The Clinical Value of 18F-Fluorodeoxyglucose Uptake on Positron Emission Tomography/Computed Tomography for Predicting Regional Lymph Node Metastasis and Non-curative Surgery in Primary Gastric Carcinoma

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Background/Aims: Accurate preoperative detection of regional lymph nodes and evaluation of tumor resectability is critical to determining the most adequate therapy for gastric cancer. The aim of this study is to identify a possible link between 18F-fluorodeoxyglucose (18F-FDG) uptake on PET scan combined with CT scan (PET/CT) and predictions of lymph node metastasis and non-curative surgery.

Methods: This study included 156 gastric cancer patients who underwent preoperative 18F-FDG PET/CT and surgery. In cases with perceptible FDG uptake in the primary tumor or lymph nodes, the maximum standardized uptake value (SUVmax) was calculated.

Results: In multivariate analysis, non-curative surgery (OR, 11.05; 95% CI, 1.10-111.08; p=0.041), tumor size ($\geq$ 3 cm) (OR, 7.39; 95% CI, 2.41-22.70; p < 0.001), and lymph node metastasis (OR, 5.47; 95% CI, 2.05-14.64; p=0.001) were significant independent predictors for 18F-FDG uptake in the primary tumors. Tumor size (tumor size $\geq$ 3 cm) (OR, 3.15; 95% CI, 1.16-8.58; p=0.025) and lymph node metastasis (OR, 3.36; 95% CI, 1.23-9.14; p=0.018) showed significant association with 18F-FDG uptake in lymph node. When the SUVmax of the primary gastric tumor was greater than 3.75, the sensitivity and specificity of PET/CT with regard to the diagnosis of metastatic lymph node were 73.5% and 74.5%. When the SUVmax of the primary gastric tumor was greater than 4.35 and the FDG uptake of lymph nodes was positive, non-curative surgery was predicted with a sensitivity of 58.8% and specificity of 91.6%.

Conclusions: A high FDG uptake of the gastric tumor was related to histologic positive lymph nodes and non-curative surgery.

Key Words: Stomach neoplasms; Lymph node; Positron-emission tomography
INTRODUCTION

The most important step after diagnosis of gastric cancer is accurate staging, which primarily evaluates the tumor resectability. Important factors that determine tumor resectability are whether the tumor can be separated from adjacent organs or important blood vessels, the extent of lymph node metastasis, and the presence of peritoneal metastasis or distant organ metastasis. Anatomical imaging has superior spatial resolution and is essential for evaluating the extent of local tumor invasion. The 18F-fluorodeoxyglucose (18F-FDG) PET scan is a useful functional whole-body imaging modality that images various types of malignancies with relatively high sensitivity and specificity in a reasonably rapid time. While CT detects malignant processes based mainly on altered anatomy, the 18F-FDG PET scan detects a lesion on the basis of abnormal glucose metabolism. The 18F-FDG PET scan has been used in the preoperative staging of gastric cancer with some promising results. In patients with gastric cancers, less than 50% of early gastric cancers (EGC) and 62-98% of advanced gastric cancers (AGC) are detected by 18F-FDG PET scan (AGC).1-6 The 18F-FDG PET scan combined with CT scan (18F-FDG PET/CT) can yield more accurate information by stereographic reconstruction.

The National Comprehensive Cancer Network recently announced that preoperative 18F-FDG PET/CT can be recommended as a preoperative staging option for gastric cancer patients; however, the benefits of 18F-FDG PET/CT remain uncertain.7,8

We analyzed information from preoperative 18F-FDG PET/CT for patients with gastric cancer and retrospectively compared this information with the surgical results. The aim of this study is to identify a possible link between 18F-FDG uptake on PET/CT in the primary tumor or local lymph node and predictions of lymph node metastasis and non-curative surgery.

SUBJECTS AND METHODS

1. Subjects

From November 2010 to March 2012, 156 patients diagnosed with gastric cancer by endoscopic biopsy who had undergone both preoperative 18F-FDG PET/CT and surgery were enrolled. The trial protocol was approved by the institutional review board of Ewha Medical Center (ECT 14-07-04). We collected the preoperative staging data and surgical results for this retrospective study.

