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Diagnostic accuracy of ^{18}F-FDG PET/CT for detecting synchronous advanced colorectal neoplasia in patients with gastric cancer

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Abstract

Preoperative screening for synchronous colorectal neoplasia (CRN) has been recommended in patients with gastric cancer because patients with gastric cancer are at increased risk for synchronous CRN. The aim of this study was to investigate the diagnostic accuracy of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) for detecting synchronous advanced CRN in patients with gastric cancer.

A total of 256 patients who underwent colonoscopy and ^{18}F-FDG PET/CT for preoperative staging were enrolled in this study. The diagnosis of focal colonic ^{18}F-FDG uptake on ^{18}F-FDG PET/CT image was made based on histopathologic results from the colonoscopic biopsy. The ^{18}F-FDG PET/CT result was considered as true positive for advanced CRN when focal ^{18}F-FDG uptake matched colorectal carcinoma or adenoma with high-grade dysplasia in the same location on colonoscopy.

Synchronous advanced CRN was detected in 21 of the 256 patients (4.7%). Sensitivity, specificity, and accuracy of ^{18}F-FDG PET/CT were 76.2%, 96.2%, and 94.5%. The size of CRN with a true positive result was significantly larger than that with a false negative result.

^{18}F-FDG PET/CT demonstrated high diagnostic accuracy for detecting synchronous advanced CRN in patients with gastric cancer. Colonoscopy is recommended as the next diagnostic step for further evaluation of a positive ^{18}F-FDG PET/CT result in patients with gastric cancer.

Abbreviations: ^{18}F-FDG = ^{18}F-fluorodeoxyglucose, CRC = colorectal carcinoma, CRN = colorectal neoplasia, HGD = high-grade dysplasia, LGD = low-grade dysplasia, PET/CT = positron emission tomography/computed tomography, SUV_{max} = maximum standardized uptake value.

Keywords: gastric cancer, positron emission tomography, sensitivity, specificity, synchronous colorectal cancer

1. Introduction

Gastric cancer is the fifth common form of cancer and the third leading cause of cancer-related deaths worldwide.[1] Increased incidence of early gastric cancer and advances in cancer treatment, including surgical skills and adjuvant and neoadjuvant therapy, have improved the survival rate of patients with gastric cancer. Patients with gastric cancer have a risk of developing second primary cancer, and colorectal carcinoma (CRC) is the most common neoplasm associated with gastric cancer.[2,3] The improved prognosis for gastric cancer has also led to an increased incidence of synchronous CRC, which negatively influences the prognosis of patients with gastric cancer.[4–6] Thus, early identification of synchronous cancer may have an impact on patient management and outcome.[7,8]

^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) is a noninvasive imaging modality that reflects glucose metabolism and has been widely accepted for diagnosing, staging, restaging, and evaluating the therapeutic response to gastric cancer[9,10] and CRC.[11,12]^{18}F-FDG PET/CT is also effective for screening synchronous cancer in patients with several different kinds of cancer,[13] because incidental ^{18}F-FDG accumulation reflects additional pathology unrelated to the primary cancer for which the patient was originally referred for PET/CT.[14] Several studies have reported that incidental colorectal ^{18}F-FDG-avid lesions are associated with colorectal neoplasia (CRN) and that ^{18}F-FDG PET/CT is

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Informed consent: The institutional review board of Dongsan Medical Center granted exempt status for this retrospective study and waived the need for informed consent.

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effective for detecting synchronous CRN in patients with different types of cancer, including lung, esophageal, pancreatic, and breast cancers.[12,15,16] However, the diagnostic value of ^{18}F-FDG PET/CT for detecting synchronous CRN in patients with gastric cancer has not been reported. The purpose of this study was to investigate the diagnostic accuracy of ^{18}F-FDG PET/CT for detecting synchronous advanced CRN in patients with gastric cancer.

