Primary Tumor ^{18}F-FDG Avidity Affects the Performance of ^{18}F-FDG PET/CT for Detecting Gastric Cancer Recurrence

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The usefulness of ^{18}F-FDG PET in gastric cancer recurrence is limited by low sensitivity. Given that detectability by PET is dependent on the tumor's metabolic characteristics, we tested whether the performance of PET for gastric cancer recurrence is enhanced in patients with ^{18}F-FDG–avid primary tumors. **Methods:** Three hundred sixty-eight patients with advanced gastric cancer underwent ^{18}F-FDG PET/CT for initial staging and for recurrence surveillance after curative surgery. On initial PET/CT, primary tumors were ^{18}F-FDG–avid if they displayed focal uptake with an SUV_{max} 4 or more. Follow-up ^{18}F-FDG PET/CT was evaluated for recurrent disease. **Results:** On initial PET/CT, the primary tumor was ^{18}F-FDG–avid in 236 of 368 (64.1%) and nonavid in 132 patients (35.9%). During follow-up for 18.9 ± 13.3 mo, 72 patients (19.6%) had recurrence. Of the 63 PET scans with recurrence, 42 (66.7%) and 21 (33.3%) were scans of patients with ^{18}F-FDG–avid and nonavid primary tumors, respectively. PET sensitivity was higher in scans of patients with ^{18}F-FDG–avid than nonavid tumors for all recurrences (81.0% vs. 52.4%; $P = 0.018$) and non-anastomosis site recurrences (82.1% vs. 47.4%; $P = 0.006$). The sensitivity for detecting peritoneal recurrence was also higher for the avid tumor group. PET specificity was similarly high (97.1% and 97.5%) for both groups. Adding cell type and Lauren classification to tumor ^{18}F-FDG avidity further enhanced PET sensitivity. **Conclusion:** Surveillance ^{18}F-FDG PET/CT after resection of gastric cancer has significantly higher sensitivity in patients with ^{18}F-FDG–avid primary tumors and may have greater value in this group.

Key Words: PET/CT; gastric cancer; ^{18}F-FDG-avidity; recurrence; sensitivity

Gastric cancer is the fifth most common cancer and a third leading cause of cancer death worldwide (1). Surgery is the standard treatment for patients with resectable disease, but the prognosis remains grave with a 5-y survival of only 26% (2). Because most deaths after gastric cancer resection occur from distant recurrence (3), surveillance for recurrent disease is an important part of the postsurgical management of patients. ^{18}F-FDG PET/CT is a valuable imaging tool for the detection and staging of various malignancies including gastric cancer (4). The current guidelines of the National Comprehensive Cancer Network state that ^{18}F-FDG PET/CT is useful for the evaluation of recurrent gastric cancer (5). However, studies to date have shown inconsistent results regarding the performance of ^{18}F-FDG PET/CT for this purpose (6–8), and there are concerns that low diagnostic sensitivity may limit its usefulness (9). As such, it would be clinically useful to identify subpopulations of gastric cancer patients who are most likely to benefit from surveillance with ^{18}F-FDG PET/CT after curative gastrectomy (10,11).

Gastric adenocarcinomas display extreme genetic complexity and biologic heterogeneity, and ^{18}F-FDG avidity is clearly dependent on the biologic and clinical–pathologic characteristics of the tumors (12–14). For instance, high ^{18}F-FDG uptake of primary gastric cancers has been shown to be associated with greater aggressiveness and poor patient survival (15,16). The histologic type of the primary tumor may also influence the sensitivity of ^{18}F-FDG PET for detecting recurrent gastric cancer. In addition, ^{18}F-FDG avidity of primary gastric cancers observed on initial PET/CT has been shown to correlate with the magnitude of ^{18}F-FDG uptake by distant metastatic lesions and lymph nodes (17,18).

Taken together, these findings suggest that ^{18}F-FDG avidity of the primary gastric cancer on initial PET/CT could be a major factor in the capacity of follow-up PET/CT to detect recurrent disease, but this has not been previously explored. In this study, we thus investigated the relation between primary gastric cancer ^{18}F-FDG avidity and the performance of surveillance PET/CT for detecting recurrent disease after curative gastrectomy.

MATERIALS AND METHODS

Study Subjects

Study subjects were selected from 919 patients with stomach cancer who underwent preoperative ^{18}F-FDG PET/CT between 2008 and 2013, had surgical resection with curative intention, and underwent follow-up ^{18}F-FDG PET/CT to screen for possible recurrence. Among these, 202 patients who had history of another malignancy or coexisting malignancy were excluded, as were 15 patients who were treated for recurrence before follow-up PET/CT. In addition, 324 patients who had early gastric cancer and 6 patients who had no residual malignancy remaining after biopsy were also excluded. Finally, 4 patients were excluded for indeterminate clinical diagnosis, and a total of 368 subjects with advanced gastric cancer were included in the study. This resulted in a total of 368 preoperative PET/CT scans and 577 follow-up PET/CT scans for analysis. The mean number of follow-up PET/CT scans per patient was 1.6 (range, 1–5).