2. 18F–FDG PET/CT imaging and interpretation

18F-FDG PET/CT images were obtained using a Siemens Biograph mCT/128 PET/CT scanner (Siemens Medical Solutions, Hoffman Estates, IL, USA). Before administration of 4.81 MBq/kg of 18F-FDG, patients fasted for at least 6 hours to ensure a serum glucose level/150 mg/dL. Low-dose CT images were used for attenuation correction. A semiquantitative and visual analysis was performed. 18F-FDG uptake was defined as positive for a primary tumor when 18F-FDG uptake in the thickened gastric wall was greater than that of the adjacent gastric wall. Lymph node metastases were divided into regional and distant lymph node metastases according to location and were considered positive or negative based on the group as a whole. Additional abnormal 18F-FDG uptake in the body was documented in order to detect the presence of distant metastases. A focal uptake with the maximum standardized uptake value (SUVmax) > 2.5 was considered pathological.

3. Contrast–enhanced CT imaging and interpretation

After fasting for over 6 hours, all of the patients ingested 500 mL of water to distend the stomach before image acquisition; 120 mL of contrast media was injected intravenously at a rate of 3 mL/sec using an automatic power injector, and venous phase images involving the diaphragm to perineum were obtained 90 seconds after injection. Radiologists reviewed all CT scans (Sensation; Siemens Medical Solutions, Erlangen, Germany) for detection of primary tumors and lymph node metastases. The patients were diagnosed with gastric cancer when their gastric wall was thickened or formed a mass that extended beyond the hypoattenuating stripe of the submucosal layer on CT. CT criteria for the diagnosis of lymph node metastases were as follows: a lymph node greater than 10 mm in the longest diameter, aggregations of 3 or more lymph nodes of greater than 7 mm along the long axis, or a lymph node greater than 7 mm in the longest diameter with contrast enhancement. Additional findings that suggested the presence of distant metastasis were recorded.
4. Surgery

An operation was defined as non-curative when open and closed bypass surgery was performed without tumor resection because of metastatic lesions in other organs or the peritoneum and retroperitoneal lymph nodes, or when non-resectable primary tumors were found during surgery. In addition, palliative resection of primary tumors in which microscopic or macroscopic tumors remained was included in the category of non-curative surgery.

5. Statistical analysis

The statistical software used was the SPSS software version 13.0 for Windows (SPSS Inc, Chicago, IL, USA). The 18F-FDG uptake rates in primary tumors or local lymph nodes were compared according to the clinicopathological factors using the chi-square test. The independent t-test was performed for evaluation of differences in SUVmax between curative and non-curative surgery groups. The sensitivity and specificity of SUVmax for prediction of non-curative surgery were assessed by the receiver operating characteristic (ROC) curve.

**RESULTS**

1. Patient and tumor characteristics

Clinicopathologic variables are shown in Table 1. A total of 156 patients with gastric cancer underwent gastrectomy. Six patients with distant metastasis underwent D0 or D1 lymph node dissection; 150 patients (96.1%) underwent extended (D2/D3) dissection. The average age of patients was 60 years (range, 40-84 years), and 104 (66.7%) patients were men. The mean tumor size was 31.4±25.2 mm. Tumors were limited to the submucosa in 94 patients (60.3%), and 53 patients (34.2%) had positive lymph nodes at histological examination. Curative surgery was performed in 132 patients (84.6%).