2. Materials and methods

2.1. Patients

The medical records of 1750 consecutive patients with gastric cancer, who underwent ^{18}F-FDG PET/CT for preoperative staging between May 2008 and July 2014 at Dongsan Medical Center, were reviewed. The exclusion criteria were applied as follows: patients who did not undergo colonoscopy, patients with more than 1 month between ^{18}F-FDG PET/CT and colonoscopy, patients who had colorectal lesions removed during colonoscopy before ^{18}F-FDG PET/CT, patients with nonepithelial or metastatic tumors in the colon, and patients with a history of other malignancies including CRC or operations of the colon. Demographic characteristics and histopathological data of the patients were obtained retrospectively. The institutional review board of Dongsan Medical Center approved this study.

2.2. Colonoscopy and histopathology

Colonoscopy was performed within 1 month before or after ^{18}F-FDG PET/CT by experienced endoscopists. All patients prepared their bowel with 4 L of polyethylene glycol solution. Conscious sedation was achieved with intravenous administration of 0.1 mg/kg midazolam and 50 mg meperidine. The procedure was mainly performed with a single-channel lower gastrointestinal endoscope (CF Q260AI; Olympus Optical Co., Tokyo, Japan).

Biopsy, polypectomy, or endoscopic mucosal resection was performed as indicated. All endoscopic specimens were evaluated by a single experienced pathologist who was completely blinded to the endoscopic diagnosis. The histopathological diagnosis was based on World Health Organization criteria.[17] Adenomas were classified into adenomas with high-grade dysplasia (HGD) and adenomas with low-grade dysplasia (LGD), depending on the degree of glandular or villous complexity, extent of nuclear stratification, and severity of abnormal nuclear morphology. An advanced CRN was defined as an adenoma with a diameter of 10 mm or more, a villous adenoma (i.e., at least 25% villous), an adenoma with HGD, or CRC.[18,19]

2.3. ^{18}F-FDG PET/CT

^{18}F-FDG PET/CT was performed using 2 different PET/CT systems (Discovery STE-16, GE Healthcare, Milwaukee, WI, and Biograph mCT-64, Siemens Healthcare, Knoxville, TN). The patients were required to fast for >6 hours before the scan, and blood glucose level was checked to confirm that the level was <180 mg/dL before injecting the ^{18}F-FDG. All diabetic patients were asked to stop taking their antihyperglycemic drugs 12 hours before the scan. Patients received intravenous administration of 4.0 MBq/kg (Biograph mCT-64) and 7.0 MBq/kg (Discovery STE-16) ^{18}F-FDG according to the PET/CT system. Patients were encouraged to rest during the ^{18}F-FDG uptake period. Images were acquired 60 minutes after the ^{18}F-FDG injection. A noncontrast CT scan was obtained for attenuation correction and localization. Immediately after the CT scan, PET images were acquired from the base of the skull or top of the brain to the proximal thigh. The PET images were reconstructed iteratively using ordered subset expectation maximization. Attenuation correction of PET images was performed using attenuation data from CT. All fusion images were viewed using dedicated workstations for each PET/CT system.

All ^{18}F-FDG PET/CT images were interpreted by a board-certified nuclear medicine physician with appropriate training and experience. Discernable foci of increased ^{18}F-FDG colon uptake that exceeded that of the normal hepatic parenchyma were regarded as positive findings. When ^{18}F-FDG uptake in the colon was segmental or diffuse pattern without focal ^{18}F-FDG uptake, it was regarded as physiologic bowel uptake. ^{18}F-FDG uptake intensity was measured as the maximum standardized uptake value (SUV_{max}) using the software provided at the workstations for each scanner. Colonoscopy was used as gold standard to confirm the results of ^{18}F-FDG PET/CT. The final diagnosis of focal colon ^{18}F-FDG uptake was made based on the histopathologic results from the colonoscopic biopsy. The ^{18}F-FDG PET/CT result was considered as true positive when focal ^{18}F-FDG uptake matched CRC or adenoma with HGD in the same location on colonoscopy.