This retrospective observational study was approved by our institutional review board with exemption for written consent of study subjects.

^{18}F-FDG PET/CT Imaging

Patients fasted for at least 6 h, and blood glucose level was less than 200 mg/dL at the time of ^{18}F-FDG injection in all cases. At 60 min after injection of ^{18}F-FDG (5 MBq/kg), imaging was performed on a Discovery LS (GE Healthcare; $n = 224$ scans) or an STe PET/CT scanner (GE Healthcare; $n = 721$ scans) without intravenous or oral contrast. Whole-body CT was performed using a continuous spiral technique with an 8-slice helical CT (140 keV; 40–120 mA; section width, 5 mm; Discovery LS) or a continuous spiral technique with 16-slice helical CT (140 keV; 30–170 mA; section width, 3.75 mm; STe).

After CT, an emission PET scan was obtained from head to thigh. This was 4 min per frame in 2-dimensional mode with attenuation-corrected images ($4.3 \times 4.3 \times 3.9$ mm) reconstructed using an ordered-subset expectation maximization algorithm (28 subsets, 2 iterations; Discovery LS) or 2.5 min per frame in 3-dimensional mode with attenuation-corrected images ($3.9 \times 3.9 \times 3.3$ mm) reconstructed using a 3-dimensional ordered-subset expectation maximization algorithm (20 subsets, 2 iterations; Discovery STe).

Medical Record Review

Histopathology of the surgical specimen was based on the Japan Gastric Cancer Association system and the Lauren classification. Medical records showed that patients underwent postoperative clinical follow-up for a mean duration of 38.1 ± 16.1 mo (range, 1–72 mo). All patients without recurrence had a follow-up period of at least 12 mo. Appropriate imaging studies or histologic tests were performed whenever recurrence was suspected. The presence or absence of recurrent disease was determined by clinical decision based on all available information. For recurrent disease, this included histopathology results ($n = 22$), characteristic radiologic findings ($n = 48$), rise of serum CA 19-9 that decreased by chemotherapy ($n = 1$), and development of intractable ascites ($n = 1$).

Analyses of Preoperative PET/CT

Preoperative PET/CT images were evaluated for ^{18}F-FDG avidity of primary gastric tumors according to criteria set at the stage of study design. Tumor sites were assessed on the basis of tumor locations described on endoscopy reports. Tumors were classified as ^{18}F-FDG–avid if there was focal uptake on the known tumor site that was visually discernable from the remaining stomach and the measured SUV_{max} was 4.0 or greater. Tumors were ^{18}F-FDG–nonavid if they were not visually discernable from the remaining stomach or if tumor SUV_{max} was less than 4. Diffuse gastric ^{18}F-FDG uptake that could not be differentiated from physiologic activity was not considered specific tumor uptake. SUV_{max} was measured by manually placing a circular region of interest on visually discernable primary tumors.

Analyses of Follow-up PET/CT

Follow-up ^{18}F-FDG PET/CT was performed as part of a routine surveillance protocol without specific symptoms in most ($n = 494$) scans. In the remaining scans, it was performed for abnormal radiologic findings ($n = 73$), abdominal pain ($n = 3$), ascites ($n = 3$), elevated CA 19-9 level ($n = 1$), or complaint of nonspecific symptoms ($n = 3$).

PET sensitivity and specificity for diagnosing recurrence were analyzed using scan-based rather than patient-based data, using 352 scans of patients with ^{18}F-FDG–avid primary tumors and 225 scans in patients with nonavid tumors. PET sensitivity for recurrence was assessed with PET/CT scans obtained within 3 mo of clinical decision on recurrence. Follow-up PET scans were categorized as positive if the formal report by experienced nuclear medicine physicians concluded high probability for recurrence. Scans with formal reports concluding low or intermediate probability for recurrence were reevaluated, and only scans with lesions with focal ^{18}F-FDG uptake clearly discernible from surrounding activity that could be differentiated from physiologic activity were categorized as positive, whereas the remaining scans were categorized as negative for recurrence. The SUV_{max} of suspected recurrent lesions was measured with circular regions of interest. PET interpretation was combined with the final clinical diagnosis to yield false- or true-positive and -negative PET results.

Statistical Analysis

Comparison of clinical characteristics between patients with ^{18}F-FDG–avid and –nonavid primary tumors was performed with Student t tests, Pearson χ^2 tests, or Fisher exact tests. The relation between SUV_{max} of primary tumors and recurrent lesions was analyzed by Pearson correlation tests. SPSS software for Windows (SPSS) was used for statistical analysis, and P values of less than 0.05 were considered significant.