2. Comparison between the status of 18F-FDG uptake and clinicopathologic characteristics

18F-FDG uptake in the primary tumors was observed in 104 patients (66.7%). The incidence of 18F-FDG uptake in the tumor was associated with AGC (AGC vs. EGC, 85.5% vs. 43.6%; p < 0.001), tumor size (≥ 3 cm vs. < 3 cm, 86.8% vs. 39.8%; p < 0.001), differentiation (moderately to poorly differentiated vs. well-differentiated adenocarcinoma, 74.7% vs. 33.3%; p < 0.001), lymph node metastases (positive vs. negative, 86.8% vs. 46.1%; p < 0.001), and non-curative surgery (non-curative surgery vs. curative surgery, 95.8% vs. 53.8%; p < 0.001) (Table 2). Increased 18F-FDG uptake in the lymph node was observed in 43 patients (27.6%). The incidence of 18F-FDG uptake in the lymph nodes was higher in the AGC group (AGC vs. EGC, 48.4% vs. 13.8%; p < 0.001), larger tumor size (≥ 3 cm vs. < 3 cm, 48.5% vs. 11.4%; p < 0.001), histology (moderately to poorly differentiated vs. well-differentiated adenocarcinoma, 74.7% vs. 33.3%; p < 0.001), lymph node metastases (positive vs. negative, 86.8% vs. 46.1%; p < 0.001), and non-curative surgery (non-curative surgery vs. curative surgery, 95.8% vs. 53.8%; p < 0.001) (Table 2).
**Table 2.** Comparison between the Status of 18F-FDG Uptake and Primary Tumor Characteristics in the Gastric Cancers

| Variable                        | 18F-FDG uptake in primary tumor | 18F-FDG uptake in lymph node |
|---------------------------------|---------------------------------|-----------------------------|
|                                 | Yes   | No   | p-value | Yes   | No   | p-value |
| Total                           | 104 (66.7) | 52 (33.3) |         | 43 (27.6) | 113 (72.4) |         |
| SUVmax of gastric tumor         | 6.7 (2.5-34.0) | 0.3 (0.2-4.0) | 0.238 | 5.0 (0.35-0.0) | 2.3 (0.23-0.23) | 0.936 |
| Age (yr)                        | ≥60   | 50 (64.9) | 27 (35.1) | 0.001 | 21 (27.3) | 56 (72.7) | 0.356 |
| <60                             | 44 (55.7) | 35 (44.3) |         | 22 (27.8) | 57 (72.7) |         |
| Gender                          | Male   | 62 (59.6) | 42 (40.4) | 0.817 | 31 (29.8) | 73 (70.2) | 0.375 |
|                                 | Female | 32 (61.5) | 20 (38.5) |         | 12 (23.1) | 40 (76.9) |         |
| Diabetes mellitus               | Positive | 17 (53.1) | 15 (46.9) | 0.355 | 12 (37.5) | 20 (62.5) | 0.158 |
|                                 | Negative | 77 (62.1) | 47 (37.9) |         | 31 (25.0) | 93 (75.0) |         |
| Depth of invasion               | AGC (T2-4) | 53 (85.5) | 9 (14.5) | <0.001 | 30 (48.4) | 32 (51.6) | <0.001 |
| EGC (T1)                        | 41 (43.6) | 53 (56.4) |         | 13 (13.8) | 81 (86.2) |         |
| Size (cm)                       | ≥3     | 59 (86.8) | 9 (13.2) | <0.001 | 33 (48.5) | 35 (51.5) | <0.001 |
|                                 | <3     | 35 (39.8) | 53 (60.2) |         | 10 (11.4) | 78 (88.6) |         |
| Tumor location (part of the stomach) | Upper | 9 (75.0) | 3 (25.0) | 0.062 | 5 (41.7) | 7 (58.3) | 0.246 |
|                                 | Middle | 32 (49.2) | 33 (50.8) |         | 15 (23.1) | 50 (76.9) |         |
|                                 | Lower  | 50 (65.8) | 26 (34.2) |         | 21 (27.6) | 55 (72.4) |         |
|                                 | Whole  | 3 (100.0) | 0 (0.0)  |         | 2 (66.7) | 1 (33.3)  |         |
| Histology                       | Tubular adenocarcinoma | 70 (61.9) | 43 (38.1) | 0.078 | 31 (27.4) | 82 (72.6) | 0.081 |
|                                 | Signet ring cell carcinoma | 19 (50.0) | 19 (50.0) |         | 10 (26.3) | 28 (73.7) |         |
| Differentiation                 | Moderately & poorly | 59 (74.7) | 20 (25.3) | <0.001 | 29 (36.7) | 50 (63.3) | 0.004 |
|                                 | Well | 11 (33.3) | 22 (66.7) | <0.001 | 2 (6.1) | 31 (93.9) |         |
| Lauren classification           | Diffuse & mixed | 49 (61.2) | 31 (38.8) | 0.982 | 27 (33.8) | 53 (66.2) | 0.094 |
|                                 | Intestinal | 43 (61.4) | 27 (38.6) |         | 15 (21.4) | 55 (78.6) |         |
| Tumor border by Ming            | Expanding | 11 (50.0) | 11 (50.0) | 0.118 | 2 (9.1) | 20 (90.9) | 0.056 |
|                                 | Infiltrating | 30 (69.8) | 13 (30.2) |         | 13 (30.2) | 30 (69.8) |         |
|                                 | Lymph node metastasis | Positive | 46 (86.8) | 7 (13.2) | <0.001 | 30 (56.6) | 23 (43.3) | <0.001 |
|                                 |         | 47 (46.1) | 55 (53.9) |         | 13 (12.7) | 89 (87.3) |         |
| Curability                      | Curative | 71 (53.8) | 61 (46.2) | <0.001 | 27 (20.5) | 105 (79.5) | <0.001 |
|                                 | Non-curative | 23 (95.8) | 1 (4.2)  |         | 16 (66.7) | 8 (33.3)  |         |