2.4. Statistical analysis

Numerical data (age and blood glucose level) are expressed as means ± standard deviation and were compared using Student *t* test. The clinicopathological features including sex, gastric cancer stage, histopathological type, or primary gastric cancer location were compared using the 2-tailed chi-square and Fisher exact tests. The clinicopathological features were analyzed by univariate logistic regression in order to identify risk factors for synchronous CRN. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 256 patients (165 men and 91 women; mean age, 62.8 ± 12.0 years) were enrolled in this study (Fig. 1). Table 1

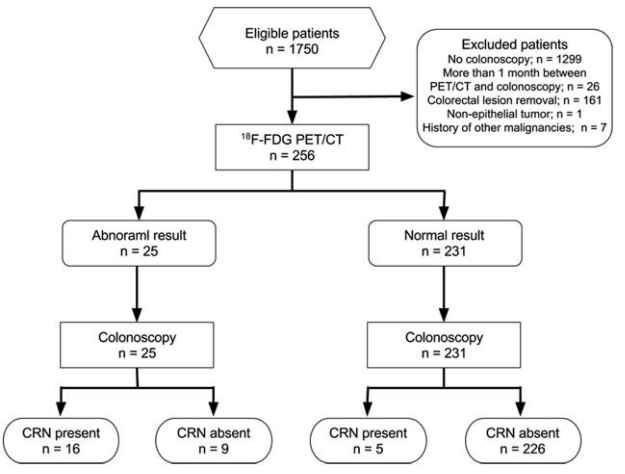

Figure 1. STARD flow diagram of study population. CRN = colorectal neoplasia, STARD = standards for reporting of diagnostic accuracy.

Table 1

Characteristics of the patients with gastric cancer.

Characteristics	Numbers of patients
Age, y	62.8 ± 12.0 (ranged 29–86)
Sex	
Male	165
Female	91
Blood glucose level, mg/dL	98.6 ± 16.2 (ranged 65–172)
Stage of gastric cancer*	
I	136
II	38
III	51
IV	31
Histopathology of gastric cancer	
Well/moderate differentiated adenocarcinoma	114
Poorly differentiated adenocarcinoma	88
Poorly cohesive carcinoma	54
Location of gastric cancer	
Upper third	41
Middle third	89
Lower third	126
Histopathology of colorectal lesion	
Colorectal carcinoma	12
Adenoma with HGD	9
Adenoma with LGD	73
Hyperplastic polyp	31
Inflammatory lesion	12
Location of advanced CRN	
Ascending colon	5
Transverse colon	3
Descending colon	2
Sigmoid colon	8
Rectum	3

CRN = colorectal neoplasia, HGD = high-grade dysplasia, LGD = low-grade dysplasia.
* American Joint Committee on Cancer (AJCC) seventh edition.

summarizes the patient characteristics. Advanced CRN was detected in 21 (8.2%) of the 256 patients. In 21 patients with advanced CRN, 12 patients (4.7%) had CRC and 9 patients (3.5%) had adenoma with HGD. Adenoma with LGD was detected in 73 (28.5%) of the 256 patients with gastric cancer. Thirty-one patients (12.1%) had hyperplastic polyps, and 12 patients (4.7%) had inflammatory lesions. The mean time interval between ^{18}F-FDG PET/CT and colonoscopy was 5.6 ± 5.3 days (range, 0–22 days).

Mean size of advanced CRN was 3.4 ± 3.6 cm (range; 0.5–13 cm). Patients with advanced CRN were significantly older than that of patients without advanced CRN (70.6 ± 9.3 vs 62.2 ± 12.0 years, $P = 0.005$). The prevalence rates of advanced CRN tended to be higher in male patients than those in female patients (10.3% vs 3.3%, $P = 0.052$). No differences in prevalence of advanced CRN were observed according to stage, histopathological type of gastric cancer, or primary gastric cancer location, respectively ($P = 0.433$, 0.382, and 0.939). Logistic regression analysis showed that age and sex were associated with prevalence of advanced CRN in patients with gastric cancer (Table 2).