RESULTS

Clinical Characteristics According to Primary Tumor ^{18}F-FDG Avidity

The clinical characteristics of the 368 study subjects are summarized in Table 1. The total population had a mean age of 57.8 ± 11.6 y, and there were 250 men and 118 women. On preoperative PET/CT, the primary tumor was ^{18}F-FDG–avid in 236 cases (60.2 ± 10.9 y; 171 men) and ^{18}F-FDG–nonavid in 132 cases (53.5 ± 11.6 y; 79 men). Patients with ^{18}F-FDG–avid primary tumors had a significantly greater incidence of intestinal-type histology according to the Lauren classification (49.2%) than those with nonavid tumors (22.7%). In contrast, patients with ^{18}F-FDG–nonavid primary tumors had a significantly greater incidence of diffuse-type histology than those with avid tumors (59.1% vs. 35.6%). Patients with ^{18}F-FDG–nonavid primary tumors also more frequently had signet ring cell carcinomas than their counterpart (24.2% vs. 8.1%). Surgical tumor size was not significantly different between the 2 groups. Pathologic staging according to the seventh edition of the American Joint Committee on Cancer staging manual (19) showed that T2 disease (58.3% vs. 44.1%) and N0 disease (50.8% vs. 28.8%) were more frequent in patients with ^{18}F-FDG–nonavid than avid primary tumors.

Clinical Follow-up and Disease Recurrence

All study subjects underwent subtotal or total gastrectomy with regional lymph node dissection under curative intention. In a total of 72 patients (19.6%), recurrent disease occurred during follow-up (Table 2). This occurred at a mean interval of 18.9 ± 13.3 mo after surgery. The remaining 296 patients showed no evidence to suggest recurrence during follow-up. The mean follow-up period of patients without recurrence was 42.8 ± 13.0 mo (range, 11–72 mo). Comparison of patients with ^{18}F-FDG–avid and –nonavid primary tumors (Table 2) showed no difference in recurrence rate (19.5% vs. 19.7%) or time to recurrence (17.3 ± 13.3 vs. 21.8 ± 12.9 mo).

Postoperative Surveillance ^{18}F-FDG PET/CT

We next investigated the sensitivity of follow-up ^{18}F-FDG PET for detecting recurrence using a total of 63 PET scans obtained within 3 mo of clinical decision of recurrence. Although an interval of 3 mo was used, the actual interval in most patients with recurrence was much shorter. Hence, the mean interval was 11.3 ± 1.6 d, and 75% of the patients had an interval of less than 2 wk. The results showed that follow-up ^{18}F-FDG PET/CT had an overall sensitivity of 71.4% for the detection of recurrent disease, which was not significantly affected (70.7%) by excluding recurrences in remnant stomach or anastomosis from analysis (Table 2). Comparison of groups revealed that the sensitivity of PET/CT for detecting

TABLE 1
Clinical Characteristics of 368 Study Subjects with Advanced Gastric Cancer

Characteristic	All subjects (n = 368)	^{18}F-FDG–avid tumor group* (n = 236)	^{18}F-FDG–nonavid tumor group† (n = 132)	P
Mean age ± SD (y)	57.8 ± 11.6	60.2 ± 10.9	53.5 ± 11.6	<0.001‡
Male (%)	250 (67.9)	171 (72.5)	79 (59.8)	0.013¶
Lauren classification				
Intestinal	146 (39.7)	116 (49.2)	30 (22.7)	<0.001¶
Diffuse	162 (44.0)	84 (35.6)	78 (59.1)	<0.001¶
Indeterminate	15 (4.1)	13 (5.5)	2 (1.5)	0.063¶
Mixed	45 (12.2)	23 (9.7)	22 (16.7)	0.052¶
Signet ring cell	51 (13.9)	19 (8.1)	32 (24.2)	<0.001¶
Nonsignet ring cell	317 (86.1)	217 (91.9)	100 (75.8)	
Mean tumor size ± SD (cm)	6.0 ± 3.3	6.2 ± 2.9	5.7 ± 3.8	0.279‡
T2	181 (49.2)	104 (44.1)	77 (58.3)	0.009¶
T3	123 (33.4)	86 (36.4)	37 (28.0)	0.101¶
T4a	60 (16.3)	42 (17.8)	18 (13.6)	0.300¶
T4b	4 (1.1)	4 (1.7)	0 (0.0)	0.301§
N0	135 (36.7)	68 (28.8)	67 (50.8)	<0.001¶
N1	66 (17.9)	51 (21.6)	15 (11.4)	0.014¶
N2	74 (20.1)	52 (22.0)	22 (16.7)	0.218¶
N3a	60 (16.3)	43 (18.2)	17 (12.9)	0.183¶
N3b	33 (9.0)	22 (9.3)	11 (8.3)	0.750¶