Values are presented as median (range) or n (%).

18F-FDG, 18F-fluorodeoxyglucose; AGC, advanced gastric cancer; EGC, early gastric cancer.

well-differentiated adenocarcinoma, 36.7% vs. 6.1%; p=0.004), and non-curative surgery (non-curative surgery vs. curative surgery, 66.7% vs. 20.5%; p < 0.001) (Table 2).

In multivariate analysis, non-curative surgery was a significant independent predictor for 18F-FDG uptake in the primary tumors. Tumour larger than 3 cm (OR, 7.39; 95% CI, 2.41-22.70; p < 0.001) and lymph node metastasis (OR, 5.47; 95% CI, 2.05-14.64; p=0.001) were also significant predictors of 18F-FDG uptake in the primary tumors. Tumour larger than 3 cm (OR, 3.15; 95% CI, 1.16-8.58; p=0.025) and lymph node metastasis (OR, 3.36; 95% CI, 1.23-9.14; p=0.018) showed significant association with 18F-FDG uptake in lymph node (Table 3).
Table 3. Significant Predictors of 18F-FDG Uptake by Multiple Regression Analysis

|                          | 18F-FDG uptake in primary tumor | 18F-FDG uptake in lymph node |
|--------------------------|---------------------------------|------------------------------|
|                          | OR                              | 95% CI                       | p-value         | OR                              | 95% CI                       | p-value         |
| Depth of invasion        | T2-4                            | 2.17                         | 0.68-6.92       | 0.191             | 1.21                          | 0.41-3.58       | 0.728           |
| Size (cm)                | ≥3                              | 7.39                         | 2.41-22.70      | <0.001            | 3.15                          | 1.16-8.58       | 0.025           |
| Differentiation          | Moderately & poorly             | 1.46                         | 0.48-4.41       | 0.506             | 1.72                          | 0.66-4.47       | 0.263           |
| Lymph node metastasis    | Positive                        | 5.47                         | 2.05-14.64      | 0.001             | 3.36                          | 1.23-9.14       | 0.018           |
| Curability of operation  | Non-curative                    | 11.05                        | 1.10-111.08     | 0.041             | 2.27                          | 0.75-6.88       | 0.147           |

18F-FDG, 18F-fluorodeoxyglucose.

![Fig. 1](image)

**Fig. 1.** Receiver operator characteristics (ROC) curve of the maximum standardized uptake value (SUVmax) of primary tumor. (A) In ROC for detecting lymph node metastasis, an area under the curve of 0.795 was obtained (95% CI, 0.719-0.871; p < 0.001). (B) In ROC for predicting non-curative surgery, area under the curve was 0.801 (95% CI, 0.722-0.879; p < 0.001).