3.2. Diagnostic value of ^{18}F-FDG PET/CT

Table 3 summarizes the diagnostic value of ^{18}F-FDG PET/CT. Sensitivity, specificity, and accuracy of ^{18}F-FDG PET/CT were 83.3%, 93.9%, and 93.4% for detecting CRC and were 76.2%, 96.2%, and 94.5% for detecting advanced CRN (Fig. 2). Nine patients with focal colonic ^{18}F-FDG uptake had false positive ^{18}F-FDG PET/CT results for advanced CRN. Focal colonic ^{18}F-FDG uptake in 8 patients with false positive result was considered as physiologic bowel uptake and 1 patient with false positive result had an inflammatory lesion of the colon.

The size of advanced CRN with true positive results was significantly larger than that with false negative results ($P = 0.006$). There were no significant differences in age, sex, and blood glucose level between patients with true positive and false negative results (Table 4). The SUV_{max} of true positive foci for advanced CRN higher than that of false positive foci on ^{18}F-FDG PET/CT, but it was not significant (12.9 ± 8.7 vs 7.8 ± 2.7, $P = 0.116$). The SUV_{max} were not significantly different between CRC and adenoma with HGD (12.0 ± 5.0 vs 14.7 ± 14.3, $P = 0.700$).

4. Discussion

Several studies have reported a high prevalence of synchronous CRN in patients with gastric cancer.[6–8] Regarding the adenoma–adenocarcinoma sequence in the colorectum, a

Table 2

Logistic regression analysis of risk factors for synchronous advanced CRN in patients with gastric cancer.

Variable	B (SE)	P	OR* (95% CI)†
Age	0.07 (0.03)	0.007	1.08 (1.02–1.14)
Sex (male)	1.50 (0.67)	0.025	4.50 (1.21–16.77)
Stage of gastric cancer			
I		0.136	1
II	1.59 (1.08)	0.141	4.89 (0.59–40.40)
III	−0.01 (1.46)	0.995	0.99 (0.06–17.45)
IV	0.40 (1.28	0.754	1.49 (0.12–18.23)
Histopathology of gastric cancer			
Well/moderate differentiated		0.789	1
Poorly differentiated	−0.02 (0.63)	0.980	0.99 (0.29–3.36)
Poorly cohesive	−0.40 (0.71)	0.574	0.67 (0.17–2.68)
Location of gastric cancer			
Upper third		0.844	1
Middle third	−0.32 (0.72)	0.654	0.73 (0.18–2.96)
Lower third	−0.27 (0.56)	0.631	0.76 (0.26–2.29)

SE = standard error.
* OR = odds ratio.
† CI = confidence interval.

Table 3

Diagnostic value of ^{18}F-FDG PET/CT for detecting advanced CRN and colorectal carcinoma.

	Sensitivity	Specificity	Accuracy	PPV*	NPV†
Colorectal carcinoma	83.3% (10/12)	93.9% (229/244)	93.4% (239/256)	40.0% (10/25)	99.1% (229/231)
Advanced CRN‡	76.2% (16/21)	96.2% (226/235)	94.5% (242/256)	64.0% (16/25)	97.8% (226/231)

* PPV = positive predictive value.
† NPV = negative predictive value.
‡ CRN = colorectal neoplasia.