*Initial primary gastric tumor uptake (+) and $SUV_{max} \geq 4$.
†Initial primary gastric tumor uptake (−) or $SUV_{max} < 4$.
‡t test.
¶Pearson χ^2 test.
§Fisher exact test.
Data in parentheses are percentages.

recurrence was superior in scans of patients with ^{18}F-FDG–avid compared with ^{18}F-FDG–nonavid primary tumors (81.0% vs. 52.4%). Furthermore, the superior sensitivity for ^{18}F-FDG–avid primary tumor persisted when recurrences at remnant stomach or anastomosis site were excluded (82.1% vs. 47.4%; Table 2).

PET specificity determined using 514 follow-up PET/CT scans without recurrent disease was 97.3%. This high specificity was obtained by interpreting mild activity on remnant stomach and anastomosis sites as nonspecific. The specificity for recurrence was similarly high for both primary tumor ^{18}F-FDG–avid and –nonavid groups (97.1% vs. 97.5%; Table 2). A representative true-positive case with an ^{18}F-FDG–avid primary tumor and a false-negative case with an ^{18}F-FDG–nonavid primary tumor are illustrated in Figures 1 and 2, respectively.

Among the 63 PET scans obtained within 3 mo of clinical decision of recurrence, 30 and 25 scans were from patients who received postsurgery adjuvant chemotherapy and chemoradiotherapy, respectively. PET sensitivity for recurrence was 73.3% in scans of patients with adjuvant chemotherapy and 72.0% in those with chemoradiotherapy, compared with 62.5% in those without adjuvant treatment. In all 3 groups, PET sensitivity for recurrence tended to be greater for those with ^{18}F-FDG–avid than –nonavid primary tumors (82.6% vs. 42.9% for those with adjuvant chemotherapy; 78.6% vs. 63.6% for those with chemoradiotherapy; and 80.0% vs. 33.3% for those without adjuvant treatment).

We additionally evaluated the performance of PET scans for recurrent disease in subjects who underwent PET/CT as surveillance tests (85.6%) or for suggestive signs or symptoms (14.4%). As a result, PET sensitivity for detecting recurrence was 66.7% in the 15 scans obtained for surveillance and 72.9% in the 48 scans obtained for suspicion of recurrence (P = 0.746). In the former group, PET sensitivity was 100% (10/10) in scans of patients with ^{18}F-FDG–avid primary tumor and 0% (0/5) in those with ^{18}F-FDG–nonavid tumor. In the latter group, PET sensitivity was 75.0% (24/32) in those with ^{18}F-FDG–avid tumor and 68.8% (11/16) in those with ^{18}F-FDG–nonavid tumor, both of which had higher sensitivity than cases with nonavid tumors when performed for surveillance (P = 0.003 and 0.012, respectively). PET specificity for detecting recurrence was 97.5% in the 479 scans acquired for surveillance and 94.3% in the 35 scans acquired for suspicion of recurrence (P = 0.246). In the former group, PET specificity was 97.3% (285/293) in scans of patients with ^{18}F-FDG–avid primary tumor and 97.8% (182/186) in those with ^{18}F-FDG–nonavid tumor. In the latter group, PET specificity was 94.1% (16/17) in those with ^{18}F-FDG–avid tumor and 94.4% (17/18) in those with ^{18}F-FDG–nonavid tumor.

We also analyzed PET performance for recurrence based on visual interpretation only. As a result, PET sensitivity for recurrence was 76.1% in scans of patients with visually discernible primary tumor ^{18}F-FDG uptake and 58.8% in those without discernible primary tumor ^{18}F-FDG uptake. Specificity was 97.3% and 97.2%, respectively.

TABLE 2
Gastric Cancer Recurrence and Diagnostic Performance of ^{18}F-FDG PET

Parameter	All subjects ($n = 368$)	^{18}F-FDG–avid tumor group* ($n = 236$)	^{18}F-FDG–nonavid tumor group† ($n = 132$)	P
Recurrence (%)	72 (19.6)	46 (19.5)	26 (19.7)	0.962‡
Mean duration to recur ± SD (mo)	18.9 ± 13.3	17.3 ± 13.3	21.8 ± 12.9	0.167¶
Follow-up PET scans within 3 mo of clinical decision of recurrence (%)	63	42	21	0.645‡
PET sensitivity for recurrence (%)				
Including all recurrences	45/63 (71.4)	34/42 (81.0)	11/21 (52.4)	0.018‡
Excluding recurrences in remnant stomach or anastomosis site	41/58 (70.7)	32/39 (82.1)	9/19 (47.4)	0.006‡
Follow-up PET scans without recurrence	514	310	204	
PET specificity for recurrence	97.3%	97.1%	97.5%	0.758‡

*Initial primary gastric tumor uptake (+) and SUV$_{max}$ ≥ 4.
†Initial primary gastric tumor uptake (−) or SUV$_{max}$ < 4.
‡Pearson χ^2 test.
¶t test.
Data in parentheses are percentages.

