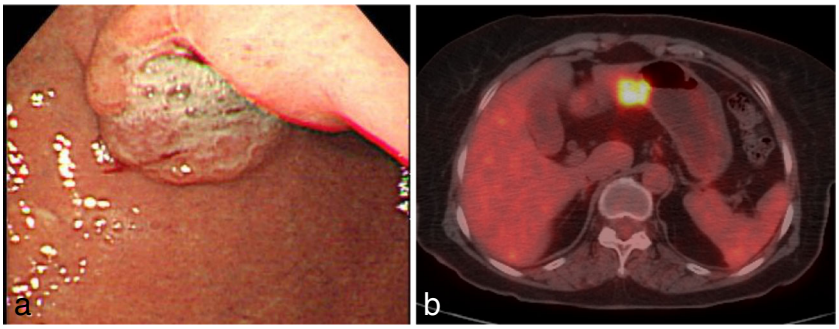

Fig. 1 A 72-year-old female with gastric cancer. Endoscopy (**a**) shows an ulcero-fungating mass in the gastric antrum. The tumor was categorized into the tubular type according to the WHO classification, into the intestinal type according to the Lauren classification, into the expanding type according to the Ming classification and into Borrmann type II. FDG PET/CT (**b**) shows a highly increased FDG uptake in the tumor, and the SUV_{max} was 11.5

classification, the detection rate of the intestinal type was higher than that of the diffuse type, but the difference was not significant (100 vs. 84.4 %, p=0.145) (Fig. 2). On comparison using the Ming classification, the detection rates were not significantly different between the infiltrative and expanding type (87.2 vs. 100 %, p=0.573). There were no significant differences in the detection rate of Borrmann type I–IV (100 vs. 83.3 % vs. 91.4 vs. 80 %, p=0.476) and in the detection rate according to the tumor locations (100 vs. 85 vs. 91.7 %, p=0.818). The detection rate of the T4 tumor was higher than that of the T3 tumor, but the difference was not significant (100 vs. 88.4 %, p=0.454). There was no significant difference in the detection rate of the tumors <6.5 cm and >6.5 cm (82.4 vs. 93.9 %, p=0.321).

Table 2 Detection rate of the primary gastric tumor according to the histopathologic classification

Classification	Detection rate (n)	p value	
WHO			
Tubular	100 %	(32/32)	0.003*
Mucinous	100 %	(1/1)	
Poorly cohesive	70.6 %	(12/17)	
Lauren			
Intestinal	100 %	(18/18)	0.145
Diffuse	84.4 %	(26/32)	
Ming			
Infiltrative	87.2 %	(33/39)	0.573
Expanding	100 %	(11/11)	
Borrmann			
Type I	100 %	(4/4)	0.476
Type II	83.3 %	(5/6)	
Type III	91.4 %	(32/35)	
Type IV	80 %	(4/5)	
T stage			
T3	88.4 %	(38/43)	0.454
T4	100 %	(7/7)	
Tumor size (cm)			
<6.5	82.4 %	(14/17)	0.321
>6.5	93.9 %	(31/33)	
Tumor location			
Upper	100 %	(6/6)	0.818
Middle	85 %	(17/20)	
Lower	91.7 %	(22/24)	