Table 4. Prediction of Lymph Node Metastasis in Patients Who Underwent Operation

|                          | Sensitivity | Specificity | Accuracy | Positive predictive value |
|--------------------------|-------------|-------------|----------|----------------------------|
| CT                       | 69.8        | 69.6        | 71.2     | 54.4                       |
| Tumor SUVmax > 3.75      | 73.5        | 74.5        | 74.1     | 60.0                       |
| Tumor SUVmax > 3.75 & lymph node uptake(+) | 47.2 | 94.1 | 96.2 | 80.6 |

SUVmax, the maximum standardized uptake value.

3. Sensitivity and specificity of 18F-FDG uptake for predicting regional lymph node metastasis and non-curative surgery

We assessed the sensitivity and specificity of the SUVmax in detecting lymph node metastasis (area under the curve [AUC] of 0.795, 95% CI, 0.719-0.871, p < 0.001) or non-curative surgery (AUC of 0.801, 95% CI, 0.722-0.879, p < 0.001) using an ROC curve (Fig. 1). We obtained the most appropriate SUVmax cutoffs for primary tumor 18F-FDG uptake for prediction of metastatic lymph node (SUVmax ≥ 3.75) and non-curative surgery (SUVmax ≥ 4.35).

Tables 4 and 5 show an overview of the calculated sensitivity, specificity, accuracy, and positive predictive value of SUVmax in detecting lymph node metastasis or non-curative surgery using SUV cutoffs for primary tumor. When the SUVmax of the primary tumor was greater than 3.75, the sensitivity and specificity of PET/CT with regard to the diagnosis of metastatic lymph node groups were 73.5% and 74.5%, respectively (Table 4). These values were higher than that obtained using CT scanning (the sensitivity, 69.8%; specificity, 69.6%). For patients with a SUVmax of 4.35 or more, non-curative surgery was predicted with a sensitivity of 83.3% and a specificity of 78.0%. When the SUVmax was greater than
Vol. 64 No. 6, December 2014

Table 5. Prediction of Non-curative Surgery in Patients Who Underwent Operation

|                | Sensitivity | Specificity | Accuracy | Positive predictive value |
|----------------|-------------|-------------|----------|--------------------------|
| CT             | 45.8        | 93.9        | 86.5     | 57.9                     |
| Tumor SUVmax > 4.35 | 83.3        | 78.0        | 78.8     | 40.8                     |
| Tumor SUVmax > 4.35 & lymph node uptake(+) | 58.8        | 91.6        | 86.5     | 56.0                     |

SUVmax, the maximum standardized uptake value.

4.35 and the FDG uptake of lymph nodes was positive, non-curative surgery was predicted with a sensitivity of 58.8%, specificity of 91.6%, accuracy of 86.5%, and a positive predictive value of 56.0%. Specificity, accuracy, and positive predictive values were similar to those of CT scanning (specificity, 93.9%; accuracy, 86.5%; and positive predictive value, 57.9%). However, the sensitivity (58.8%) was higher than that obtained using CT scanning (45.8%) (Table 5).

Table 6. Role of CT and 18F-FDG PET/CT in Detecting Distant Metastasis and Peritoneal Carcinomatosis

| No  | Metastasis in the pathologic finding | Metastasis in the radiologic finding |
|-----|--------------------------------------|--------------------------------------|
|     | Peritonium | Other organ | CT finding | PET/CT finding |
| 1   | Peritonium | -           | Peritoneum | Peritoneum     |
| 2   | Peritonium | Colon, small bowel | -         | Peritoneum     |
| 3   | Peritonium | -           | Peritoneum | Peritoneum     |
| 4   | Peritonium | Colon, spleen | -         | Peritoneum     |
| 5   | Peritonium | Colon       | -         | Liver          |
| 6   | Peritonium | Liver       | -         | Liver          |
| 7   | -          | Small bowel | -         | -              |
| 8   | Peritonium | Pancreas    | Ovary     | Ovary          |
| 9   | Peritonium | -           | Peritoneum | Peritoneum     |
| 10  | Peritonium | -           | -         | -              |
| 11  | -          | Pancreas    | -         | -              |

-, negative finding.