Distribution of Recurrence Site and Detection by ^{18}F-FDG PET

The distribution of recurrence sites and number of lesions detected by ^{18}F-FDG uptake in the 63 patients with recurrent disease (and PET/CT within 3 mo) are summarized in Supplemental Table 1 (supplemental materials are available at http://jnm.snmjournals.org). In 53 of these patients, recurrence occurred in a single organ (53 sites), whereas the remaining 10 patients had recurrence in multiple sites (28 sites). The most common site of recurrence was the peritoneum

FIGURE 1. Representative case of ^{18}F-FDG–avid primary tumor. (A) Preoperative PET/CT and PET images of 75-y-old patient show a gastric cancer with high ^{18}F-FDG uptake (SUV$_{max}$, 11.9). Primary tumor was moderately differentiated tubular adenocarcinoma (4.5 × 4 × 0.6 cm) located in center of high body and posterior wall. (B) Follow-up PET/CT and PET images 27 mo later demonstrated increased ^{18}F-FDG uptake in mesenteric lymph node (SUV$_{max}$ 7.5) that was confirmed to be recurrent disease by radiologic studies.

($n = 19$). Notably, recurrent lesions in the peritoneum were detected with substantially greater sensitivity in the primary tumor ^{18}F-FDG–avid group (10/13) compared with the non-^{18}F-FDG–avid group (1/6; $P = 0.041$). PET/CT in patients with ^{18}F-FDG–avid primary tumor also detected recurrence in other sites with high sensitivity, including liver and lymph nodes.

When we compared ^{18}F-FDG uptake levels, patients with ^{18}F-FDG–avid primary tumors showed significantly greater recurrent lesion SUV$_{max}$ than those with ^{18}F-FDG–nonavid primary tumors (7.3 ± 3.4 vs. 4.5 ± 2.2; Fig. 3A). However, linear regression was unable to show a significant correlation between primary tumor and recurrent lesion SUV$_{max}$ ($r = 0.075$, Fig. 3B).

Other Variables That May Enhance Recurrence Detection

We additionally evaluated whether other tumor characteristics that are potentially linked with glucose metabolism may also provide stratification of patients with enhanced PET performance for detecting recurrence. Categorization into patients with ($n = 11$) and without signet ring cell carcinoma ($n = 52$) did not lead to significant difference in PET sensitivity for recurrence (63.6% vs. 73.1%). These groups also showed no difference in PET sensitivity when patients with anastomosis site recurrence were excluded (66.7% vs. 71.4%).

Patients with intestinal-type cancers ($n = 23$) had a significantly higher PET sensitivity for recurrence than those with diffuse-type cancers ($n = 33$; 91.3% vs. 54.5%; $P = 0.003$), and this remained true when patients with anastomosis site recurrence were excluded (90.1% vs. 51.7%; $P = 0.003$). Comparison of patients with intestinal-type cancer to those with all other cancer types ($n = 40$) also showed similar results when including (91.3% vs. 60%; $P = 0.008$) and excluding anastomosis site recurrence (90.1% vs. 58.3%; $P = 0.011$). However, the number of patients with intestinal-type cancers was only 54.8% (23/42) of that with ^{18}F-FDG–avid primary tumor, limiting its usefulness. We therefore attempted to evaluate whether combining information of primary tumor ^{18}F-FDG avidity and Lauren classification type can offer further benefit. However, all but 1 of the 23 patients with intestinal-type cancers and recurrent
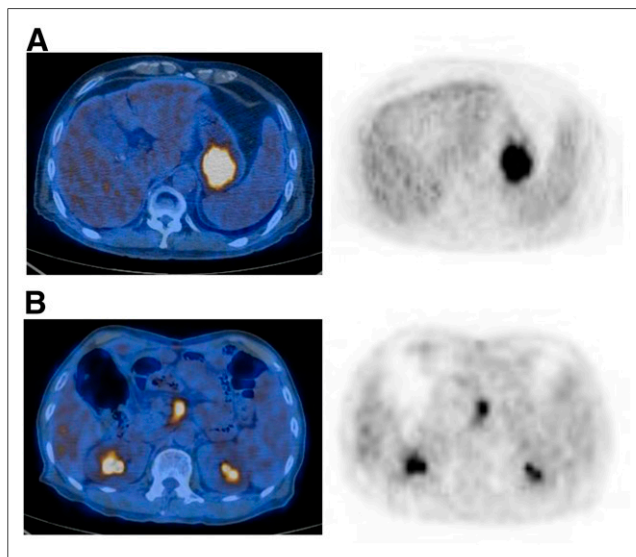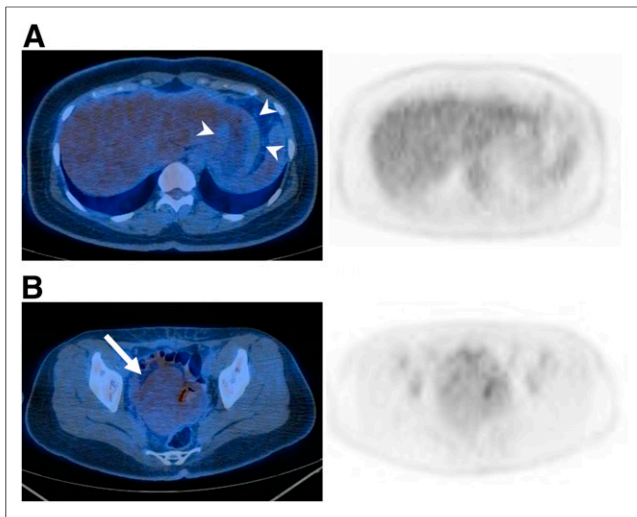
FIGURE 2. Representative case of ^{18}F-FDG–nonavid primary tumor. (A) Preoperative PET/CT and PET images of 38-y-old patient showed gastric cancer without visually discernable ^{18}F-FDG uptake. CT findings show diffuse thickening involving most of the stomach wall (arrowheads). Primary tumor was poorly differentiated tubular adenocarcinoma (14 × 13 cm) located in body and anterior wall. (B) Follow-up PET/CT and PET images 10 mo later failed to detect any suggestive ^{18}F-FDG uptake, but recurrence in right ovary (arrow) was pathologically confirmed.