* p value for tubular adenocarcinoma vs. poorly cohesive carcinoma

FDG Uptake of the Primary Tumor

The SUV_{max} of primary gastric adenocarcinoma was 12.1±8.2. On comparison of the FDG uptake using the WHO classification, the SUV_{max} of the tubular type was 15.3±8.4, and the SUV_{max} of the poorly cohesive type was 6.5±3.7. The SUV_{max} of the tubular type was significantly higher than that of the poorly cohesive type (p<0.001) (Table 3). The SUV_{max} of the moderately differentiated type of tubular adenocarcinoma was higher than that of the poorly differentiated type of tubular adenocarcinoma, but not significantly so (18.3±7.6 vs. 14.6±8.5, p=0.308). On comparison of the FDG uptake using the Lauren classification, the SUV_{max} of the intestinal type was significantly higher than that of the diffuse type (15.7±9.0 vs. 10.1±7.1, p=0.013). On comparison of the FDG uptake using the Ming classification, the SUV_{max} of the expanding type was significantly higher than that of the infiltrative type (15.2±5.7 vs. 11.2±8.6, p=0.029). The SUV_{max} was not significantly different among the four types of the Borrmann classification (22.3±8.8 vs. 11.5±8.0 vs. 11.4±7.6 vs. 9.4±9.3, p=0.082). The SUV_{max} of the T4 tumor was higher than that of the T3 tumor, but the difference was not significant (16.1±8.5 vs. 11.4±8.1, p=0.164). There was no significant correlation between the tumor size and SUV_{max} (r=0.066, p=0.651). There were no significant differences in the SUV_{max} of the tumors <6.5 cm and >6.5 cm (9.3±6.2 vs. 13.5±8.8, p=0.084) and in the SUV_{max} of the tumors with different locations (p=0.369).

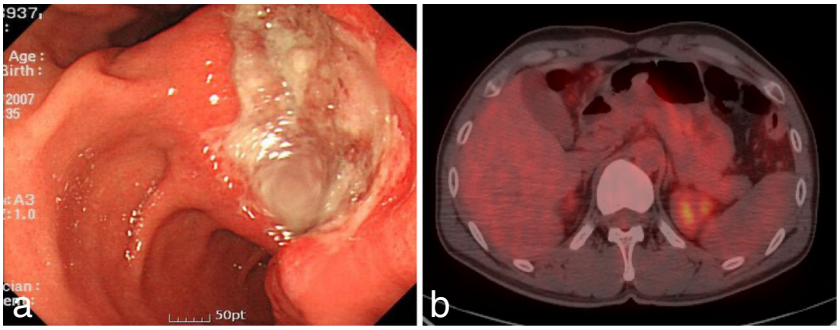

Fig. 2 A 34-year-old male with stomach cancer. Endoscopy (**a**) shows an ulcero-infiltrating mass in the gastric antrum. The tumor was categorized into poorly cohesive, diffuse, infiltrative and type III according to the WHO, Lauren, Ming and Borrmann classifications, respectively. FDG PET/CT (**b**) shows no discernible FDG uptake in the stomach

Discussion

The present study showed that FDG uptake of primary gastric tumors is correlated with various histopathologic features according to the WHO, Lauren and Ming classifications. On comparison using the WHO classification, the FDG uptake of the tubular type was significantly higher than that of the poorly cohesive type. Using the Lauren classification, the FDG uptake of the intestinal type was significantly higher than that of the diffuse type. Using the Ming classification, the FDG uptake of the expanding type was significantly higher than that of the infiltrative type. Knowledge of the correlation between the degree of FDG uptake and histopathologic features is important, because histopathologic features could affect the PET/CT visibility of primary cancer lesions [21–23]. To the best of our knowledge, this is the first study to assess the FDG uptake characteristics of the primary tumor according to the WHO, Lauren, Ming and Borrmann histopathologic classifications in the same patients with advanced gastric cancer.

Table 3 FDG uptake of the primary gastric tumor according to the histopathologic classification

Classification	SUVmax	*p* value
WHO		
Tubular	15.3±8.4	< 0.001*
Mucinous	5.2	
Poorly cohesive	6.5±3.7	
Histologic grade		
Moderately differentiated	18.3±7.6	0.308
Poorly differentiated	14.6±8.5	
Lauren		
Intestinal	15.7±9.0	0.013
Diffuse	10.1±7.1	
Ming		
Infiltrative	11.2±8.6	0.029
Expanding	15.2±5.7	
Borrmann		
Type I	22.3±8.8	0.082
Type II	11.5±8.0	
Type III	11.4±7.6	
Type IV	9.4±9.3	
T stage		
T3	11.4±8.1	0.164
T4	16.1±8.5	
Tumor size (cm)		
<6.5	9.3±6.2	0.084
>6.5	13.5±8.8	
Tumor location		
Upper	16.5±10.6	0.369
Middle	11.0±7.9	
Lower	12.0±7.8	