4. 18F-FDG PET/CT in detecting distant metastasis and peritoneal carcinomatosis

In nine patients, pathological examination of peritoneal lesions showed malignant cells. Seven patients had metastatic lesion of colon, small bowel, liver, or pancreas. 18F-FDG PET/CT had a low sensitivity (2/9, 22.2%) in detecting peritoneal carcinomatosis when compared with that of CT scanning (44.4%). In one case, a focal intense hypermetabolic lesion in the liver was found by 18F-FDG PET/CT. However, the lesion was not detected on CT (Table 6).

DISCUSSION

Accurate preoperative staging is critical for determining the most adequate therapy for gastric cancer, and CT scanning is the standard imaging modality for preoperative staging. However, as an anatomic imaging method, CT scanning is known to have a low sensitivity and specificity at N staging of the disease.1,9,10 In addition, several studies have shown that 18F-FDG PET had a lower sensitivity for detection of lymph node metastasis and had no definite role as a preoperative imaging method in gastric cancer.11 This is related to the low resolution of 18F-FDG PET (5-7 mm), which does not allow easy differentiation of the perigastric lymph nodes from the primary tumor.6 In recent years, 18F-FDG PET/CT has been reported to offer several potential advantages over the use of 18F-FDG-PET images or CT images alone.12 18F-FDG PET/CT provides more precise anatomical data along with metabolic information. What is notable is that in a previous PET study, the “sensitivity for metastasis to lymph nodes” was 17.6% to 46.4% (median 27.5%).1,4,6,13 In this study, we found that the sensitivity for metastasis to lymph nodes in our PET/CT study was rather high, recording 56.6%. Such difference can be explained by the advantage provided by the combination of PET and CT, and the technological development that has made high-resolution images with an accuracy of below 5 mm possible.

A challenging image obtained by the fusion of 18F-FDG PET and CT would have been regarded as having improved diagnostic performance for lymph node staging. Many factors, including location, depth, size, macroscopic type, and histological type of the AGC, affect the incidence and distribution of lymph node metastasis.14 Increased 18F-FDG uptake related to rapidly growing and poorly differentiated tumor can reflect the regional lymph node metastasis.15,16 Using the derived criterion for lymph node metastasis of SUVmax 3.75 or greater, 18F-FDG PET/CT was predicted with a sensitivity of 73.5%, a specificity of 74.5%, an accuracy of 74.1%, and a
PET/CT. Ames et al.20 presented a case in which 18F-FDG uptake without ovarian metastases but showed 18F-FDG uptake on the urinary collecting system.18,19 We had a patient who was taking (e.g., bowel) and because 18F-FDG is excreted through multiple structures with variable physiologic 18F-FDG uptake, challenging, particularly in the abdomen and pelvis because of 18F-FDG uptake. Physiologic 18F-FDG uptake can be challenging, particularly in the abdomen and pelvis because of multiple structures with variable physiologic 18F-FDG uptake (e.g., bowel) and because 18F-FDG is excreted through the urinary collecting system.18,19 We had a patient who was without ovarian metastases but showed 18F-FDG uptake on PET/CT. Ames et al.20 presented a case in which 18F-FDG uptake in a normal ovary was misinterpreted initially as a metastatic lesion. Change in the ovary associated with ovulation is the likely explanation for the increased 18F-FDG accumulation in the ovary. Lerman et al.21 observed increased 18F-FDG uptake in the ovaries of 21 of 112 premenopausal patients without known gynecologic malignancy using PET/CT. Fifteen of these patients were imaged near the time of ovulation as determined by the presence of functional ovarian cysts.

Our study has a limitation. The number of enrolled patients might have been too small to confirm the clinical validity of 18F-FDG PET/CT for gastric cancer. Therefore, studies with larger populations should be planned in order to confirm the correlation between preoperative 18F-FDG PET/CT and surgical findings.

In conclusion, it is difficult to assert that PET/CT scanning is far superior to CT scanning in prediction of non-curative surgery or lymph node metastasis. However, we did find that a higher SUVmax of primary gastric cancer is correlated with both non-curative surgery and lymph node metastasis. Therefore, information from the preoperative 18F-FDG PET/CT might be helpful to physicians in deciding the extent of lymphadenectomy and optimal treatment modalities.

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