disease had ^{18}F-FDG–avid primary tumors. As such, the addition of information on cell type or Lauren classification to that of primary tumor ^{18}F-FDG avidity did not offer incremental benefit in augmenting sensitivity for recurrence.

There were 2 patients, among a total of 63 patients with recurrence, who did not have measurable disease by imaging studies including PET and contrast-enhanced CT. One patient had an ^{18}F-FDG–nonavid primary tumor, and recurrence was diagnosed on the basis of a 3-fold rise of serum CA 19-9 that decreased by chemotherapy. The second patient had an ^{18}F-FDG–avid primary tumor, and recurrence was diagnosed on the basis of development of intractable ascites.

Another 25 patients had recurrent lesions that were small. These were soft-tissue or hepatic lesions less than 2 cm, lymph nodes without enlargement, peritoneal enhancement or bowel wall thickenings without nodule formation, and anastomosis site lesions not seen on enhanced

CT. PET had lower sensitivity for detecting these small lesions than larger recurrent lesions (56% vs. 86.1%; $P = 0.009$). In patients with small recurrent lesions, the primary tumors were ^{18}F-FDG–avid in 14 cases and –nonavid in 11 cases, and PET sensitivity was 64.3% in the former group and 45.5% the latter group ($P = 0.435$).

DISCUSSION

This study demonstrates that the sensitivity of surveillance ^{18}F-FDG PET/CT for detecting recurrent disease after curative resection of advanced gastric cancer is significantly enhanced by the ^{18}F-FDG avidity of the resected primary tumor.

On initial staging PET/CT, 64.1% of the locally advanced primary gastric cancers in our study were ^{18}F-FDG–avid. This rate of visible tumor ^{18}F-FDG uptake is well within the 34%–94% range of sensitivity reported for PET/CT in detecting advanced gastric cancer (20). The wide range of reported sensitivity indicates that multiple factors influence the magnitude of gastric tumor ^{18}F-FDG uptake. Gastric adenocarcinomas actually comprise a heterogeneous group of tumors with dissimilar biologic characteristics, which in turn can lead to divergent metabolic and bioenergetic properties. In our study, ^{18}F-FDG–avid and –nonavid gastric cancers showed different histopathologic makeups. Although nonsignet ring cell type was more common in both groups, signet ring cell type was 3-fold more frequent in nonavid compared with avid tumors. This finding is consistent with previous observations that signet ring cell and mucinous type gastric cancers tend to have lower ^{18}F-FDG uptake (11–13), a feature that has been attributed to lower glucose transporter-1 expression (12).