* *p* value for tubular adenocarcinoma vs. poorly cohesive carcinoma

The present study showed that the FDG uptake of the primary gastric tumor was correlated with various histopathologic features according to the WHO, Lauren and Ming classifications. On comparison using the WHO classification, the FDG uptake of the tubular type was significantly higher than that of the poorly cohesive type. Using the Lauren classification, the FDG uptake of the intestinal type was significantly higher than that of the diffuse type. Using the Ming classification, the FDG uptake of the expanding type was significantly higher than that of the infiltrative type. Knowledge of the correlation between the degree of FDG uptake and histopathologic features is important, because histopathologic features could affect the PET/CT visibility of primary cancer lesions [21–23]. To the best of our knowledge, this is the first study to assess the FDG uptake characteristics of the primary tumor according to the WHO, Lauren, Ming and Borrmann histopathologic classifications in the same patients with advanced gastric cancer.

Several studies have reported lower FDG uptake in the diffuse type than in the intestinal type according to the Lauren classification [20, 29, 30]. Although a few studies have reported no significant differences because of different study populations compared with those in the present study, the FDG uptake and detection rate of the diffuse type were lower than those of the intestinal type [31, 32]. In accordance with the previous studies, the present study showed that the diffuse type had lower FDG uptake than the intestinal type. Also, the present study showed that the infiltrative type had lower FDG uptake than the expanding type according to the Ming classification. None of the studies have reported the degree of FDG uptake according to the Ming classification. As a rationale for low FDG uptake of the diffuse and infiltrative type, it has been postulated that the high number of signet ring cells in the tumors with diffuse type and infiltrative type lead to a reduced FDG concentration in the tumor [4, 33]. Another reason could be the lack of expression of the glucose transporter Glut-1 on the cell membrane of most diffuse types of gastric carcinoma [34].

Several studies have reported that the histopathologic type is a prognostic factor in gastric cancer. According to the Lauren classification, the diffuse type has a worse prognosis than the intestinal type [8, 9]. According to the Ming

classification, the infiltrative type has a worse prognosis than the expansive type [4, 9]. In addition to the histopathologic type, FDG PET/CT plays a significant role in predicting the prognosis of many kinds of cancers, and several studies have shown that a higher degree of FDG uptake is associated with worse prognosis [14, 15]. In gastric cancer, there are controversies about whether the FDG uptake is a prognostic factor. Chung et al. [17] reported that high FDG uptake of the primary tumor in patients with metastatic gastric adenocarcinoma is associated with poor overall survival. Park et al. [35] demonstrated that progression-free survival was significantly longer in patients with lower FDG uptake of the primary tumor than in those with higher FDG uptake and suggested that pretreatment metabolic activity is a useful prognostic marker in patients with advanced gastric cancer undergoing palliative chemotherapy. However, Vallbohmer et al. [36, 37] reported that no significant correlation between the FDG uptake of the primary tumor and prognosis was noted in patients with gastric cancer following multimodality treatment. Stahl et al. found that the survival rate was not significantly different in patients with detectable tumors on FDG PET and patients with non-detectable tumors and suggested that advanced gastric cancer with a poor prognosis may show low FDG uptake because of special histopathological characteristics. This discrepancy in the prognostic value of the FDG uptake may result from the study population including different histopathologic types of gastric cancer, because both the diffuse and infiltrative types of gastric adenocarcinomas have a poor prognosis but show lower FDG uptake than the other histopathologic subtypes. In this respect, Pak et al. [18] reported that in advanced signet ring cell carcinoma, higher FDG uptake of the primary tumor is associated with a more advanced stage and indicates more aggressive tumor biology. Lee et al. [19] performed subgroup analysis according to the WHO classification and demonstrated that patients with negative FDG uptake had a significantly higher recurrence-free survival rate than patients with positive FDG uptake in the tubular adenocarcinoma and papillary adenocarcinoma groups. Studies according to the specific histopathologic subtypes seem to provide better information on the association between FDG uptake and patient prognosis.