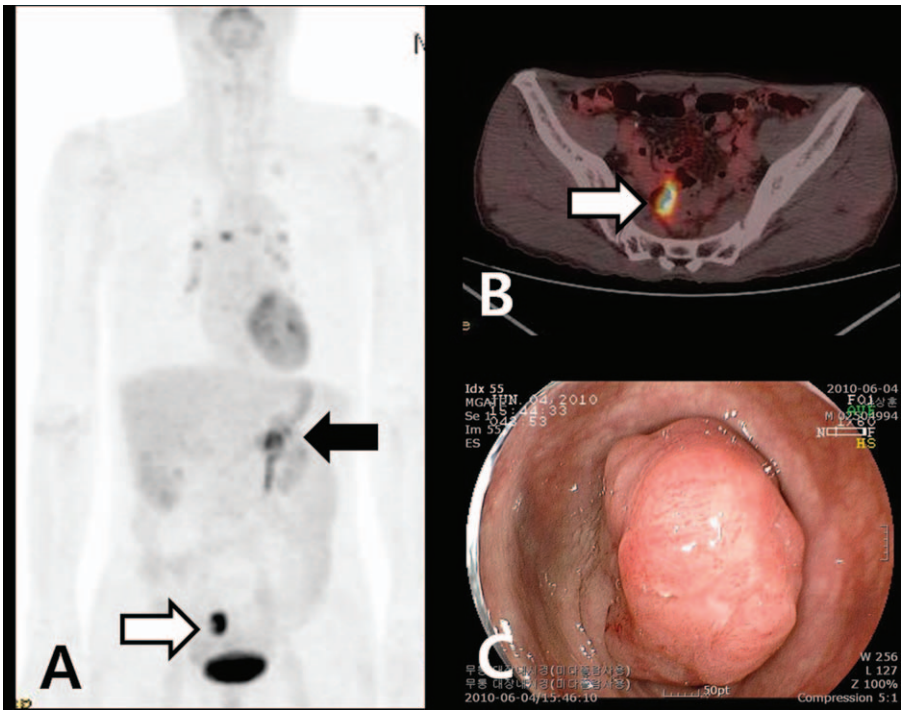

Figure 2. A 68-year-old man with gastric cancer. Preoperative maximum-intensity-projection (A) and transaxial (B) ^{18}F-FDG PET/CT images show 2 foci of increased ^{18}F-FDG uptake in the gastric body (arrow) and sigmoid colon (open arrow). Colonoscopy (C) reveals a 3.2-cm-sized polypoid mass in the sigmoid colon, which was histopathologically diagnosed as colorectal carcinoma.

synchronous CRN should be screened and eliminated in the preoperative workup in selected high-risk patients. Although several studies have reported that incidental colonic foci of ^{18}F-FDG uptake are related with CRN,[12,15,16] the diagnostic value of ^{18}F-FDG PET/CT for detecting synchronous CRN has not been reported in patients with gastric cancer. We revealed that ^{18}F-FDG PET/CT had high diagnostic value for detecting synchronous advanced CRN in patients with gastric cancer. Sensitivity, specificity, and accuracy of ^{18}F-FDG PET/CT were 76.2%, 96.2%, and 94.5% for detecting advanced CRN.

Table 4

Comparison of characteristics between patients with true positive and false negative ^{18}F-FDG PET/CT results for detecting advanced CRN.

	True positive (%)	False negative (%)	*P*
Age, y	71.5±8.5	67.0±11.2	0.357
Sex (male/female)	13/3	4/1	0.134
Blood glucose level, mg/dL	99.5±14.7	92.8±11.1	0.369
Tumor size, cm	4.2±3.8	1.0±4.6	0.006

^{18}F-FDG PET/CT has high sensitivity (94%–100%) for detecting primary tumors of the colon.[11,20–22] Kantorova et al[11] reported that ^{18}F-FDG PET/CT detected 35 of 37 (94.6%) CRC lesions, and this was the highest sensitivity compared with that of other modalities, including conventional CT and ultrasonography. The sensitivity of ^{18}F-FDG PET/CT to detect colonic adenoma is correlated with size and grade of dysplasia.[12,23,24] Previous reports have shown that the rate of visualizing colorectal polyps on PET/CT image increases with polyp size, and histological grade of colonic adenoma was the most important independent factor affecting detectability by ^{18}F-FDG PET/CT.[12,24] Nonpremalignant lesions, such as hyperplastic polyps, do not tend to accumulate ^{18}F-FDG.[22] In this study, ^{18}F-FDG PET/CT missed relatively small CRN lesions in 5 of 21 patients with advanced CRN. The sizes of true positive CRN were significantly larger than that of false negative CRN. Possible reason for a false negative ^{18}F-FDG PET/CT result could be a limitation in the current subcentimeter spatial resolution of PET scanners relative to the small size of the CRN and the partial volume effects, as nonlinear partial volume effects lead to underestimates of radioactivity concentration.[26,27] Also,

physiological ^{18}F-FDG uptake in the colon could obscure pathologic ^{18}F-FDG uptake of advanced CRN.[28]