Lauren described 2 major gastric cancer types with distinct molecular pathogenesis and clinical–pathologic profiles. Intestinal-type gastric carcinomas occur more frequently in older subjects and are thought to arise from chronic gastritis that progress to intestinal metaplasia and dysplasia. Diffuse-type gastric carcinomas are more common in younger individuals and roughly correspond to poorly cohesive carcinomas of the World Health Organization classification. In our study, intestinal-type tumors occurred more frequently in ^{18}F-FDG–avid than –nonavid tumors, whereas the reverse was true for diffuse-type tumors. Several previous studies showed higher ^{18}F-FDG uptake intestinal-type than diffuse-type gastric cancers (4,11,21,22). Although the mechanism has not been clearly elucidated, greater mucin content in diffuse-type cancers has been proposed as an explanation for this phenomenon (21).

Patients with ^{18}F-FDG–avid primary tumors in our study were also slightly less likely to have lower T stage (T2) and N stage (N0) disease at presentation. These findings are in line with previously described associations between degree of ^{18}F-FDG uptake and tumor invasion depth or nodal involvement (14,21,22) and may be explained by aggressiveness of tumors that have high glycolytic activity. Small tumors can cause underestimation of ^{18}F-FDG measurements by partial-volume effects, but primary tumor size between ^{18}F-FDG avidity groups was not different in our study.

During a mean clinical follow-up of 38.1 mo, recurrent disease was diagnosed in 19.6% of our study subjects. However,
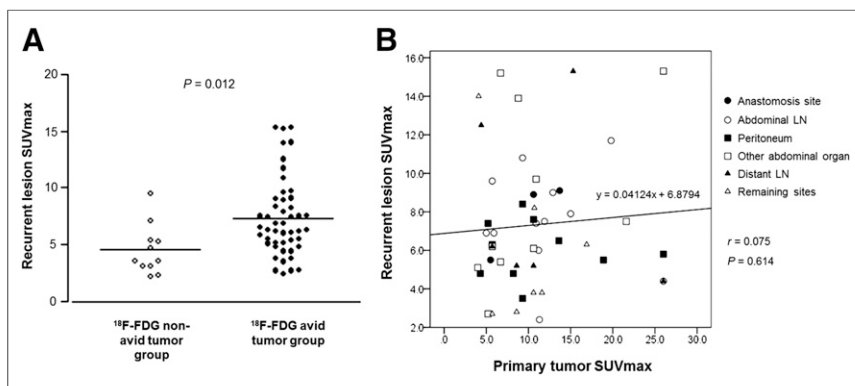

FIGURE 3. Relation between primary tumor and recurrent lesion ^{18}F-FDG avidity. (A) Scatterplot comparing distribution of recurrent lesion SUV$_{max}$ between patients with ^{18}F-FDG–avid and –nonavid primary tumors. (B) Correlation analysis between recurrent lesion SUV$_{max}$ and primary gastric tumor. LN = lymph node.

despite the slightly higher T and N stage of patients with ^{18}F-FDG–avid primary tumors, the recurrence rate and duration to recurrence were not different between tumor ^{18}F-FDG avidity groups. Tumor ^{18}F-FDG uptake levels have been shown to have significant prognostic associations in various types of malignancies. However, there have been limited data regarding the relation between tumor ^{18}F-FDG uptake level and outcome of patients with gastric cancer. Indeed, previous reports have shown inconsistent results, possibly from differences in proportion of histopathologic subtypes among study populations (15,16,23). For instance, signet ring cell carcinomas and other poorly differentiated tumors with attenuated cell densities generally have low ^{18}F-FDG uptake even though they carry adverse prognosis.

Compared with advanced gastric cancer, early gastric cancers are known to have low ^{18}F-FDG uptake (22) and are associated with a low rate of recurrence. Our database showed 324 early gastric cancer patients who underwent follow-up PET/CT during the same time period of our study population, but only 1 of these patients developed recurrent disease. This is consistent with the report by Sano et al., in which early gastric cancer was estimated to have a recurrence rate of only 1.9% (24). This is the reason patients with early gastric cancers were excluded in our study.

When we investigated the performance of PET for detecting recurrent disease in the entire study population, a diagnostic sensitivity of 71.4% was obtained, which is similar to the 78% recently reported by a meta-analysis study (7). PET sensitivity in our study was similar regardless of whether or not cases with locoregional recurrence were included. The specificity reported in the meta-analysis by Wu et al. was 82% (7). A significant number of false-positive results arise from nonspecific physiologic radioactivity in the anastomosis site or remnant stomach, but these recurrences can be readily excluded by endoscopic surveillance. Furthermore, distant, rather than locoregional, recurrence is responsible for most patient deaths (3). Therefore, when analyzing PET specificity, we considered mild activity on remnant stomach and anastomosis sites as nonspecific findings. As a result, we obtained a high overall PET specificity of 97.3% for detecting recurrent disease.