The WHO classification recognizes four major histologic patterns of gastric cancers: tubular, papillary, mucinous and poorly cohesive carcinoma [5]. There are controversial, limited data on whether the WHO classification has a prognostic value. A few studies reported that poorly cohesive carcinoma had a worse prognosis than the other types according to the WHO classification [9], but other studies reported that the WHO classification did not exert a prognostic effect on the multivariate analysis [4, 19]. Although the WHO classification may not be meaningful with respect to the prognosis, knowledge of the relationship between the primary tumor FDG uptake and histopathologic subtypes according to the WHO classification is important in patients with gastric cancer, because a low detection rate and FDG uptake have been reported in the poorly cohesive type of gastric carcinoma compared to the tubular type [24, 38, 39]. The reason for the low detection rate and FDG uptake in the poorly cohesive type is that the primary tumor is correlated with the mucin content within the tumor and is positively correlated with tumor cellularity [23, 40], and poorly cohesive carcinoma is often composed of a mixture of signet ring cells and non-signet ring cells with a high mucinous pool [5, 41]. In accordance with previous studies, the detection rate and FDG uptake in the tubular type were significantly higher than those in the poorly cohesive type in the present study. With respect to tumor differentiation, in contrast to various other tumor entities [42, 43], several studies have revealed that the poorly differentiated type of gastric adenocarcinoma has a lower FDG uptake than the well-differentiated type [20, 24, 29]. In accordance with previous research, the present study showed that the FDG uptake of moderately differentiated adenocarcinoma was higher than that of poorly differentiated adenocarcinoma, although not significantly so. It appears that other factors such as the mucin content within the tumor or tumor cellularity affect the degree of FDG uptake in poorly differentiated adenocarcinomas.

The tumor size is also important in the detection of the primary tumor by FDG PET/CT in patients with gastric cancer. Tian et al. [29] found a positive correlation between the FDG uptake and tumor size in early and advanced gastric adenocarcinomas. Mukai et al. [32] reported that the detection rate of small-sized tumors was significantly lower than that of large-sized tumors. In these studies, the patients with early gastric cancer who had small-sized tumors were included for the evaluation of FDG uptake. However, in contrast with previous studies, the present one revealed no significant correlation between the tumor size and FDG uptake and no significant difference in the detection rate according to the tumor size. The explanation for our result is that all primary tumors in the present study were >2.8 cm in size and the partial volume averaging effect would be minimal for primary tumor FDG uptake. It has generally been accepted that FDG uptake is underestimated because of the partial volume averaging effect of small-sized tumors <2 cm on PET/CT [44]. Kim et al. [31] also reported a poor correlation between tumor size and FDG uptake in patients with advanced gastric cancer.

There are some limitations to the present study. There are controversial, limited data on whether the Borrmann classification affects the FDG uptake and detectability of the primary gastric tumor [18, 20, 24, 29]. Pak et al. [18] and Stahl et al. [20] reported that the Borrmann classification was not significantly related to the FDG uptake of the primary gastric tumor and tumor detectability. However, Yun et al. [24] reported that Borrmann type I had higher FDG uptake than the other three types. In the present study, there were no differences among Borrmann types I–IV. This may be due to the limited number

of patients included in the present study. Another limitation is the lack of survival analysis for evaluating the prognostic values of the FDG uptake and histopathologic types. The analysis of survival data in patients with specific histopathologic subtypes seems to provide better information on the association between FDG uptake and patient prognosis. A large randomized controlled study is needed for further evaluation of this issue.

Conclusion

This study demonstrates that the poorly cohesive type according to the WHO classification, diffuse type according to the Lauren classification and infiltrative type according to the Ming classification have low FDG uptake in patients with locally advanced gastric carcinoma. Understanding the relationship between the primary tumor FDG uptake and histopathologic features would be helpful in detecting the primary tumor by FDG PET/CT in patients with gastric cancer. The analysis of survival data in patients with specific histopathologic subtypes seems to provide better information on the association between FDG uptake and patient prognosis. A large randomized controlled study is needed for further evaluation of this issue.

Disclosure

Conflict of Interest Hae Won Kim, Kyoung Sook Won, Bong-Il Song and Yu Na Kang declare that they have no conflicts of interest.

Ethical Statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was waived by the IRB considering the retrospective nature of the current analysis.

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