Varying physiological ^{18}F-FDG uptake and localization patterns in the colon have been described previously.[16,25] The physiological accumulation of ^{18}F-FDG in the colon could create a false positive ^{18}F-FDG PET/CT result.[28] The physiologic ^{18}F-FDG uptake in the colon has been attributed to uptake by smooth muscles, swallowed secretions, or excretion and intraluminal concentrations of ^{18}F-FDG.[29] The intensity of ^{18}F-FDG uptake in terms of SUV_{max} does not discriminate between malignant, premalignant, and benign lesions as does physiologic uptake.[16] In the present study, 9 patients (3.5%) had false positive results for advanced CRN, and no significant difference in SUV_{max} was noted between the true positive and false positive foci. Despite possible false positive results, focal colonic ^{18}F-FDG uptake has a high probability (70%–80%) of showing corresponding abnormal histopathological findings.[15,16,25] Treglia et al[25] reported that incidental colonic uptake of ^{18}F-FDG was detected in 64 of 6000 patients (1.1%) who underwent an ^{18}F-FDG PET/CT scan for diagnosis, staging, and restaging of different types of cancer, and that 65% of those patients had advanced CRN. In accordance with previous studies, we revealed a positive predictive value of 64% for advanced CRN. Colonoscopy is recommended as the next diagnostic step for further evaluation of an ^{18}F-FDG PET/CT positive result.

Several studies have reported that patients with gastric cancer have an increased risk of synchronous and metachronous CRC.[6–8] A meta-analysis of 24 case–control studies revealed that patients with gastric neoplasms have higher risk (odds ratio, 1.72; 95% confidence interval, 1.42–2.09) of CRN compared with their controls.[30] The prevalence of CRC in asymptomatic adult in the United States is 0.6% to 1.6%, and the prevalence of advanced CRN is 2.5% to 3.1%.[18,19] The prevalence of CRC in asymptomatic adults in Korea is 0.2%, and the prevalence of advanced CRN is 3.7%.[31] Previous studies with gastric cancer patients revealed that the prevalence of synchronous CRC is 2.0% to 4.8% and the prevalence of advanced CRN is 3.0% to 6.0%.[8,30,32,33] In agreement with these studies, we demonstrated relatively high prevalence rates of CRC and advanced CRN of 4.7% and 8.2%, respectively, in patients with gastric cancer. It has been reported that older age and male sex are associated with an increased risk of CRC.[6,8,19,31] Present study also revealed that risk factors for synchronous advanced CRN were older age and male sex in patients with gastric cancer.

The present study had some limitations. Patients with diabetes taking metformin were included in the present study. Metformin is an antihyperglycemic drug that is widely used to treat patients with type 2 diabetes mellitus, but can significantly increase ^{18}F-FDG uptake in the colon for at least 2 days and can affect visualization of CRC on the ^{18}F-FDG PET/CT image.[34,35] In the present study, although 2 patients with false negative ^{18}F-FDG PET/CT results for CRC did not have diabetic mellitus, colonic ^{18}F-FDG uptake by metformin could affect visualization of colonic adenoma with HGD on ^{18}F-FDG PET/CT. Discontinuing metformin for a few days would reduce physiological ^{18}F-FDG uptake in the gastrointestinal tract and improve the performance of ^{18}F-FDG PET/CT for detecting advanced CRN in patients with diabetes.[34] Another limitation is the use of different PET scanners for the investigations with different acquisition parameters. However, this may minimally affect on the accuracy of ^{18}F-FDG PET/CT in detecting advanced CRN.

In conclusion, ^{18}F-FDG PET/CT demonstrated high diagnostic accuracy for detecting synchronous advanced CRN in patients with gastric cancer. Colonoscopy is recommended as the next diagnostic step for a further evaluation of focal ^{18}F-FDG colonic uptake in patients with gastric cancer.

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