Using an SUV_{max} threshold of 4.0, we compared the performance of PET for detecting recurrent disease in ^{18}F-FDG–avid and –nonavid primary tumor groups. The results revealed that patients with ^{18}F-FDG–avid primary tumors had a significantly greater diagnostic sensitivity than those with ^{18}F-FDG–nonavid tumors, whether or not cases with local recurrence were excluded from the analysis. Hence, the former group had a moderate sensitivity of 81.0% (82.1% when excluding local recurrence) for ^{18}F-FDG PET/CT in detecting recurrent disease. The diagnostic specificity was similarly high for both groups. Taken together, these results indicate that ^{18}F-FDG avidity of the primary gastric cancer on initial PET may help select patients likely to benefit from follow-up PET studies. When PET was performed for suspicion of recurrence, cases with ^{18}F-FDG–avid and –nonavid primary tumors both had higher sensitivity than cases with ^{18}F-FDG–nonavid tumors undergoing PET for surveillance. This indicates that whereas routine follow-up PET/CT may be efficient only for ^{18}F-FDG–avid primary tumors, it may benefit patients with both ^{18}F-FDG–avid and ^{18}F-FDG–nonavid tumors when recurrence is suspected.

We performed receiver-operating-characteristic curve analysis to evaluate how different SUV_{max} thresholds would influence performance of scans in patients with ^{18}F-FDG–avid primary tumors. As a result, PET sensitivity and specificity were 76.1% and 97.3% for SUV_{max} 3.0, 77.8% and 97.2% for SUV_{max} 3.5, 81.0% and 97.1% for SUV_{max} 4.0, and 78.9% and 97.1% for SUV_{max} 4.5.

These findings show that the results are not remarkably affected by the choice of SUV_{max} threshold. A value of 4.0 also coincides with the observation by Salaun et al. that ^{18}F-FDG uptake in the stomach with a lower SUV_{max} is usually associated with benign rather than malignant disease (25). Although all primary tumors with discernable ^{18}F-FDG uptake in our study had an SUV_{max} of more than 3.0, a value of 4.0 corresponded to the 5 percentile SUV_{max} among such tumors. As such, 17 patients with discernable primary tumor ^{18}F-FDG uptake had an SUV_{max} between 3.0 and 4.0 and were categorized as ^{18}F-FDG–nonavid tumors.

The compositions of cell types and Lauren classification were found to be different between ^{18}F-FDG–avid and –nonavid primary tumor groups. Given that these differences may themselves influence tumor metabolic profile, we investigated whether histopathologic findings can also help select subjects with improved PET sensitivity for recurrence. The results showed that classification of patients according to signet ring cell types does not affect PET sensitivity. On the other hand, classification according to intestinal-type cancers significantly increased PET sensitivity. However, a substantially smaller portion of patients had this characteristic than tumor ^{18}F-FDG avidity. Furthermore, as it turns out, all but 1 recurrence patient with intestinal-type cancer showed ^{18}F-FDG–avid tumors on initial PET/CT (22/23), whereas only 52.4% (22/42) of those with an ^{18}F-FDG–avid tumor had intestinal-type cancer. These findings support that ^{18}F-FDG avidity of primary tumors is a significantly more robust method to select patients with higher PET/CT sensitivity for recurrence.

Detection performance for recurrent gastric cancer may differ according to involved site. In particular, peritoneal involvement is notoriously difficult to detect by ^{18}F-FDG PET (8,26). We also found a low overall PET sensitivity of 57.9% for detecting peritoneal recurrence. Among scans of patients with ^{18}F-FDG–avid primary tumors, however, PET sensitivity for peritoneal recurrence was increased to 76.9%. In contrast, the sensitivity was reduced to 16.7% for scans of patients with nonavid primary tumors. Other sites of recurrence also showed a trend for higher sensitivity in the ^{18}F-FDG–avid than the –nonavid group. Therefore, PET appeared to detect recurrent disease better in all sites including the peritoneum in patients who had ^{18}F-FDG–avid primary tumors.

The mechanism for the greater PET sensitivity for recurrence evidently lies in the similarity of biologic characteristics between primary and recurrent malignant lesions. This is supported by the significantly greater level of ^{18}F-FDG uptake in recurrent lesions for scans of patients whose primary tumors had higher uptake. Although the positive relation between the level of ^{18}F-FDG uptake by primary and recurrent lesions did not reach statistical significance, this is to be expected given the different sizes and divergent environment of the recurrent compared with the primary tumor.

This study is limited by its retrospective design with a nonsystematic and nonstandardized follow-up imaging schedule. As such, further investigations will be required to help establish an ^{18}F-FDG PET/CT follow-up algorithm for gastric cancer patients after curative resection.

CONCLUSION

The sensitivity of PET for detecting recurrent disease after curative resection is significantly enhanced in patients with ^{18}F-FDG–avid primary gastric cancers. Hence, follow-up PET for surveillance of possible recurrence may be better suited for cases that have high ^{18}F-FDG uptake of the primary tumor on initial PET studies.

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